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Complement in neurobiology

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1. ABSTRACT

The complement (C) system is a vital arm of innate immunity with many roles, including control of inflammation. This article examines the (C) system with emphasis on recent developments on complement relevant to neurobiology, in particular regarding our understanding and treatment of immune-mediated diseases. We will briefly outline the C system, and provide an updated review of its many receptors and regulatory factors. This section concludes with a listing of important roles of the C system, from recruitment of neural stem/progenitor cells, to its' relation to coagulation and adaptive immunity, and its lesser-known but beneficial roles in physiology. We also review evidence for C-mediated diseases, which include multiple sclerosis and Alzheimer's disease. Therapeutic approaches for C-mediated diseases, considers emphasizing modulators of the C system including several less widely studied approaches such as heparinoids, vitamin D, and intravenous IgM. Finally, we summarize cutting-edge work on the role of C-mediated natural antibodies in autoimmunity and treatment strategies based on those findings, e.g., for remyelination and post-ischemic stroke repair. Improved understanding of the C system may hold great promise for the treatment of neurodegenerative diseases.

2. INTRODUCTION

The complement (C) system is a major arm of innate immunity, distinct from adaptive immunity (production of antibodies and effector T cells). It is an evolutionarily ancient and widely conserved system (1), yet significant differences in details are seen even between closely related species, such as human vs. mouse. It is analogous to the system of blood clotting insofar as it is comprised of a set of circulating proteins (zymogens, or pro-enzymes) which when triggered results in a cascade of reactions leading to several outcomes, all of which are aimed at killing pathogens and eliminating infected or damaged self-cells, and repair of collateral damage. However, complement also plays many other vital roles.

It is also "ancient" in terms of the history of immunology, having been discovered more than a century ago, and its main outlines were well delineated by the 1980's. For this reason, and because more recent discoveries such as the Toll-like receptors (TLR's), captured the limelight, the C system lapsed into relative obscurity. Fortunately, however, it has recently been "rediscovered" (2) and is again enjoying a renaissance of exciting new discoveries, many of which are reviewed here. Much of this new work has done by a comparatively small number of specialists, and is not yet widely appreciated. A recent special issue of *Science* on innate immunity (3), while highlighting important new discoveries, scarcely mentions the C system, (nor did a special issue of *Nature* on autoimmunity) (4). We shall see that some of the most exciting work on autoimmunity hinges on the C system. Likewise, reviews of the "inflammasomes" of innate immunity (5, 6) make no mention of the C system, although many pathogens and other signals can activate both, suggesting their connection. Lastly, because many reviews have thoroughly reviewed intracellular signalling pathways activated by C, it is not a focus of this examination.

3. OUTLINES OF THE COMPLEMENT SYSTEM

A major resource describing these pathways is Halkers' textbook 'Mechanisms in Blood Coagulation, Fibrinolysis and the Complement System' (7) and several other accounts (8, 9) and as noted below. Other general reviews are available (10, 11) but do not stress the detailed steps.

3.1. The classical pathway

The classical pathway is shown in Figure 1. Panel (**A)** shows the starting players in circulation: C1q, C1r and C1s. The C1r and C1s are widely understood to each circulate as dimers, but have also been shown to exist as

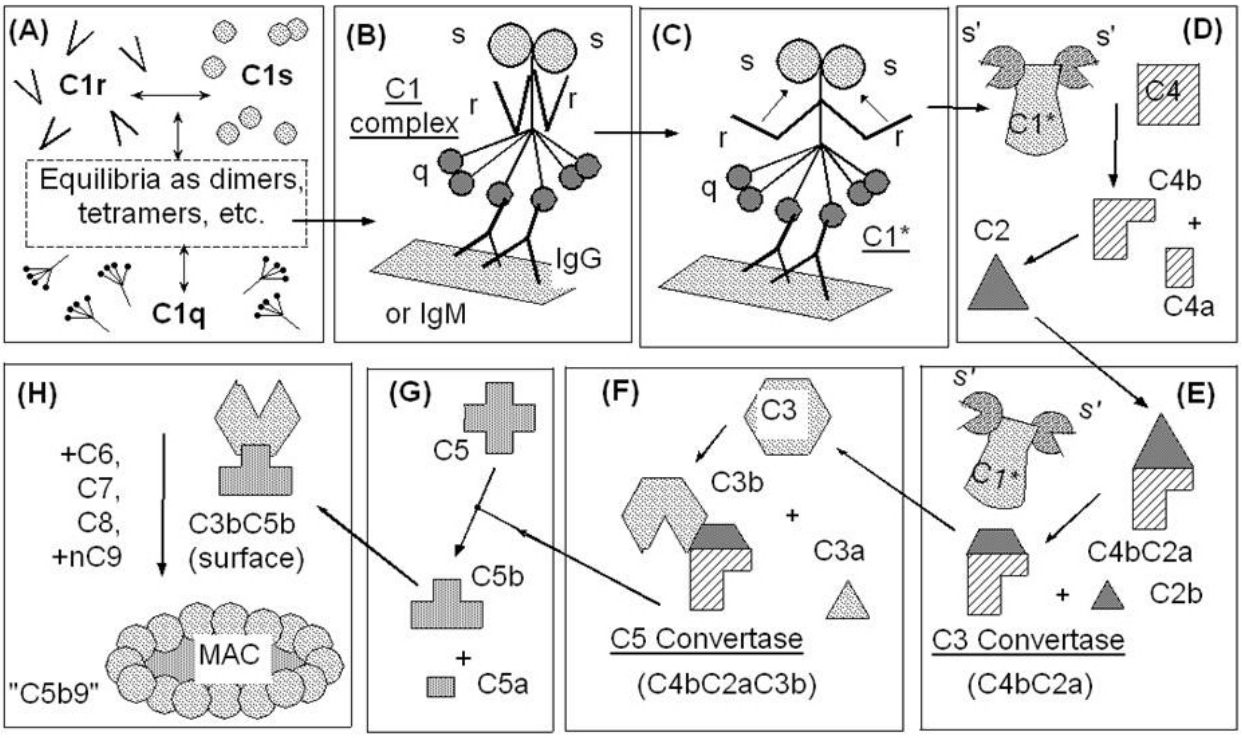

Figure 1. Classical pathway.

tetramers, $C1r_2C1s_2$, with some in complex with C1q (12), as more recently discussed (13). Panel (B) describes the classical triggering event, binding of C1q to IgG or IgM bound at plasma membranes. The C1q resembles a bouquet of 6 flowers. A single IgM is theoretically sufficient, or at least two IgG. Activation of this pathway by IgG is sensitive to subclass, usually IgG3 > IgG2 ≈ IgG1 > IgG4, but this may vary with specific conditions (14). This binding causes a conformation change in C1q giving increased affinity for C1r and C1s, binding a pair of each, as in (B). The bound C1r is then spontaneously activated, then immediately activates the bound C1s, resulting in the activated C1 complex, symbol C1* in panel (C). The active C1s, called s' in the figure, then attacks circulating C4, breaking it into C4a + C4b, as in panel (D). The C4b then binds C2, and in this state, the C2 is split, also by active C1s in the complex, yielding C2a + C2b, in which the C2a remains bound to the C4b, as in panel (E). This complex, C4bC2a, is known as the *C3 convertase* because it converts C3 to C3a + C3b, as in panel (F). The C3b remains bound to C4bC2a, giving the trimolecular complex, C4bC2aC3b, called the *C5 convertase* because it converts C5 into C5a + C5b, shown in (F). The C3b readily binds covalently to pathogen (or other) surfaces *via* its thioester, and is a key *opsonin*, i.e., marks the cell for phagocytosis. The C3bC5b complex may then set in motion the sequential recruitment of C6, C7, C8, and C9, assembling the "membrane attack complex" (MAC), or "terminal complement complex" (TCC), also called "C5b-9", which punches a hole (pore) in the membrane of the invading cell, killing it. Like all of the steps, details of MAC formation are complex. Briefly, it is C5b-7 that inserts in the membrane, which then captures C8, which induces polymerization of a ring of C9 (as many as 18 C9 per pore) to form either a toroidal ("donut") or non-tubular pore (7). Some readers will notice that the sequence of interactions of the C1q complex is not first with C2, then C3, C4, but rather is with C4, C2, then C3. This is because the factors were discovered and numbered before these steps were established.

Thus, there are two main routes of pathogen killing, one being lysis by MAC ("lytic pathway"), the other being opsonization, meaning C fragments are deposited on the pathogen which designate it for phagocytosis. The relative importance of these routes depends on specifics (one example *Neisseria meningitidis* is discussed by Granoff) (15). Numerous regulatory mechanisms control all steps. For example, 'self'-cells are protected against the C3b opsonin in several ways, including heparin-like substances (like heparan sulfate) in the extracellular matrix (ECM) which potentiate the actions of specific C inhibitors (16), discussed presently.

3.2. The alternative pathway

A key distinction of this pathway is that it does not depend on immunoglobulin (Ig). This route involves two additional core components, complement factors B (CFB) and D (CFD), plus three main regulators (discussed later, CFH, CFI, CFP), and a hydrolyzed form of C3 in which water (H:OH) is added to its thioester bond; see Figure 2, top left (17). A small fraction of circulating C3 is always in this evanescent form, C3•HOH, which is able to bind CFB, keeping the system poised for explosive

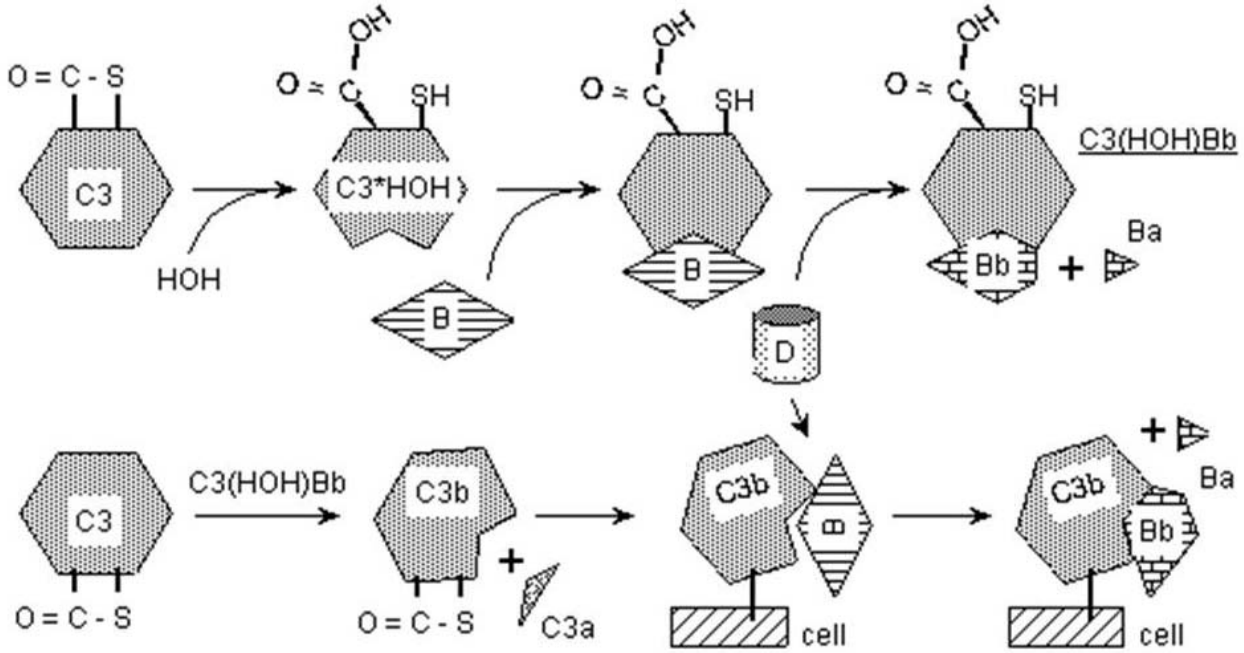

Figure 2. Alternative pathway.

amplification. Bound B can then be cleaved by CFD, a serine protease present in trace amounts in plasma fully active but specific for B in the form, C3 (HOH)B, yielding C3 (HOH)Bb + Ba. This product has the ability to directly produce C3b from C3; (see lower left of Figure 2). Now, factor B can bind to C3b, whose thioester can covalently bond to the pathogen surface, where B is attacked by D, yielding surface-bound C3bBb, known as the "alternative pathway C3 convertase". Since this produces more C3b, this sequence is called the "amplification loop". Mechanisms which normally restrict this amplification are considered in following articles. Mechanisms for distinguishing 'self'-cells from pathogens are discussed by Pangburn *et al* (18) and are described later.

3.3. The lectin pathway

This 'ancient' pathway (1, 19), which does not need a separate figure, adds a few more players: the ***mannose binding lectin*** (MBL) - a.k.a. mannan-binding protein (MBP) - and the ***MBL-associated serine proteases*** (MASP-1, -2, -3), plus a smaller one, sMAP (20-22). Here, MBL functions as the recognition element, similar to C1q, except in binding to unfamiliar carbohydrates or dying 'self'-cells rather than Ig. MBL circulates bound to a MASP, which is activated upon engagement, to split C4 and C2 into C4b and C2b, generating the C3 convertase. The rest is similar as previously described, with C3 the central effector. Recent work on this finds even closer parallels with the classical pathway (23), already evident by 1996 (20).

3.4. The extrinsic pathway

A fourth pathway, the "extrinsic" pathway operates through the proteolytic action of thrombin which directly cleaves C3 and C5 (24-26). Thrombin is normally active in appreciable amounts only briefly and locally during coagulation. This pathway may therefore be important in cerebral hemorrhage (27); other relations of the C system to coagulation are discussed.

4. REGULATORY FACTORS OF THE COMPLEMENT SYSTEM

It is often noted that the number of C regulatory factors is considerably greater than the number of core constituents, yet they are equally vital to the proper regulation of the system. The number of these "accessory factors" continues to grow.

4.1. Early or general regulators

The ***C1 inhibitor*** (or C1 esterase inhibitor) is a serine protease inhibitor ('serpin'), C1 inhibitor being the only known inhibitor of C1r (and, less potently, of C1s). It is inhibits MASP-1 in the lectin pathway (13), and is an important regulator of the contact pathway of coagulation, acting on factors XIa and XIIa, and on fibrinolysis by inhibiting plasmin, which interacts with the C system as discussed in part 4 (4). C1 inhibitors' official name is SERPING1 (28) and is abbreviated C1-INH. ***Carboxypeptidase N*** (CPN) acts to detoxify the anaphylatoxins (C3a, C5a) by removal of the carboxy terminal arginine. An important recent discovery is that the plasma carboxypeptidase B (CPB) of the fibrinolytic system, (also known as the ***thrombin-activatable fibrinolysis inhibitor***, TAFI), is at least equally effective (29), as may be other recently described CP's (e.g. CPM) (30). They are also important in thrombin-mediated inflammation (31). The ***C4b binding protein*** (C4b-BP, or C4BP) promote assembly of the convertases of C3 and C5, and when bound to membranes can function as a C

receptor. Sjoberg *et al*. have suggested multiple regulatory roles for C4BP (32). The gene for C4BP is found in close proximity to those for several other C factors, on the long arm of chromosome 1, this cluster being known as the '*regulators of complement activation'* (RCA).

4.2. Modulators of the alternative pathway

Complement factor H (CFH) binds to C3b or C3:HOH to inhibit binding to factor B, limiting formation of the C3bB proenzyme (33). Equally important, CFH is a cofactor for ***factor I***, which degrades C3bH to inactive C3b, (designated iC3b). Factor I circulates in active form. Further degradation of iC3b releases the fragment, C3c (150 kDa), leaving the degraded portion, C3dg, to persist on circulating cells. The ***factor H-related proteins*** (FHR), of which there are 5, are similar in their short concensus repeats (SCR's) and amino acid sequence at the N terminus (34, 35). For example, unlike CFH, CFHR1 is not a cofactor of I, but it does bind C3b and so can be detected on pathogen surfaces. Most of these five FHR bind heparin, and associate with circulating lipids, but their specific functions remain unclear. (The "R" in acronym CFHR1 here indicates '*related'*, not 'receptor'.)

Properdin, or complement factor P (CFP), has been known for more than 50 years to stabilize C3bBb, sustaining C activation in the alternative pathway. This action is opposite to that of factor H. However, the details of this scheme have long remained obscure, and solid work was too rapidly dismissed, with the result that it came to be viewed as only a minor component, hardly even mentioned in many reviews. That has now changed due to work by Fourcade, Kemper, and others (recently reviewed in ref erence36). Briefly, in addition to the above function, CFP is itself a pattern recognition molecule capable of binding to the surfaces of certain pathogens, as well as to apoptotic and necrotic 'self'-cells and fragments, leading to convertase formation and destruction of the target. Deficiencies of CFP predispose to several pathologies including certain infections, abdominal aortic aneurysms, and other inflammatory and autoimmune disorders (36).

4.3. The complement receptors

The chief function of complement receptor 1 (CR1, CD35) is to clear immune complexs (IC) (37). CR1 was formerly known as the C3b/C4b receptor because its main ligands are those components bearing immune complex (IC). It is widely distributed, but CR1 of erythrocytes (RBC) dominate because of their vast numbers. After capture, the IC is removed in the liver and the RBC return to the circulation unscathed (38). CR2 (CD21) is found on B lymphocytes, and can complex with CR1, CD18, CD81 and TAPA (39, 40). It binds the antigen-bearing C3 fragments, iC3b, C3dg, and C3d, by which it functions in linking innate immunity to adaptive immunity, as outlined in part 4 (4) below. Some authors classify CR1 and CR2 among the 'RCAs' (41, 42).

CR3 is the CD11b/CD18 complex and CR4 is the CD11c/CD18 complex, also known as integrin $Alpha_2Beta_1$. These are often referred to collectively as "beta-2 integrins". A fourth member, CD11d/CD18 is described but is not yet understood in this system (43). Lambris mentions evidence for a "CR5" (his quotation marks) but it is not yet defined (44). CR3 on neutrophils recognizes β-glucans (45) and promotes T cell priming in viral infections (46). CR3 expression on splenic B cells is regulated in part by C3 (47). Of note, the T-regulatory (T_{reg}) subpopulation are $CD11c^{+}CD8^{+}$ (48), but those authors do not discuss their findings in terms of CR4, or the role of C in modulating T_{reg} population.

Ghebrehowet and Peerschke identified two C receptors, cC1qR, which is identical to calreticulin, and gC1qR/p33, where the prefix 'c' denotes binding to the collagen-like tail of C1q, and 'g' the globnular head (49). That review provides evidence of key roles of these receptors in infection (50), in the contact pathway leading to bradykinin generation, in the activation of platelets and endothelial cells, in inflammation, and in B-cells, T-cells, and other immune cell proliferation and responsiveness. For example, the hepatitis C virus appears to evade immunity *via* gC1aR (51, 52). The gC1qR/p33 (also '*hyaluronic acid binding protein'* HABP-1) is located in various subcellular compartments, including mitochondria, as well as the plasma membrane (50), bringing up the important fact that the C system is now known to operates *inside* cells as well as in the plasma and at external cell surfaces. In the same journal issue, another C1q receptor was identified, integrin $Alpha_2Beta_1$, on T cells, natural killer (NK) cells, and some others (53). Its ligands include all the 'collectins'.

Phagocytosis of pathogens proceeds by several machanisms involving C, illustrated by the fact that some fungi avoid phagocytic engulfment by blockade of CR2 and CR3 (54). Those authors suggest that CR3 is another link between the C system to adaptive immunity. With regard to the phagocytic clearance of apoptotic self-cells, which is highly relevant to autoimmune disease, both CR3 and CR4 have been implicated (55), as has the opsonin iC3b (56). It had been observed that C1q stimulated phagocytosis of apoptotic cells, and CD93 was implicated in this effect, whence it was termed C1qRp, where suffix 'p' stands for phagocytosis (57). However, knock-out of this gene in 2004 failed to eliminate the C1q-stimulation of phagocytosis (58), though it did hamper phagocytosis, as more recently discussed (59, 60). Thus, there must be redundancy, or yet-undiscovered receptors. Because of its many ligands and putative functions, some authors assert that the function of CD93 is unknown (61) while others support its role in phagocytosis (62). Another putative C-related receptor, or co-receptor, involved with phagocytosis is CD91 in complex with cC1qR / calreticulin (49, 63). However, CD91 (a.k.a. *low-density lipoprotein-related receptor 1* (LRP1)) does not appear to be responsible for the C1q-triggered enhancement of phagocytosis (60).

The topic of C receptors is complicated by the different terminologies used by various authors, which may stem partly from the fact that multiple receptor complexes seem to be involved, partly from the promiscuity of these receptors leading to alternative names, and partly from the unsettled state of knowledge. For example, a recent review of calreticulin (cC1qR) does not discuss it as a C receptor

at all (64), though it does discuss its role with CD91 in phagocytosis, as does Gardai *et al* (63), who find that it can either suppress or enhance inflammation.

4.4. Membrane-bound self-cell protecting proteins

Three proteins protect self-cells against autologous (self) C-mediated injury: the ***membrane cofactor protein*** (MCP, CD46), the ***decay accelerating factor*** (DAF, CD55), and the ***membrane inhibitor of reactive lysis*** (MIRL, CD59), a.k.a. ***protectin***, a.k.a. ***homologous restriction factor*** (HRF). Both DAF and MIRL are anchored to the membrane by a glycosyl phosphatidyl inositol (GPI) tether, which can be cut by a specific phospholipase C (65). This topic was comprehensively reviewed by Morgan and Meri in 1994 (66) but new details and relations to disease have since come to light (67, 68). MCP, as its name implies, acts as a cofactor for the degradation of C3b and C4b by CFH and CFI. It is widely distributed but absent from RBC. *Protectin* protects self-cells by blocking completion of MAC *via* binding C8 and/or C9. DAF accelerates the decay of C3 convertase, and binds C3bBb (42) and is of interest in Alzheimer's disease (AlzD) (69).

4.5. Anaphylatoxins and their receptors

The cleavage fragments C3a and C5a are the main *anaphylatoxins* (AT's), so called for their inflammatory effects. Both are potent chemotactic agents which play essential roles in innate immunity (70, 71), and adaptive immunity, contributing to many pathologies such as sepsis (72), which will come up again in this review. When bound, the C5a receptor (C5aR, CD88) activates neutrophils increasing intracellular calcium, degranulation and respiratory burst. Less clear is the function of the pool of C5aR-like receptor-2 (C5L2), which is mainly stored in cytoplasm, and binds C5a or $C5a_{desArg}$. This may be involved with lipid metabolism in adipocytes, where it is known as *acylation-stimulating protein* (ASP) (73). ASP can sequester and internalize C5a to act as an anti-inflammatory, opposing C5aR. The duties of C5aR and C5L2 in chemotaxis overlap with the N-formyl peptide receptors (74). In the CNS, C5L2 is found on glia and neurons, and is reportedly anti-inflammatory (75).

Roles of AT's in neurodegenerative diseases have been discussed by Klos *et al.* (72) and chemotaxis towards AT gradients have been described (76). The gene for C5aR is near that of other peptide receptors e.g. bradykinin receptor. The AT's can also be generated directly by the mast cell enzyme, β-tryptase, acting on C3, C4 or C5 (77). Other AT's are known, such as C3f and $C3f_{des\text{-}Arg}$ (78).

4.6. Additional pathogen recognition factors

In addition to C1q and MBL, several other proteins function in the C system to recognize *pathogen-associated molecular patterns* (PAMP's) (79). These are mainly lectins, proteins which bind to specific carbohydrates, usually those foreign to the host, or those which mark injured or dying self-cells. Lectins, also recognize some lipids, e.g. lyso-phosphatidyl choline. MBL belongs to the collectin family, which also includes the pulmonary surfactant proteins (SP) (21, 80), which participate in C regulation in the lung (81). Ficolins, also of the collectin family where ("coll-" denotes collagen-like), are active participants in the lectin pathway which recognize pathogens and activating MASP-2, similarly to MBL (82, 83). Runza et al. noted differences among species in ficolin specificities, which underlie species differences in susceptibilities to particular pathogens or strains.

C-reactive protein (CRP) and serum amyloid protein (SAP) belong to the *pentraxin* family (84, 85), so called for their five subunits, and both are "acute phase reactants" (APR's). CRP was discovered and named for its ability to precipitate polysaccharides from pneumococci. CRP can bind pathogens and function like IgG or IgM, including by binding to FcγRI, II (86), by activation of C *via* C1q, as well as by binding to the inhibitory Fc receptor, FcγRIIb. CRP protects mice against infections which would otherwise be fatal (87), proving its role in immunity. Botazzi *et al.* (84) citing Szalai *et al.* (87) claim that CRP protects even when it does not bind pathogen but that citation does not support that. However, Agrawal *et al.* discuss theories about CRP functions, including bacterial killing without binding, concluding that it is an unsolved enigma (88). In addition to SAP and CRP, which are "short" pentraxins, there are "long" pentraxins such as PRX3, produced in macrophages and dendritic cells in response to proinflammatory stimuli (89).

This listing should also include at least some of the C-type lectins (90), as it has been demonstrated that SIGN-R1, a relative of DC-SIGN and the main receptor on macrophages for certain pathogens, initiates the classical C pathway, independent of IgG/M (91, 92). Also likely to be involved with the C system are the galectins, which are released or actively secreted by infected or dying cells, and which recognize many PAMP's and "danger-associated molecular patterns" (DAMP's) (93, 94). These authors do not discuss relationships of galectins to the C system.

4.7. Additional compelemet modulators

4.7.1. Clusterin

Clusterin (CLU) was known in earlier C literature as protein SP-40,40, owing to its two chains of 40 kDa each; or as complement lysis inhibitor (CLI). Clusterin was the name originally given for its ability to cluster several cell types (95). However, CLU has other functions, including lipid trafficking in lipids where it is known as apolipoprotein J (apoJ); CLU also acts as a chaperonin. CLU may be regarded as another acute phase reactant insofar as CLU serum levels often rise in stress. In the brain, CLU is secreted mainly by astrocytes. Its function in the C system is to sequester terminal C components C7, C8, C9, blocking assembly of the MAC (42). The relevance of CLU to the C system has been challenged (96), this finding was not conclusive in view of decades of papers supporting CLU modulation of C, and for technical reasons. Current interest in CLU is increasing in cancer research. Its potential relevance to MS and Alzheimer's disease (AlzD) has also resurfaced (see part 5).

4.7.2. Osteopontin

Osteopontin (OPN) is a protein known to neurologists as one of a trio on the 'radar screen' of the MS

community (97). OPN has been described as a proinflammatory mediator (98) but in the C-system, it can block or shut down the alternative pathway by potentiating inhibitory factor H, following binding to the vitronectin receptor, $Alpha_VBeta_3$ (S protein receptor) or CD44 (99). OPN can protect self-cells against C attack in a manner similar to the MCP, as does bone sialoprotein-1 (BSP1) (99, 100). Other authors find OPN to participate in tissue repair as a guidance molecule (101). Its Janus-like properties remind us of other C-related molecules in neurological disorders (such as CLU), a fact which gives pause when hearing them proposed as "targets of therapy" – should we inhibit, or increase them?

4.7.3. S protein, also vitronectin

Perhaps the best evidence that vitronectin (VTN) is important is the fact that at least two pathogens (*Moraxella catarrhalis* and *H. influenzae*) acquire this protein, using it as a defensive shield against C attack (102, 103). For example, if the serum source of C is first depleted of VTN, it kills the pathogen; if VTN is added back it survives (102). VTN contains the canonical RGD sequence (Arg-Gly-Asp) of fibrinogen and fibronectin which can bind to platelet GP IIb/IIIa and other integrins with this motif. VTN is also a heparin-binding protein with several important functions (104) including coagulation. In the C system, it binds incomplete MAC such as C5-b7, as well as to complete MAC (C5b-9), preventing MAC from harming cells, known as "non-lytic MAC", (referenced in 103). Of course, if plasma VTN always had this action the C system would be crippled, therefore this might happen mainly at the extracellular matrix (ECM), which is VTN-rich, for protection of self-cells, in much the way that the above-mentioned bacteria protect themselves by 'donning a cloak' of VTN.

4.7.4. Phospholipase A_2

Although phospholipase A2 (PLA2) is not usually listed among the C factors, it is an acute phase reactant (89), increasing up to 1000-fold in inflammation, closely paralleling CRP (105). PLA_2 participates in the C-mediated task of clearing apoptotic cells or debris, particularly those displaying anionic phospholipids such as phosphatidyl serine (PS), by inducing uptake of such particles, in partnership with CRP (106, 107). PLA_2 cooperates with C in killing *Staphylococcus aureus* and *Listeria monocuytogenes,* and doubtless many other pathogens (108), establishing its role in innate immunity. Its role in the eicosanoid pathway (producing arachadonic acid) is one of several links between the C system and lipid mediators. Since it specifically degrades anionic phospholipids such as PS, it acts as an anticoagulant *in vitro*; however, this activity is inhibited in plasma (109). Interestingly, PLA_2 was inhibited by the multiple sclerosis therapy, FTY720 (fingolamide) (110). PLA_2 is a current drug target of neurodegenerative disease (111) including AlzD (112). In spinal cord injury, it leads to the production of the highly inflammatory *platelet activating factor* (PAF) (113). Plasma gelsolin, implicated in AlzD (114), is a regulator of PAF (115). In the brain, *Herpes simplex,* (a neurotropic virus), generates an miRNA that down-regulates factor H to evade C killing, and also up-regulates PLA_2, in experiments bearing on AlzD (116).

4.7.5. Note on acute phase reactants

As mentioned earlier, plasma levels of several C factors rise dramatically in the hours following infection. Therefore, experiments using serum as a source of C can yield very different results if serum from acute phase subjects is used compared to normal serum (108). A 1994 review of acute phase reactants (APR's) (117) listed about 30 APR's but did not include PLA_2 or several others more recently proposed, e.g., M-ficolin (83), pentraxin 3 (89). Several APR's are now used as clinicalinflammatory biomarkers, most notably CRP.

4.7.6. Apha-2 Macroglobulin

Most authors do not include Alpha-2 Macroglobulin **(**A2M) among the C factors but it is one of many accessory proteins which modulate the C system (7). It is believed that A2M is the original ancestor of the core C factors (C3, C4, C5), the latter having arisen from gene duplications (11). A2M inhibits many proteases, including MASP-1 in the lectin pathway (118). Since many pathogens use proteases as virulence factors, A2M can be anti-microbial. For example, A2M is a key effector against trypanosomatids (119). A2M inhibit proteases by an unusual mechanism, offering its "bait" region to the likely protease, then trapping it by covalent attachment through trans-acylation to its thioester (11, 120). In humans, this large (700 kDa) plasma protein is abundant (2 mg/mL), is an acute-phase reactant (APR), and can also inhibit the coagulation enzymes, kallikrein, thrombin, and plasmin. Depletion of >35% of A2M in rats or dogs is lethal. It may also inhibiting the zinc-dependent matrix metalloproteases (MMP's) which participate in neurodegenerative disease (121) and is of interest in AlzD.

4.7.7. The A2M receptor

CD91 is the A2M receptor **(**A2MR) and was originally termed the *lipoprotein receptor-related protein* (LPR). A2M engages CD91 with high affinity (Kd=0.5 nM) following capture of a protease (120). It is now considered to be also the receptor for heat-shock proteins such as HSP70 and HSP90, chaperonins (122) which govern proper protein folding. As mentioned earlier, CD91 complexes with calreticulin, which binds to the collagen-like tail of C1q (cC1q) and to lung surfactant proteins, SP-A and SP-D, to promote or suppress inflammation (63). Thus, CD91 is another C1qR. Other reports not here cited document its interactions with C1q and CD93, its role in antigen presentation and autoimmunity, in HIV infection, and its function as a "scavenger receptor". CD91 expression on monocytes was the only marker distinguishing HIV^+ patients who did not progress to AIDS, and of melanoma patients with exceptionally long survival (122). In that study, however, the assay was by antibody against A2M, not CD91 *per se*, raising technical questions of interpretation. (For a review, see 123).

4.7.8. Others

Another plasma protein which deserves mention among the modulators of the C system is ***histidine-rich glycoprotein*** (HRG). HRG prevents aggregation of immune complexes, blocking inappropriate interaction of IgG with Fc receptors (FcR), aiding in safe disposal of apoptotic cells, and other effects involving the C system (124). The

family of ***small leucine-rich regulatory proteins*** (SLRP's) of the extra-cellular matrix have also been shown to be important in governing C activation at the cell surface *via* factor H (125); those authors discuss implications of SLRPs' in inflammatory disorders. A more recent review of some members of this family in innate immunity focuses on the Toll-like receptors (TLR's) (and does not mention the C system at all) (126).

4.8. Mouse models of C-mediated disorders

Since many studies are done in mice, it must be emphasized that significant differences between murine and human C systems are known to exist, which may confound or even invalidate the relevance to humans, depending on the study. These differences arise from variations in C gene duplications, alternative splicings, post-translational modifications, and tissue distribution (127). For example, the membrane cofactor protein (MCP) is ubiquitous in humans, but in mice is restricted to the testes. Mouse erythrocytes express a protein known as Crry (*complement receptor-1 related protein, y*), considered to be the functional counterpart of human MCP (68, 128). Common polymorphisms occur in human C4 and differ from those in the mouse (129). Such differences will affect sensitivity to a given activator, as might be expected from pronounced differences in species susceptibility to infectious diseases. This has been a serious impediment in some research fields. In transplant surgery, rodents do not mount C-mediated graft rejection as readily as humans (130). In murine models of Alzheimer's disease (AlzD), the mouse C system is less responsive to the Aβ protein than human, especially in formation of the terminal MAC (131, 132). In an effort to improve this situation for AlzD models, the murine C1q A chain was humanized, this strategy failed to improve sensitivity to Aβ (133).

5. OTHER ROLES, OTHER SYSTEMS

An understanding is emerging that the C system has major roles beyond those traditionally recognized, and overlaps or interacts with other systems.

5.1. Neuroprotective roles of C

The C system has traditionally been viewed as a source of destructive inflammation but is now increasingly recognized as having beneficial actions as well (apart from immune defense). One of these is recruitment of neural stem cells. It was shown in 2006 that neural stem / progenitor cells are recruited *via* C factors, C3a, C5a and their receptors (134). Those studies suggest important therapeutic applications of this finding. Kimberly *et al.* cite three references which show a role for C factors in limb regeneration (135). The anaphylatoxins are believed to be critical also for recruiting hematopoietic stem cells (136, 137). On the other hand, blockade of inflammation by NSAIDs (e.g. indomethacin) was said to restore neurogenesis after endotoxin-induced inflammation or irradiation (138). That finding is not necessarily inconsistent, or may involve different pathways, since NSAIDs are not known to block the C system, (except possibly in platelets). With regard to stem cell recruitment, transformation of stem cells requires vitamin C (139) as an factor essential in cell culture (140).

Tegla *et al.* have discussed the neuroprotective effects of C in multiple sclerosis (MS) with a focus on oligodendrocytes (oligo's) (141). Oligo's are able to defensively shed off MAC with vesicles (142), as can other cell types (143, 144), but MAC readily lyses them if present in sufficient levels (145). Not mentioned by Tegla *et al.* is the fact that oligo's are exquisitely sensitive to C since they lack GPI-anchored proteins which are protective against autologous C (146). Tegla *et al.* cite data that sub-lytic MAC can protect oligo's from apoptosis, and that C5a protects axons, promotes remyelination, and inhibits gliosis. Support for this is found in several papers by them and others using the EAE mouse model of MS which showing that deficiency of C5 (and C6) *worsens* disease, and alters expression of some 2500 genes, about 900 of which were differentially regulated in acute *vs.* recovery of EAE (147).

Three independent reports found that deficiency of the early C components not only failed to protect in the AlzD mouse, but exacerbated progression (148-150), suggesting a protective action of C. However, as noted above, mouse models do not always faithfully reproduce human C activation in AlzD. Their meaning remains controversial and uncertain. Relatedly, it was reported that C5a was strongly neuroprotective against glutamate toxicity (151); but in a mouse model of AlzD, others found that blocking the C5a receptor (C5aR, CD88) was protective (152). Reiter *et al.* described "C-induced protection" by which sub-lytic amounts of C protected against subsequent lytic doses (153). Others have also reported neuroprotection by MAC in sub-lytic amounts (141, 154). This may be similar to the phenomenon of "accomodation" (155), the significance of which is not limited to transplant medicine. This refers to the observation that normally harmful antibodies can become benign, in a manner different from tolerance. Systemic lupus erythematosus (SLE) is a well-known example in which C appears to play a protective role, since deficiencies of early components (e.g., C1q, C4) predisposes to the disease (156). Turning again to AlzD, Veerhuis *et al.* report that Aβ in the presence of C1q and SAP, (but not in their absence), promoted secretion of proinflammatory cytokines from microglia *in vitro* (157). Hence, the putative protective role of C in AlzD mouse models remains an open question. Perhaps C is protective in the early stage of AlzD, since C can clear circulating Aβ (158), but is adverse in the later stages.

The broader question has been debated as to whether inflammation generally, and C in particular, is harmful or helpful in progressive neurodegeneration. This was recently discussed in light of new evidence implicating inflammation and C activation in AlzD (159). The term, inflammation, is exceedingly broad, obscuring important mechanistic differences among its pathways, including the *compensatory anti-inflammatory response syndrome* (CARS) (160). Our laborartory entered the debate about whether inflammation was helpful or harmful in surviving

sepsis, and reported clear association of *reduced* mortality with *increased* inflammatory markers (161).

It was recently reported that the sushi domains characteristic of the C control proteins are vital to the proper clustering of acetylcholine receptors in the worm, *C. elegans*, leading those authors to expect a similarly vital role for C factors in human nerves (162). Findings from other lower organisms are also instructive. As noted later (part 6 (4)), the C system is involved in the release of antimicrobial peptides. It has been shown in the medicinal leech, (which depends on the C system for its immune function) (19, 163), that these peptides are synthesized in neurons and glia, and act to promote neuronal regeneration following axotomy (164).

5.2. Role in autoimmunity

As mentioned above, nearly all individuals who are deficient in early C factors, C1q, C2, or C4 develop SLE, as do mouse models with these defects (156). However, C activation is also responsible for progression of the disease in later stages, so this presents a paradox. According to Carroll (165), the tentative explanation has been based on evidence that these factors, which trap cellular debris such as apoptotic blebs, "present" these self-antigens to autoreactive B cells to induce anergic tolerance. Mice lacking C1q or C3 resist induction of tolerance (166). Similar observations have been made in ischemia-reperfusion (I/R) injury (167), and may apply also to MS and AlzD models. The role of C in clearance of apoptotic cells had been controversial but now appears to be established, such as by Fraser *et al* (62), who show C1q to play the central role, but C3b opsonization, the alternative pathway, and other serum factors contribute to this complex process. The scenario is modified somewhat in the CNS where the glia (astrocytes, microglia, ependymal cells) play prominent roles (168).

Defective clearance of apoptotic cells and debris by the C system is now thought to promote systemic autoimmune disease (62, 169). This mechanism has been discussed with specific regard to the brain (168). A mouse that spontaneously develops autoimmune diabetes and other autoimmunities was persuasively attributed to defective clearance of apoptotic cells (170). The role of C in autoimmune diseases is complex, as further considered later in this review.

5.3. Role in adaptive immunity

It had been known since the 1970's that depletion of C3 impaired the antibody response to antigens, and that lymphocytes possessed C receptors, yet two decades elapsed before the pivotal role of C in adaptive immunity came to be widely accepted (171). The key evidence clarifying this connection was supplied by Fearon, Dempsey and colleagues, who demonstrated that antigen bound to C3d greatly enhanced the humoral response, *via* CR2 (CD21) interacting with CD19 on B cells (39, 172). In effect, the C3d was acting as a natural adjuvant, greatly lowering the threshold of response (173). Another class of natural adjuvants was subsequently appreciated, namely, natural antibodies (174-176), discussed later. Additional C factors are now known to be involved with T- and B-cell signaling, such as MIRL (CD59) (135, 177). Interestingly, transcription of C genes increased when adaptive immunity was disabled by deletion of the *recombination activation gene 1* (rag1), in zebra fish (178).

5.4. Links to coagulation

Some of the connections between C and the coagulation system have been recognized since the 1980s or before (179, 180). More recent developments include the thrombin-activated "extrinsic pathway" of C, and the role of TAFI in the C system, cited earlier. Plasmin can partner with MAC to induce the inflammatory lipid, PAF (181). Of growing importance in C research is the kinin-kallikrein system (KKS) of the contact pathway of coagulation, in part because of its possible involvement in MS (182), and because one of its most potent products, bradykinin, is controlled by C1-INH (183). Endothelial cells (EC) are a target of both the KKS and C systems (184). Already in 1993, the anaphylaxis caused by insect stings was attributed to enzymes of the contact pathway, which in turn induces activation of C (185). More recently, it was shown that coagulation factors Xa and XIa can directly cleave C5 and C3 to produce C5a and C3a (25, 26). In their most recent work, Amara *et al.* show how both coagulation and C are activated at a wound site and work together, including inflammatory response (26).

Other enzymes released in the micro-environment can likewise produce C3a and C5a directly, such as by neutrophils and mast cells (77, 186). Tissue factor (TF), the main initiator of coagulation and thrombosis, is now also linked to the C system (187, 188). Protein S, a cofactor in the protein-C anticoagulant system (not to be confused with the S protein, vitronectin) circulates bound to C4b BP (189). C4-BP genetic variant is a risk factor for venous thromboembolism (190). Another component of the protein C anticoagulant system, thrombomodulin (TM), was shown to be an important inhibitor of the C system (191), of special interest in neurology for several reasons: (**i)** the distribution of TM in brain endothelium is very uneven (192); (**ii)** coagulation products are found in lesions of several neurological diseases such as MS. Fibrinogen, a signal transducer in the CNS, interacts with CR3 and CR4 (CD11b/CD18, CD11c/CD18) and with platelets in brain (193). Last, (**iii)** recombinant soluble TM provided neuroprotection in spinal cord injury (194), as did C1-INH (195).

Platelets, which partner with coagulation in blood clotting, are themselves a rich source of C factors, receptors (C1qR, CR2, 3, 4), regulators (H, C1-INH, CD59, DAF), and factor D (196), and can deploy the C5b-9 attack complex (MAC) (197). For more recent perspective on how platelets and their microparticles (PMP) can "focus complement to sites of vascular injury", see Peerschke *et al* (198). Platelets can bind the S protein (VTN) of the C system at several of its receptors, especially $Alpha_VBeta_3$. The neurotoxic effects of thrombin following cerebral hemorrhage were ameliorated by inhibiting C (27). For the many roles of thrombin in the CNS, see Festoff *et al* (199).

Since osteopontin (OPN, also Eta-1) is of much current interest in MS (200), it is worth noting that

thrombin can cleave OPN to yield OPN-Arg, which has greatly increased chemotactic potency for neutrophils and T cell subsets. At the same time it exposes a new integrin binding sequence (SVVYGLR) which increases its affinity for the more restricted ß$_1$ subset, $\alpha_4\beta_1$ and $\alpha_9\beta_1$. Finally, thrombin can further cleave this transiently active molecule into inactive OPN-Lys. OPN may also be cleaved by plasmin, cathepsin D, and even some matrix metalloproteases (201).

5.5. CNS influence, and roles in lipid traffic

It is reported that centrally administered C3a suppresses food intake, while C5a stimulates (202). In that report, the authors suggest that this is prostaglandin mediated. The C fragment, $C3_{desArg}$, also called '*acylation stimulating protein'* (ASP), interacts with C5L2 to govern fat metabolism via adipokines (203). Several C factors are lipid-associated, notably CLU (ApoJ).

According to Baciu (204), a role for the CNS in regulating the immune system was proposed in 1945, and by 2005 the vagus nerve was established as an important conduit for this control (205). CNS regulation of innate immunity / inflammation has been well reviewed (206, 207) but the focus there is largely on cytokines, not the C system *per se*. It is now known that many leukocytes can themselves produce and secrete neurotransmitters which regulate and coordinate their functions in an autocrine / paracrine manner (C-mediated acute lung injury for example) (208). On the other hand, it has been shown that C1q family members present in the brain can function as "trans-neuronal cytokines" regulating synpase development and plasticity (209), though it is not clear how or if they participate in the C system *per se*.

The febrile response to endotoxin (lipopolysaccharide, LPS) was impaired by reducing C components (210) or by cutting the vagus nerve (211), implying that there is cross-talk between C and CNS. The febrile response to LPS had been attributed to cytokines, but Sehic *et al.* demonstrated that the cytokines emerge only *after* the febrile response, and hence, that C activation *triggers* the cytokine release (210). The same is likely true for many other phenomena attributed to cytokines or "cytokine storms".

5.6. Links to other arms of innate immunity

As mentioned in the introduction, the C system has been overshadowed by the more recently discovered Toll-like receptors (TLR's) (212), NOD-like receptors, inflammasomes, and other new elements of innate immunity (5, 6). We could not find articles devoted to connections among these arms but many lines of evidence suggest inter-connections. For example, dextran sulfate, a potent inhibitor of the C system, inhibited the TLR-mediated activation of human NK cells (213). The TLR's are involved in the vitamin D anti-microbial response (214), but so is the C system (215). A component of *Neisseria meningitidis* is a ligand for TLR2 (216) but this bacterium is also recognized by C, and likewise for numerous viruses and other pathogens beyond the scope of this article. Certain particles such as silica and alum which activate inflammasomes (5) are also classic activators of the contact pathway of coagulation which, as noted above, is intimately linked to the C system. The traditional distinction, that C acts in the plasma phase while TLR's are intracellular, is no longer valid since it is known that many C components are synthesized and active *within* many cell types, including neurons and glia of the CNS (168). There is no clear distinction in the kinds or classes of PAMP's and DAMP's that can activate the C system *vs.* TLR's *vs.* inflammasomes. Consequently, it is safe to assume that all components of immunity function cooperatively as an integrated whole; and that if hierarchy exists among them, the C system likely predominates; Zhang *et al.* provide evidence that TLR-mediated inflammation and adaptive immunity are *controlled by* the C system, chiefly *via* C3aR and C5aR (217).

6. COMPLEMENT MEDIATED DISEASES

The following paragraphs briefly review diseases known or suspected to involve C. Since the emphasis here is on neurological conditions, several major groups (cancers, heart disease, sepsis, etc.) are not included. On the other hand, some are included which are of limited interest in neurology, either for historical reasons or because they illustrate general or unusual mechanisms. There are various ways to group or classify these disorders, such as genetic, acquired, autoimmune, and secondary to other states; or by the C pathway involved; etc., but no such classification is attempted here. The section on therapeutic approaches, which follows this section, provides added dimension on some of the examples. For general review of manifestations of C deficiencies, see (218).

6.1. CNS infections & relation to autoimmune disease

Deficiency of late-acting components (C5 - C9) confers up to 10,000-fold increased risk of bacterial meningitis (219), while defective properdin (CFP) conferred a 250-fold higher risk (220). Most cases are caused by *Streptococcus pneumoniae, Haemophilus influenza*, or *Neisseria meningititis,* which gain entry to CNS *via* the laminin receptor at the BBB (221). Interestingly, meningitis related to C deficiency, although far more common than in the general population, is milder and has lower mortality. Welsch and Ram offer an hypothesis for why this is so, suggesting that the reduced level of terminal C components also reduces the C-induced release of lipid A from the bacteria, which in turn reduces the inflammatory response (219). They also mention that persons with these C deficiencies are more prone to less virulent strains (reasons are not given), offering this as another hypothesis for the lower mortality in these individuals.

Of special interest here is the close association between deficiencies of C and autoimmune diseases. Table 2, adapted from Tedesco (220), shows the frequency of some infections in relation to the factors deficient. Deficit of C5 - C9 are the "late-acting C component deficiencies" (LCCD). The reader may note that deficits of the early acting components (C1 - C4) correlate most strongly with autoimmunity.

Table 1. Listing of principal C factors

Core Constituents		
Classical	C1q, C1r, C1s	
	C1 complex:	C1q(C1r)2(C1s)2
	"Early"	C1, C2, C3, C4
	"Late"	C5,C6,C7,C8,C9
Alternative	B, D, H, I, P	
Lectin	MBL, MASP's & ficolins	
Extrinsic	Thrombin and others (see text)	
Membrane Regulators:		
	DAF	CD35
	MCP	CD46
	MIRL	CD59 (HRF20)
Receptors	CD	a.k.a.
CR1		
CR2	CD21	EBV receptor
CR3	CD11b/CD18	CD11b= Mo1
CR4	CD11c/CD18	CD11c= leukocyte surface antigen p150,95
C3aR		
C5aR	CD88	
C5L2		
C1qR	CD93	(gC1qR)
SIGNR1	CD209	
Regulators on plasma membrane	a.k.a.	
DAF	CD35	
MCP	CD46	
MIRL	CD59	HRF or HRF20
Regulators in fluid phase (plasma)	a.k.a.	
	C1 inhibitor (C1-INH)	
	Properdin (CFP)	
	Factor H (CFH)	
	C4b binding protein	
	S protein	Vitronectin (VTN)
	Clusterin (CLU)	Protein S40, 40
	Carboxypeptidase N	CPN (& others, see text)
Others	LPS binding protein	CD14
	Alpha-2-macroglobulin	(A2M)
	A2M receptor	CD91
	Phospholipase A (PLA2)	

For full names of the acronymns, see Glossary, Table 2. For details such as plasma concentrations, molecular weights, genes and chromosomes, subunit and chain compositions, see Halkier (7).

Table 2. Glossary of acronymns

C-related		**Diseases**	
CFHR1	C factor H related protein 1	AIHA	Autoimmune hemolytic anemia
CPB	Carboxypeptidase B (a.k.a. TAFI)	AMG	Age-related macular degeneration
CPN	Carboxypeptidase N	AML	Amyotropic lateral sclerosis
CRP	C reactive protein	APL	Anti-phospholipid antibody (aPL)
DAF	Decay accelerating factor	APS	Anti-phospholipid syndrome
DAMP	Danger-associated molecular pattern	HUS	Hemolytic uremic syndrome
FHL1	Factor H-like protein 1	I/R	Ischemia reperfusion injury
GPCR	G protein coupled receptors	ITP	Immune thrombocytopenic purpura
GPI	Glycosyl phosphatidyl inositol	MS	Multiple sclerosis
HRF20	Homologous restriction factor, a.k.a MIRL	PNH	Paroxysmal nocturnal hemoglobinuria
MASP	Mannan-binding lectin serine protease	SLE	Systemic lupus erythematosus
MBL	Mannan-binding lectin (=MBP)	TTP	Thrombotic thrombocytopenic purpura
MBP	Mannose-binding protein		
MCP	Membrane cofactor protein		
MIRL	Membrane inhib'r of reactive lysis (=HRF)		
P	Properdin		
PAMP	Pathogen-associated molecular pattern		
SCR	Short concensus repeat		
VTN	Vitronectin (S protein)		

6.2. Age-related macular degeneration

This leading cause of blindness is recently understood as a C-mediated disease. According to a perspective in *Science* (222), much credit goes to G. Hagerman and colleagues who over many years of study detected C components, including C5b-9, in eye deposits termed "*drusen*", from patients with age-related macular degeneration (AMD). In 2005, three groups independently found mutations in a gene for factor H in AMD patients, and in the following year the original group reported defects also in factor B and CR2, pushing the gene-based prediction rate (penetrance) to 74% of afflicted patients (223). (For an overview of the factor H genes in disease, see 34). Patel *et al.* discuss a single nucleotide

Table 3. Consequences of factor deficiencies

(A)	C1, C4, C2	C3, H, I	C5-C8
Neisseria	65%	28%	65%
S. Pneumonia	17%	28%	1%
H. Influenza	3%	4%	05
S. Aureus	2%	0%	0%
(B)			
Deficit	Infection	Autoimmune	Both
C1	9%	39%	45%
C4	2%	16%	40%
C2	16%	18%	20%
C3	71%	2%	17%
C5	80%	7%	2%
C6	76%	2%	9%
C7	51%	6%	14%
C8	55%	2%	8%
C9	16%	1%	2%
P	73%	2%	2%
I	96%	1%	2%

Adapted with permission (220). (A) Percentage of individuals deficient in the indicated factors (early, late) who suffer high frequency of the infections listed. High frequency of infections associated with deficits of late factors imply importance of MAC (C5b-9), while infections related to defects in others (such as properdin) suggest that alternative or other pathways are more important for those infections. (B) Frequencies of autoimmune diseases associated with defects in various C factors

polymorphism (SNP) in the C3 gene conferring an odds ratio of 2.6 for risk of AMD (if two copies) (224), and cites additional strong associations subsequently found for the genes of factors H and B, and for C2 in humans. As might be expected, this multiplicity of risk factors has resulted in some controversy, as discussed (225), but there is an emerging concensus that C defects are responsible for AMD. There is also evidence that prior infection with *Chlamydia pneumoniae* predisposes to AMD; not all studies agree on this (224). Exactly why the retina is targeted is not clear, or why it generally happens only after age 60. Several C-related disorders show high specificity for particular organs or tissues, and many transgenic rodent models of C-mediated diseases show characteristic age of onset of symptoms. It should be added that there are two main forms of AMD, "wet" and "dry"; the wet form is effectively treated by anti-VEGF to inhibit angiogenesis.

6.3. Myasthenia gravis

In 1993 myasthenia gravis (MG) was identified as an autoimmune disease against the bungarotoxin-binding receptor for acetylcholine (AChR) (226). Approximately 80% of patients have this AutoAb. However, it was subsequently found that C3 levels correlate with severity of MG (227), and that an SNP) of the DAF gene was closely associated with that subtype of MG involving extraocular muscle paresis (228). Further supporting C-mediation of MG is that an inhibitor of C ameliorated symptoms in animal model (229).

Sheng *et al.* made the interesting observation that AChR become over-expressed in the mouse model of MG, possibly compensating for the blockade by AutoAb, but these hastily-assembled receptors are defective in failing to bind bugarotoxin (230). The authors suggest that this helps drive the autoimmune response. Several C-mediated diseases exhibit age-dependent onset, including the model of MG used by Graus *et al.* (231).

6.4. Alzheimer's disease

The etiology and pathophysiology of Alzheimer's disease is complex and controversial, including with regard to the role of C in it. Accordingly, this article is limited to a few paragraphs suggesting a major role for the C system, supplementing earlier comments. Deposits of C components have been detected in AlzD brains since the 1980s in close proximity to the amyloid-beta (Aβ) plaques and neurofibrillary tangles. They occur along with other so called *Aβ-associated proteins*, many of which are acute phase reactants (232). Several of the Aβ-associated proteins, such as SAP, A2M and CLU, earlier discussed in part 3 (6-7), are often listed apart from the C factors but are important modulators of the C system. In 1989, McGeer and colleagues documented the presence of terminal MAC in these deposits, but no evidence for participation of the alternative pathway was found (233, 234). A further advance was the discovery by Rodgers *et al.* (235), subsequently confirmed by others, that Aβ could itself activate the C cascade directly, independent of antibody, indicating activation by pattern recognition of altered self (236). More recently, it was shown by Rodgers *et al* that Aβ peptides occur also in the peripheral circulation but are normally eliminated *via* CR1 of erythrocytes in a C3b-dependent manner (158).

Work on the role of C in AlzD was for a time overshadowed by the clear association of *APOE* gene polymorphism with AlzD. However, a subsequent large study found strong new associations, notably including variants of the C factors, CR1 and clusterin (CLU) (237), now confirmed and extended (238). Similar results were found in another large study published in the same journal issue (239), the latter emphasizing also the *PICALM* gene, which participates in lipid traffic. As mentioned earlier, the C system has links with lipid mediators, such as via CLU (ApoJ) and phospholipase A2 (PLA2), implicated in AlzD (112), as is gelsolin (114), a modulator of the inflammatory lipid, PAF (115). There is more limited evidence supporting involvement also of polymorphism of A2M (240). A2M, a zinc-binding protein which aids in control of matrix metalloproteases, is a mediator of TNF-a, and has also been discussed in relation to AlzD (121).

We have earlier mentioned the finding by three independent groups that deficiency of early C factors (such as C3) in mouse models of AlzD not only failed to protect, but actually exacerbated disease progression (148-150), consistent with protection mediated by C, at least in early stages. However, the transgenic mouse models of AlzD are considered unreliable (131), therefore the significance of these findings for human AlzD is uncertain. Nevertheless, Nuutinen *et al.* have outlined a good case for a central role of C in AlzD (95). Their article concludes by questioning if CLU, and C generally, are a "guardian or enemy" in AlzD. The high levels of CLU observed could be viewed

as a protective response since CLU is a classical C inhibitor.

There is a great deal evidence showing systemic inflammation in AlzD, such as the recent study showing that inflammatory markers, especially TNF-α, correlated with cognitive decline (241), and discussed in other reports (159). According to Emmerling *et al.* writing in 2000, "more than 20 studies" have documented the efficacy of NSAID in AlzD (242). Unfortunately, several later and larger studies failed to confirm their benefit. To our knowledge, NSAIDs have limited impact on C activation (except possibly in platelets), so those failures might be interpreted as evidence for the clinical significance of C in AlzD. Salminen *et al.*, in reviewing the role of innate immunity in AlzD, listed a large number of components besides the C system that may be implicated in AlzD, e.g., TLRs, NOD-like receptors, N-formyl peptide receptors, cytokines, etc. (236). It is tempting to suggest that many or most of these effects might share a common cause, and might be networked with the C system.

6.5. Prion diseases

Like AlzD, the prion diseases are considered to be protein-misfolding diseases, and oligomers of prions, like oligomers of Aβ, appear to be cytotoxic. It is now emerging that the C system is involved in prion disease pathogenesis, recently by the demonstration that C1q binds oligomerice forms of cytotoxic prion (243).

6.6. Amyotropic lateral sclerosis

Amyotropic lateral sclerosis (ALS) is considered a motor neuron disease and several candidate causal factors are identified including defect in the superoxide dismusase (SOD) gene, immune involvement, and the C system (244). To further evaluate the role of C, Chiu *et al.* confirmed dense deposition of C in the affected areas of a mouse ALS model, but knockout of C4 failed to alter the age of onset or survival (245). However, this work may not have been completely interpretable. Others have shown that C activation can occur independent of C4, such as *via* the extrinsic pathway by which coagulation factors (thrombin, plasmin, FXa, FXIa) can activate C3 and C5 directly (26, 71). This possibility is supported by the fact that C4 deficiency does not predispose to infections as markedly as do deficits of C3 or C5 (220), suggesting that C4 is not essential to the efficacy of C3, C5 in fighting infection. The possibility therefore remains that ALS is significantly a C-driven disease.

6.7. Multiple sclerosis

Complement components were identified in multiple sclerosis (MS) lesions as early as the 1960's-70's, and the role of C in MS has been debated ever since. By the newer method of gene microarray analysis, several C components were identified in lesions at autopsy (246). It is of great interest that AutoAb's against C regulatory proteins, nootably against CD46, were identified in CSF of MS patients, and correlated with exacerbations and EDSS (247). This is of special interest because herpesviruses like EBV and HHV6, which are incresingly implicated in MS etiology, express this protein in their genomes possibly as a means of protection against C-mediated attack or entry (248). The presence of these antibodies could impair the normal function of CD46, rendering self-cells more sensitive to C-mediated injury. Although it is not possible in the space available here to review the 'infectious etiology' hypothesis of MS, a history of mononucleosis was shown to be more than additive with the MS risk haplotype, HLA-DRB*15 (249), the mechanistic significance of that haplotype is not yet clear (250). However, even in absence of genetic C dysfunction, it is possible for C activation to contribute significant inflammatory burden (or possibly to exert protective effects (141)), particularly if self-defense against C is impaired.

The role of C in MS was recently briefly reviewed (251), and pointed out that comparatively little research on C in MS has been accomplished. It was reported that the demyelinating influence of AutoAb towards MS target antigens was directly related to their ability to fix C (252). Space limitations prevent us from discussing some of the interesting but complicated relationships that could support a role of C in MS, such as amelioration of symptoms in a rodent model of MS by vasoactive intestinal peptide (VIP) (253), known to act on CR1 (CD35) and CR3 (CD11b) as well as on the VIP receptor (VPAC1) and the N-formyl peptide receptor-like-1 (FPRL1) (254), all of which seem to be related through certain C-relevant ligands. Relatedly, interferon-Alpha (IFN-Alpha) has been identified as a fourth class of ligand for CR2 (40), which is of great interest in regulating autoimmunity (255). In a study of the classes and subclasses of AutoAb against two target antigens described to be MS-specific (MOG, MBP), it was found that IgM predominated; however, only IgG3 correlated with exacerbations (256), which is noteworthy since IgG3 is most potent at activating C. On the other hand, we observed that anti-phospholipid antibodies in RRMS correlated with exacerbations, and were exclusively IgM (257). The specific protein target of those antibodies is not yet known.

6.8. Hereditary angioedema (HAE)

Although not strictly neurological, hereditary angioedema (HAE) well illustrates the complexity of C-mediated diseases, and in 1971, was historically the first non-infectious hereditary disease shown to be caused by a C deficiency, namely, lack of C1 inhibitor (C1-INH) (258, 259). Nearly 200 mutations or polymorphisms are now known, classified as types I and, II. (260). The disease has a highly variable course, and triggers of flareups are unclear, but seem to include psychological stress. Acquired forms can be induced by drugs such as ACE inhibitors or by AutoAb (261). It has been hypothesized that all of these effects involve altered B cell proliferation (262). A rare homozygous deficiency has been reported which is believed to be non-responsive to androgens for that reason (263).

The cause of the disease appears to be excessive bradykinin production, not C activation *per se* (183). Accordingly, HAE can also be caused by defects in coagulation factor XII gene responsible for bradykinin, termed type III HAE (264). Symptoms are often related to estrogen (oral contraceptives, onset at puberty) but

according to Cugno *et al.*, it is not clear why HAE responds to androgens such as danazol (183). Although C1-INH is the only known inhibitor of C1r and C1s, it also functions to control MASP-1, -2, and coagulation factors XI, XII, thrombin, plasmin, tissue plasminogen activator (tPA), and crucially, kallikrein, which yields bradykinin (28). It is beyond this review to convey the complicated interplay among systems resulting in the disease (183), but the reason for discussing it at all is to point out that complexity. Moreover, C1-INH, which is an effective therapy, has important functions which are independent of its action as an enzyme inhibitor; Davis *et al* list five roles: binding to components of the extracellular matrix; inhibiting the alternative pathway by binding C3b; binding to E- and P-selectins of endothelial cells; etc. (265). Thorgersen *et al* find other broad anti-inflammatory effects of C1-INH (266).

6.9. Ischemia reperfusion injury

Ischemia reperfusion injury (I/R) refers to the injury sustained by tissues when blood circulation is restored following ischemia and is of great importance in many areas of medicine, especially ischemic stroke. I/R injury has been recognized to be largely C-mediated since at least the 1980's (267), and was thoroughly confirmed through the 1990s (268, 269). One report questioned if the role of C was primary or secondary, based on experiments using cobra venom to deplete C (270). The concensus holds it to be primary, involving the role of C in clearing apoptotic and necrotic cells. Recent advances in understanding I/R injury are presented in part 7.

6.10. Paroxysmal nocturnal hemoglobinuria

Many important membrane proteins are anchored to the membrane by a glycosyl phosphatidyl inositide (GPI) linkage, including the C-protective DAF and MIRL (271). Paroxysmal nocturnal hemoglobinuria **(**PNH) was long of interest in hematology but is now known to have neurological consequences (272, 273), notably, persistent absence seizures in a familial pattern, although the affected children had no hematologic symptoms (272). The mystery of PNH was resolved with discovery of a PNH-associated gene, PIG-A, preventing formation of the GPI linkage and resulting in deficiency of cell-bound GPI-linked proteins (274). Most important for PNH is deficiency of MIRL (CD59), leading to sporadic episdoes of self-cell destruction by C, the most obvious symptom being hemolysis, often at night. To our knowledge, it is not yet clear how this leads to the neurological complications, since absence of GPI-linked proteins unrelated to C could be responsible. It may be relevant to note that brain oligodendrocytes are reported to naturally lack these proteins (146).

6.11. Traumatic brain and spinal cord injuries

Activation of C is believed to contribute substantially to the sequelae of traumatic brain injury, including the systemic inflammatory responses syndrome (SIRS) (160). These events, both early and late, are very complex but the totality of data suggests that C activation could be the central and unifying player. The neuroactive steroid, progesterone, is known to alleviate symptoms by reduction of proinflammatory cytokines, and has been shown to upregulation the potent C inhibitor, DAF (CD55) which has been proposed to explain its observed benefits (275). Complement activation markers such as C5b9 in CSF correlated closely over time with the injury marker S100B in 20 patients post-TBI (276). Administration of C1-INH was protective against traumatic spinal cord injury (SCI) (195). Inhibition of the alternative pathway by a monoclonal antibody against factor B gave dramatic protection in a mouse model of TBI (277). On the other hand, it was reported that deficiency of mannan bindling lectin (MBL) by gene knock-out worsened outcome of TBI in mice, suggesting a protective role for MBL (278). The review of Lu *et al.* cited above devotes a section to coagulopathy in TBI, stating that thrombin is a major player in brain edema, and that PAF, whose expression has links also to coagulation, is also implicated in TBI (160). That is to say, the coagulopathy seen post-TBI may be viewed as linked to C activation. For example, links between thrombomodulin (TM) and the C system were mentioned earlier (part 4 (4)) and TM was seen to be neuroprotective in SCI (194). The brain edema seen following intracranial hemorrhage in rats was also attenuated by systemic depletion of C (by cobra venom factor) (279). Work by Nguyen *et al*. demonstrates clearly a sharp upregulation of C factors, including MAC, specifically in PMN infiltrating the SCI site with time, and associated inflammatory markers (280), and other work by those authors demonstrates protection against SCI sequelae by C1q deficiency.

6.12. Atypical hemolytic uremic syndrome

Atypical hemolytic uremic syndrome (aHUS) is a thrombotic microangiopathy (TMA) which frequently manifests with neurological symptoms (281, 282) and is a leading cause of renal failure. It was shown in 1983 that the majority of HUS cases (≈75%) are caused by certain strains of *E. coli*, chiefly 0157:H7, carried by cattle, which secretes a shiga-like verotoxin (283) as well as several secondary toxins (284). The remaining cases are termed "atypical" (aHUS) and have been shown to associate with hereditary C deficiencies. It must be added, however, that it was recently shown that the *E. coli* toxin itself strongly activates C (285), hence both HUS and aHUS can be C-mediated, but in different ways. The familial pattern of aHUS was known since 1980 but only in 1999 was a mutation of factor H implicated (286). Multiple reports in 2000 and later amply confirmed that finding, and at least a dozen papers on aHUIS appeared in 2009 alone. In brief, gene variants of C factors now implicated in aHUS include those for factors C3, H, I, B, MCP (CD46), and factor H-related proteins (CFHR1, CFHR3, CFHR4). Some 14 mutations of factor I alone are related to aHUS (287). Most recently, a defect in the gene for clusterin (CLU) was associated with aHUS, bringing to 75% the number of aHUS cases accounted for by C-related genetic anomalies (288). It is instructive that such a profusion of defects all predispose to aHUS. Of particular interest in this review is the parallel frequency of AutoAb to C factors in aHUS, such as anti-factor H (289). Skerka *et al* has identified a subtype, DEAP-HUS, the acronym being "**de**ficiency of

CFHR1 and CFHR3 and **a**utoantibody **p**ositive" (34, 290); see also (42, 291).

6.13. Thrombotic thrombocytopenic purpura

Fluctuating neurological disturbances are hallmarks of this thrombotic microangiopathy (TMA), which is often discussed along with HUS. The cause of thrombotic thrombocytopenic purpura (TTP) was identified by Moake and colleages as a defect in the enzyme ADAMTS13 which cleaves von Willebrand factor (vWF) (292, 293). However many have questioned if this is a complete explanation, or if it applies to all cases. Evidence that C is a major culprit of TTP was suggested in 1989 (294), and further supported more recently (295, 296). Rock *et al.* had reported AutoAb to CD36 in TTP (297), as investigated further by our lab (298). AutoAb to ADAMTS13 has been found in TTP (299), as have antibodies to unspecified antigens on the microvascular endothelium (300).

6.14. Systemic lupus erythematosus

Cource and manifestations of systemic lupus erythematosus (SLE**)** are very diverse, notably including neurological, renal, cutaneous, infectious, and thrombotic. These effects are attributed to a broad array of AutoAb including anti-nuclear and antiphospholipid (aPL), together with their immune complexes (IC) (301, 302). The IC which most strongly activate C are also the most pathogenic (303). The detailed role of C in SLE is highly convoluted and well beyond the scope of this review; (see 156). Of special interest in that review is discussion of the paradox of protective *vs.* harmful effects of C, as mentioned earlier. Carroll also discusses this paradox (165). More recently, genetic polymorphisms of CR2 were shown to associate with SLE (304), supporting prior reports back to the 1970's, such as familial deficiency of C2 with SLE-like syndromes (305, 306).

Recent reviews of SLE genetics cite evidence for association with deficits of C1q, C2 and C4 (307, 308). The association with deficit of C1q is most persuasive since nearly all with this defect develop SLE-like symptoms, as do mice deficient in C1q. A novel explanation for this, involving interferon-alpha, has been proposed (309). A study of 17 pairs of monozygotic twins, one with SLE the other not, revealed epigenetic differences in 49 genes, including several immune-related (e.g. interferon) but not C factors *per se* (310). Neuro-psychiatric lupus appears to result from cross-reaction of certain anti-nuclear antibodies with brain NMDA receptors (311). Exposure to Epstein-Barr virus has been proposed as a triggering event for SLE (312); it would be interesting to know if EBV+ SLE have AutoAb to CD46. Impaired opsonization of bacteria in a cohort of SLE patients was reported (313), consistent with high frequency of infections and C deficits. Platelet-bound C4d was found to be a highly specific biomarker for SLE (314).

6.15. Antiphospholipid syndrome and antibodies

The "lupus anticoagulant" was originally thought to be specific for SLE patients, most of whom are antiphospholipid antibodies (aPL^+). In view of this and other facts, it has been proposed that antiphospholipid syndrome (APS) and SLE lie on the same etiologic spectrum (315). It has been pointed out that APS and MS also often have very similar clinical presentations (316, 317). We have briefly reviewed the role of C in APS (318). Some but not all reviews of APS assign high importance to the role of C (319-321). Munakata *et al.* found that C-fixing aPL were specifically associated with thrombosis (322). Important work in this area concerns recurrent fetal loss (RFL), which is among the defining criteria of APS. Following suggstive early work and later work by Shoenfeld and colleagues (323), Salmon and colleagues demonstrated an absolute requirement of C for RFL (324, 325). A related advance was establishing the role of C in preeclampsia (326), also by assay of C factor Bb in plasma. APS often has neurological involvement but the role of C in this specific regard has not been extensively investigated.

6.16. Immune thrombocytopenia

Although not considered a neurological disorder, a subgroup of immune thrombocytopenia (ITP) with progressive vascular dementia has been identified (327). Apart from that, ITP is the archetype of autoimmune diseases, first identified as such in the early 1950's (328). Evidence for a role of C in platelet destruction in ITP was widely debated in the 1980s (329-331) but interest in that has since waned. In preliminary studies, we identified two subgroups of ITP, one with evidence of deposition of C, the other not (332)

6.17. Note on detection of C deposition

It has been shown that deposition of C can induce vesiculation, carrying off the C from the parent cell (143, 144, 333). Accordingly, evidence of C-mediated attack may not be detectable on the cell but will be found on the microparticles (MP) released. Biro *et al* detected elevation of several C fragments on MP from the synovial fluid and plasma of patients with rheumatoid arthritis (RA) (334). These observations suggest that so-called soluble C5b-9 often detected in plasma and CSF may in reality be MP-bound. Relatedly, it is possible that in the work of Lynch et al., who found that elevated Bb levels in plasma correlated with pre-term birth (325) and preeclampsia (326), the Bb may have been bound to MP.

6.18. Progress in gene association studies

Improved methods have revealed gene associations previously missed. Here we mention some other opportunities. One is post-translational editing of RNA transcripts by adenosine deaminases RNA-binding (ADAR's), termed "RNA re-coding". According to Cies and Maas, re-coding effects have been mistaken for SNP's by certain methods, but still show great promise (335). Remarkably, they find sharply different outcomes in different brain regions. Also of potential importance are copy number variations, not commonly tabulated, but recently shown to be major determinants of the phenotype of C factors (336). Another avenue only beginning to be explored are epigenetic marks, which are expected to be most relevant in diseases suspected to have environmental components such as MS.

7. ANTI-COMPLEMENT THERAPIES, OLD AND NEW

A central role of C in many pathologies has long been known or suspected but therapeutic options have been limited. That situation is poised to change (337). This section emphasizes C-targeting therapies that are less well covered in other reviews (337-339), and also serves to introduce the next and final section.

7.1. Recently approved, in trials, or in pipe-line

Already in 1998, about ten C-targeting drugs were listed in commercial development (340, 341). Since this topic is covered in depth by others, only highlights are considered here. Among the first to reach phase 3 clinical trials is a monoclonal antibody, ***eculizumab*** (Soliris™, Alexion), which blocks activation of C5; it is FDA-approved for treatment of PNH (342, 343) but is expected to have wide off-label applications. General inhibition of C will increase risk of infection, but blocking C5 should minimally affect activation of C3.

Compstatin is a cyclic tri-decapeptide discovered by J. Lambris using phage display libraries, which binds C3 to inhibit its activation (344, 345). It is in clinical trials for some types of age-related macular degeneration (AMD) and if approved, will also probably find other off-label uses. It has been useful in research to elucidate problems such as the role of the C5a receptor (C5aR) in bacterial killing (346), the role of C in cancers (347), and in the adverse effects of extra-corporeal blood circulation devices (338). Of note, since CR3, together with CR2 (CD21), is important for B cell activation and anergy (47, 348, 349). Inhibitors such as compstatin may have far-reaching effects not limited to reducing inflammation. Lambris has since found compstatin related peptides which have increased potency. Others are also working with other peptidic C inhibitors, such as one targeting C5a (350). (For more complete reviews see references 338, 339).

FUT-175 is a serine protease inhibitor which has been in use as an anti-thrombotic but is also known to have potent inhibitory actions against several C factors. Therefore, it was tested in the EAE mouse model of MS with promising results (351). That paper also briefly reviews new insights on C production and activation *within and between* T cells and antigen presenting cells (APC's), *in relation to* MS. Also of interest is use of ***cobra venom factor*** (CVF) for anti-C therapy (352). CVF has long been used to deplete C in laboratory animals, by causing massive C activation. It is remarkable that a single treatment has few ill-effects, hence is continuing consideration for human use.

7.2. Previously established C-targeting therapies

As early as 1980, a partially purified ***C1 inhibitor*** (C1-INH) from pooled plasma came into use for treating hereditary angioedema (HAE) in emergencies such as laryngeal edema, and is still used. More recently, C1-INH gave significant protection in acute spinal cord injury, $p<0.01$ (195). A recombinant C1-INH from transgenic animals is now in development (183). Animal studies also support benefit of C1-INH in sepsis (353). C1-INH therapy has been recently reviewed (354). Like many C components, C1-INH has several actions apart from its best-known role as protease inhibitor (265).

In the 1990's, many reports demonstrated great reduction of I/R injury by a ***soluble form of CR1*** (sCR1), in several organs of animal models of I/R, e.g., (355, 356). In that form, it presumably acts as a "*decoy receptor*", capturing otherwise injurious products, especially immune complexes. The observed benefits further support the central role of C in I/R injury. Of note, at least one of those reports presented reasonable evidence that neutrophil-mediated I/R injury, (which had been an alternative hypothesis), was secondary to C activation (357), confirmed in the paper cited above (280). A glycosylated (sialyl Lewis x) form of sCR1 also proved highly promising (358) for neuronal protection in stroke.

7.3. Insights from pathogen evasion strategies

By definition, a pathogen has means of evading or neutralizing immune defenses. A highlight of recent research has been elucidation of the strategies for evading the C system, all pointing to a "next generation" of C inhibitors, as well as new vaccines and other approaches to infection control. For example, the ***vaccinia complement control protein*** (VCP) has been termed a "potential wonder drug" (359); see also (360, 361). The ***smallpox inhibitor of C enzymes*** (SPICE) is another case in point (362). The authors compared inhibitors from several pox viruses and found SPICE to be most potent and, aside from potential therapies based on SPICE, suggest that mAb against it could be therapeutic against the disease. In other work by the same group, the ***rhesus rhadinovirus C control protein*** (RCP) was shown to promote degradation of C3b and C4b by factor I, and to accelerate decay of the C3 convertase (363). The authors state that this is the first known such inhibitor that does not require a heparin binding site (364).

Not only viruses but pathogens of every kind have developed means of evading C-mediated killing. *Candida albicans* produces an iC3b receptor reminiscent of integrins CD11b,c which is required for its infectivity in mice (365). The *Candida* strategies are discussed by Zipfel (366), who cites more comprehensive treatments of the many "*cloaks and disguises*" used by pathogens to evade C.

The tick-borne pathogen *Borrelia hermsii* acquires factor H as well as plasminogen (367), as does *Pseudomonas aeruginosa* (368). The latter authors offer several likely reasons for the capture of plasminogen, such as its' ability to degrade vitronectin (S protein). The former authors point out that *Staphylococcus aureus* activates plasminogen to plasmin, which in turn degrades IgG and C3b at the bacterium's surface, citing Rooijakkers *et al.* (369). This supports the paradigm that ***plasmin***, an enzyme of fibrinolysis, may have *C-suppressing* actions. Rossmann *et al.* list ~10 other bacterial pathogens which also capture factor H, among their tactics (367). Kunert *et al.* (368) mention several other pathogens known to bind plasminogen (e.g. *S. pneumoniae, B. Burgdorferi, S. Pyogenes*, and the yeast *C. albicans*) but the plasminogen

binding motif they find on *P. aeruginosa* is unique. From an evolutionary perspective this is interesting since it implies independent invention (parallel evolution) of the same strategy rather than horizontal gene transmission or common heritage.

Another approach to therapy is suggested by Welsch and Ram, who point out that susceptibility to many diseases (e.g., meningococci) are human-specific, implying that the C systems of resistant mammals, such as rats, have slightly different components - in this case factor H - which might be exploited for our own protection (219). (For a consideration of the role of CFH in human diseases, see ref. 370). These references are only a small sampler of a large and growing literature on this topic, aimed at new therapies.

Note on role of C in viral attack. It is obvious from the above that the C system is a component of the defense again many viral pathogens. Examples of this include viral influenza (46), Herpes (371), flaviviruses such as West Nile and Dengue (372), and others (361). We mention this because several reviews of innate defenses against viruses fail to mention the C system at all, focusing instead and exclusively on the TLR's and signaling pathways such as the interferon (IFN) response, e.g., (373, 374). This could lead to an inappropriate bias against C, especially for students.

7.4. Vitamin D and the C system

Recent discoveries on the role of vitamin D in immunity may be of great importance to public health. Deficiency of this vitamin has purportedly been linked to neurological disorders, notably MS (375-378). In view of the known latitude gradient in the epidemiology of MS (375), and of cancers, hypertension, and many autoimmune diseases (379), many have suggested a connection. To our knowledge, discovery of the immune benefits of vitamin D3 was by Cannelli (380), after his reading of the role of this vitamin in generating the antimicrobial peptide, cathelicidin (381). This seminal paper was followed by numerous studies, including on the role of this vitamin in autoimmune diseases such as MS, SLE, RA, and others (382, 383). A key link between vitamin D3 and the C system is the vitamin D binding protein (Gc-globulin), a cofactor in the chemotactic activity of C5a (384-387). Mice deficient in vitamin D receptor (VDR) show an increased propensity for autoimmune diseases (388). Conversely, it had been earlier shown that production of C3 in bone marrow stromal cells and osteoblasts is regulated by vitamin D (215), this finding has been extended to monocytes (389). Gene polymorphisms for Gc-globulin and for properdin were found to be in Hardy-Weinberg equilibrium (390). In a proteomic study of autoimmune uveitis, Gc-globulin was down-regulated in parallel with C1q and C4 (391). In pediatric MS, a proteomic study revealed 12 proteins significantly elevated including Gc-globulin together with several C factors, *viz.*, factor I, serum amyloid P (SAP), clusterin (CLU), kininogen-1, and others more distantly involved such as gelsolin and hemopexin (392). As we have noted earlier, plasma gelsolin is a regulator of PAF (115), and PAF, in turn, can be up-regulated *via* C activation, e.g. (181). According to Roach *et al.*, PAF is syngergistic with C5a signaling (393). In summary, these observations may warrant further study of the relation of C to vitamin D in autoimmune diseases such as MS.

7.5. Heparin and "heparinoids"

This glycosaminoglycan (GAG), heparin, has been known as an inhibitor of the C system since 1929 (394) and some of its pleiotropic benefits doubtless owe to this fact. Heparin is best known as an anticoagulant, acting chiefly by potentiating the inhibition of thrombin by antithrombin III and heparin cofactor II. It also inhibits other serine proteases to varying degrees, as well as von Willebrand factor (395) but it has many other actions as well (396, 397), notably including "immunomodulation" (398), as reviewed more recently (399). This might be expected since heparin binds to some 22% of total plasma protein, while a related polyanion, dermatan sulfate, binds 7%, and chondroitin sulfate, 0.23% (400). Heparin is normally present in plasma in modest amounts (401) but to our knowledge, has not been measured in disease states. The related GAG, heparan sulfate, is also an important constituant of the ECM, (mentioned earlier).

Related GAG's were shown *in vitro* to inhibit the neurodegenerative effects of the C-related factor, serum amyloid P (SAP), which is thought to contribute to AlzD *via* binding to Aβ (402). Many studies have documented the efficacy of heparin in reducing C-mediate damage from ischemia-reperfusion (I/R) (403). This effect likely contributes to its benefits in surgical procedures. Spring *et al.* provide evidence for benefit of the heparinoid, dextran sulfate, for I/R injury, allografts, and immune tolerance by "impeding the link between innate and adaptive immunity" (404). Heparin proved useful for treating C-mediated intravascular hemolysis (405), was more effective than IVIG for recurring APS-related pregnancy loss (406). Its value in obstetrics is attributed in large measure to its passivation of C (407). Although we did not perform a meta-analysis, our readings in the APS literature suggest that heparin was most often the most effective treatment, consistent with a central role of C in APS (321).

Mechanistically, heparin inhibits the C system at several points, notably by potentiating C inhibitors such as factor H (16) and C1-INH (408, 409) the details are complex but are now being elucidated (404). Heparin also inhibits CR4 signaling (CD11c/CD18) (410). Many of the C factors have heparin binding domains, and this has been exploited for assessing mutations in C components that result in reduced heparin binding, e.g. in aHUS (411). Black *et al.* used acetylated heparin, (which lacks anticoagulant activity), in a canine model of I/R injury, and observed protection as good as native heparin (412). It was also protective in cerebral hemorrhage (413) and reduced neurological deficits induced by thrombin (27). (On the other hand, C1 selectively bound the fraction of heparin with highest anticoagulant activity (414).) The question has been raised if such protection can be entirely attributable to C inhibition since many other actions are known (397). Thourani *et al.* used a different chemically modified heparin, which in addition to

lacking anticoagulant activity had greatly reduced C inhibition (415), yet still observed good protection in canine I/R. However, some technical caveats could be raised about this study, especially the assay method used to show absence of C inhibition. The concentration of native heparin needed for 90% inhibition of lysis (1 mg/mL, ≈ 500 units/mL) in this study was supra-physiological and 100-fold more than needed by other workers (408). Groth *et al.* has carefully compared the C-inhibiting power of several GAG's, revealing important differences (416). An orally-available pentosan polyphosphate showed good promise as a practical C inhibitor (417).

7.6. Intravenous immunoglobulins

The use of intravenous immunoglobulins (IVIG) for treatment of a wide variety of immune-mediated and inflammatory disorders is growing, including for treatment of MS (418, 419), neurological critical care (420), SLE (421), APS (406), sepsis, and other conditions (422). Many explanations are proposed, the most prominent include C modulation, however the mechanism of benefit remains unsettled (423). One recent hypothesis centers on dendritic cells (DC) (424). The hypothesis that it ameliorates C-mediated inflammation is attractive because this could cooperate with some other putative mechanisms, e.g., correction of "cytokine imbalance". On the other hand, (as reviewed in the next article), the hypothesis that IVIG acts by supplying corrective natural antibodies is increasingly persuasive.

In MS, many reports had shown benefit of IVIG but the large PRIVIG study showed no benefit of monthly treatment over 1 year (418). (Interestingly, the placebo group receiving albumin did show benefit, prompting comments (425).) This negative conclusion provoked letters objecting to the study design, chiefly on the grounds that dosing was too low. Bayry *et al.* (419), asserting that alternative novel therapies (426) are unrealistic, still advocates IVIG for MS despite that negative report. In other autoimmune disorders such as SLE and APS, results with IVIG are consistently favorable.

7.7. Intravenous IgM and the idiotype hypothesis introduced

If it is true that normal humans naturally harbor many auto-antibodies which are masked by IgM antibodies against them (anti-idiotypes), then we have the hypothesis that autoimmune diseases are often caused by insufficient IgM control. On this hypothesis, here over-simplified, Hurez *et al* in 1997 prepared IgM-enriched immunoglobulins (IVIgM) and showed that it could suppress auto-antibodies from patients with autoimmune diseases more effectively than IVIG (427). Moreover, rats infused with IVIgM were protected against experimental uveitis. Under this hypothesis, the active agent in IVIG is IgM. If true, this could explain explain why such a high dose of IVIG is required for effective therapy, e.g., in MS.

More recently, Hoffmann *et al.*, after observing by meta-analyses of literature that IVIgM showed a trend for improved survival in sepsis patients compared to IVIG, demonstrated in hamsters that IVIgM, but not IVIG, significantly reduced leukocyte adhesion in venules and normalized capillary perfusion 24 hours post-endotoxemia induction (428). The discussion in their paper cites further references on IVIG vs. IVIgM. One such report showed that IVIgM was significantly better than IVIG in preventing renal damage in a rat model of inflammation, which was attributed to reduced C activation (429). Another study by that group showed that despite C inhibition by IVIgM, bacterial killing by C was not impaired (430). The next section further explores these important issues.

8. NATURAL ANTIBODIES, COMPLEMENT, AND AUTOIMMUNITY

8.1. Introduction

When we reviewed the antiphospholipid syndrome (APS) (318), two hypotheses for its etiology emerged as the most convincing, (i) C activation, and/or (ii) dysregulation of natural auto-antibodies (NatAb) which are normally suppressed by antibodies against them (anti-idiotypes). Here we summarize recent evidence uniting and further supporting these two hypotheses.

8.2. Background on natural auto-antibodies (auto-Ab)

Compelling evidence accumulated over decades shows that the general population carries a large repertoire of auto-antibodies (auto-Ab) which are normally masked by inhibitory IgM. For example, Adib *et al.* showed in 1990 that mouse sera reacted only weakly to selected self-antigens but after the IgG was purified, it reacted strongly, indicating the presence of an inhibitor of IgG in plasma, ultimately shown to be IgM (431). When the mouse was infected with *Trypanosoma cruzi*, the IgM was less inhibitory. The authors concluded that their findings, together with previous work by co-author Ternynck and colleagues, are consistent with an "idiotype-like network" in which self-reactive IgG is normally suppressed by IgM ant-idiotypes.

(The idiotype network theory, first proposed by Jerne in 1974 (432), is beyond the scope of this review. It was widely discussed after Jerne's paper but grew quite complicated and fell out of fashion. However, Behn's review of 2007 refers to a "renaissance" of interest (433). His review is from the perspective of a physicist, who speaks of immunology as a "playground for physicists" because of its daunting complexity. For a succint review with emphasis on the example of factor VIII inhibitors, see Gilles *et al* (434); and see Menshikov and Beduleva for the example of autoimmune hemolytic anemia (435).)

We earlier mentioned the report of Hurez *et al.* (427), (the title of which explicitly states the hypothesis as a *fact* supported by the findings. Cheng *et al.* observed that all normal sera became positive for several aPL after heating (436), and this was repeatedly confirmed by several groups by different methods (437-440). The few negative reports (441) are likely explained by technical issues. For example, as noted by Adib *et al.* (431), recovery of antibodies from adsorption columns can be impaired by

acid elution compared to the gentler method of concentrated $MgCl_2$ for example. (437). Pan *et al.* demonstrated SLE IgG AutoAb's in all normal sera, and showed they were masked by IgG anti-Id's (442). Stahl *et al.* demonstrated that AutoAb's responsible for autoimmune hemolytic anemia (AIHA) are very similar to natural antibodies in the general population. Using methods similar to those above (purification of IgG/M, re-mixing, etc.), they propose that the disease likely results from failure of control by IgM (443).

Some natural antibodies are not masked. The best example of this are those natural antibodies directed against non-self ABO blood group antigens. In such cases, masking is not needed since the antigen is absent. Natural Ab's are part of the humoral innate immune response, encoded in the germ line, and are believed to be important to distinguish self from non-self (434). Work by Gyorgy *et al.* on Natural Ab in rheumatoid arthritis (RA) shows them to be at least a biomarker of disease activity (444). Interestingly, they report that high levels of IgM against the antigens of interest correlate with *mild* disease and low IgM with *severe* disease. Our study of aPL in MS revealed exclusively IgM aPL associated with exacerbations (257).

8.3. The complement connection

Assuming that auto-immune disease can be caused by loss of anti-Id control, a role for the C system may be implied by the observed high frequency of autoimmune diseases associated with defects in the C system. However, it now appears that not only C, but also Natural Ab's are crucial players in adaptive immunity (176). That reference updates Carroll's description of the role of C in the selection and expansion of B-1 cells (171), which are $CD5^+$ and the source of Natural Ab (434). Holers and Kulik have review new findings showing relations between CR2, Natural Ab, and autoimmunity in SLE and I/R (175). Those studies include intriguing findings on interferon-Alpha (IFN-Alpha), a known ligand of CR2 (40).

The main point in these studies is that C plays a pivotal role in regulating Natural Ab in autoimmune disease, and probably also the regulatory anti-Id's. Moreover, since several auto-immune diseases are linked to HLA haplotypes, it is noteworthy that serum levels of Natural Ab are significant associated with those genotypes (445).

8.4. Remyelination mediated by C and natural antibodies

Warrington *et al*, building on prior work aimed at MS (446), produced a recombinant IgM from a patient with lymphoproliferative disorder, and demonstrated that it restored remyelination in several EAE mouse models of MS (447). More recently, they reported upcoming clinical trials using this product (448). In view of its source, this antibody is presumably a natural IgM. It did not, however, protect against neurodegeneration, (i.e., of loss of motor neurons). In this regard, it is of great interest to note that axon cell death in EAE results not from MAC deposition but from another pore-forming weapon, *perforin* (449, 450), wielded by NK cells and cytotoxic T lymphocytes (CTL); i.e., neuron death in EAE was prevented by deletion of the perforin gene, but demyelination was not affected (451, 452). Relatedly, it was shown that MIRL (CD59), which normally protects against autologous MAC attack, provided no protection against the molecularly comparable perforin (453). Some of the same authors have also implicated kallikreins (182). They have discussed their exciting findings in terms of clinical applications (454, 455). Later findings from that group were recently reviewed (448, 456), with a specific emphasis on natural antibodies (457)

Cid *et al.* attribute failure of remyelination in MS to the depletion of oligodendrocyte precursor cells (OPC's) by AutoAb's to heat-shock protein 90 (HSP90) in CSF of patients. They find that C activation is critical in this mainly by demonstrating that C1-INH could prevent the anti-HSP90-mediated death of OPC's (458). Earlier in this review we cited evidence for the role of C in recruitment of neural stem / progenitor cells. Interestingly, HSP90 is liberated by glucocorticoids (206).

Following work by them and others documenting that sublytic C5b-9 inhibits apoptosis of oligodendrocytes, and that C5 promoted remyelination in EAE (459), Cudrici *et al.* performed a genetic study of EAE mice with knockout of the C5 gene (147). Their aim was to identify which other genes (proteins) might be associated with the C5-dependent remyelination. About 400 genes were found to be differentially expressed in the $C5^{-/-}$ mice, and in various pairwise analyses (acute EAE *vs.* baseline, recovery, chronic, and wild-type $C5^{+/+}$). The authors concluded that insulin-like growth factor binding proteins (ILGF-BP) were perhaps of greatest interest, (for reasons given in their discussion (147). For a full discussion of their findings, see Tegla (141).

8.5. Natural antibodies and ischemia/ reperfusion injury

From similar clues, Zhang *et al.* were able to identify the target of the natural auto-Ab responsible for ischemia-reperfusion (I/R) injury as a non-muscle myosin heavy chain, which promotes C activation and tissue damage (460, 461); (reviewed in 462). This appears to be a real conceptual breakthrough, since it implies effective treatment using the anti-Id. They documented this mechanism for two different tissues, it may well apply to I/R of all organs and tissues.

It may be relevant to note early work by Pinckard *et al*, who demonstrated strong activation of the classical C pathway by mitochondria from human heart *in vitro* and in coronary surgery patients, in absence of anti-mitochondrial antibodies (463, 464). It is tempting to suggest that this was caused by natural anti-cardiolipin antibodies (since mitochondria are rich in cardiolipin) but the authors convincingly exclude a role of antibodies in this instance.

8.6. Natural antibodies, C, and adaptive immunity

The purpose of natural antibodies (NatAb) has been uncertain, but in 1998, an important role for them,

particularly IgM, in C-mediated activation of antigen-specific B cells, and in the elimination of self-reactive B cells, was considered (171). More recently, that author (M.C. Carroll) has discussed the broader role of C as a major regulator of multiple pathways in adaptive immunity (465), and in the processing of antigens for antigen-presenting cells (APC's) (466). Gonzalez *et al.* have shown that natural IgM, acting in concert with C3 and CR1/CR2, are essential for long-term immunological 'memory' (176). They also stated in that study, that IgM and C are in general, essential for normal antibody responses.

The C system mkght also be involved in the locomotion of leukocytes and formation of immune synapses. It has been shown that the Wiskott-Aldrich syndrome protein (WASP) binds specifically to C5aR (467). It is known that WASP is important to cell locomotion at the level of the actin cytoskeleton, supported by a study of that syndome in which the WASP protein is defective, entailing recurring infections, a high rate of autoimmune disease, cancers, thrombocytopenic bleeding, and eczema (468, 469). The syndrome also shows reduced C receptors on B cells, low plasma IgM, and an impaired ability to form immune synapses (470, 471). Thus, C5aR may represent a common denominator of these activities that require actin cytoskeletal reorganization: dysregulation of C-mediated control of auto-Ab's could be among the consequences.

8.7. Concepts of anti-idiotypes

A now-classic example was the production of a monoclonal antibody from an SLE patient, called idiotype 16/6 (16/6 Id), which occurs commonly in SLE patients, correlates with disease activity, and is deposited in afflicted tissues, (reviewed by Shoenfeld in 1990, 472). Mice immunized with 16/6 Id developed SLE-like disease and a spectrum of antibodies similar to SLE. (Patients with SLE have antibodies to as many as 25 self-targets, many of them intracellular.) Briefly, they explain this by supposing that some of the anti-Id generated in the mouse duplicate the original antigen pattern, which in turn could yield an anti-anti Id to drive the SLE-like response. (For related perspectives, see McGuire and Holmes (473).) The details are complex but generally support this broad concept (472). Similar work had been accomplished earlier by Johnson and Smalley (474), who immunized mice with rheumatoid factor (RF) from RA patients, which is known to react with streptococcal polysaccharides (PS), to obtain antibodies reactive to the original PS; i.e., anti-Id. Implications for autoimmunity are obvious, including potential etiologies attributable to pathogen exposure; but it is equally apparent that mechanisms must normally exist which limit this from happening.

8.8. More roles of natural antibodies

Su *et al* have demonstrated that natural anti-phosphoryl choline (PC), which can be extracted from pooled normal IVIG, appears to play a protective role in SLE (475). It has been argued that autoimmune hemolytic anemia (AIHA) results from disruption of an idiotype network (435). Quan *et al.* also made interesting observations on shifts in the repertoire of natural antibodies in treated *vs.* untreated HIV patients (476). Deliberate construction of anti-idiotypes against pathogenic AutoAb has been proposed for treatment of autoimmune diseases such as ITP (477). The significance of natural antibodies in IVIG therapy was recently reviewed (457).

9. SUMMARY AND PERSPECTIVE

This review clearly shows that the C system can no longer be viewed as in independent arm of the immune system, but is rather intricately connected to many aspects of immunity, including auto-immunity, and self-repair. In addition, the C system is closely connected with the coagulation system, accounting for many otherwise puzzling observations, reflecting its appreciation as a source of inflammatory mediators.

From the standpoint of new paradigms leading to potential therapies for several neurological diseases, perhaps most promising is the work reviewed in the last section pertaining to natural antibodies, raising hopes for effective treatments of dymelinating disease, I/R injury, and other immune-mediated disorders, entirely free of generalized immune suppression. Equally exciting is the new insight on the role of C in recruiting neural stem / progenitor cells, and related insights on neuronal repair after injury, e.g. remyelination.

Among the take-home lessons is to proceed with caution on the use of the many C inhibitors now in development because of the numerous beneficial activities of the C system. Another lesson, (a humbling one), concerns our ignorance of the detailed operation of the C system and its relation to other arms of immunity. It seems paradoxical, but true, that the more we learn about biological systems, the less certain we are that we understand them. Ulrich Behn best phrased it this way: *"There is a need to better understand the immune system at all temporal and spatial scales and at all levels of complexity"* (433).

10. ACKNOWLEDGEMENTS

All authors equally contributed to this article.

11. REFERENCES

1. Fujita, T.: Evolution of the lectin-complement pathway and its role in innate immunity. *Nat Rev Immunol* 2 (May), 346-353 (2002)

2. Finco, O. and Rappuoli, R.: Rediscovering complement, the first barrier of innate immunity (Preface to special issue) *Vaccine* 26 (sup8), I 1-2 (2008)

3. Thomas, P. S. and Doherty, P. C.: New approaches to immunotherapy (Editorial to special issue, "Innate Immunity" p283-300) *Science* 327 (Jan15), 249 (2010)

4. Authors, M.: Autoimmunity (Special issue, 6 articles) *Nature* 435 (June 2), 584-627 (2005)

5. Martinon, F., Mayor, A. and Tschopp, J.: The inflammasomes: guardians of the body. Annu Rev Immunol 27, 229-265 (2009)

6. Schroder, K., Zhou, R. and Tschopp, J.: The NLRP3 inflammasome: A sensor for metabolic danger? (see also pg 286-90 this issue) Science 327 (Jan15), 296-300 (2010)

7. Halkier, T. Mechanisms in Blood Coagulation, Fibrinolysis and the Complement System. New York, London: Cambridge Univ. Press, (1991)

8. Sims, P. J. and Wiedmer, T. Complement Biology (Ch. 37) In: Hoffman R, Benz EJ, Shattil SJ, Furie B, Cohen HJ, Silberstein LE, McGlave P, eds. Hematology: Basic Principles and Practice (3rd ed'n) Philadelphia: Elsevier, Churchill, Livingstone, pp. 651-667, 2000.

9. Muller-Eberhard, H. J.: Molecular organization and function of the complement system. *Annu Rev Biochem* 57, 321-347 (1988)

10. Walport, M. J.: Complement, Part I (Part II in next issue, pg 1140) *New Engl J Med* 344 (14), 1058-1066 (2001)

11. Nicholsen-Weller, A. Complement. In: Aird WC, ed. Endothelial Biomedicine. Cambridge, MA: Cambridge Univ. Press, pp. 430-443, (2007)

12. Ziccardi, R. J. and Tschopp, J.: The dissociation properties of native C1. *Biochem Biophys Res Commun* 107 (2), 618-623 (1982)

13. Caliezi, C., Weuillemin, W. A., Zeerleder, S., Redondo, M., Eisele, B. and Hack, E.: C1-esterase inhibitor: An anti-inflammatory agent and its potential use in the treatment of diseases other than hereditary angioedema. *Pharm Rev* 52 (1), 91-112 (2000)

14. Michaelsen, T. E., Garred, P. and Aase, A.: Human IgG subclass pattern of inducing complement-mediated cytolysis depends on antigen concentration and to a lesser extent on epitope patchiness, antibody affinity and complement concentration *Eur J Immunol* 21 (1), 11-16 (1991)

15. Granoff, D. M.: Relative importance of complement-mediated bactericidal and opsonic activity for protection against meningococcal disease. *Vaccine* 27 (sup2), B 117-125 (2009)

16. Pangburn, M. K., Rawa, N., Cortes, C., Alam, M. N., Ferreira, V. P. and Atkinson, M. A.: Polyanion-induced self-association of complement factor H. *J Immunol* 182 (2), 1061-1068 (2009)

17. Halkier, T. Regulation of blood coagulation (Ch. 8) Mechanisms in Blood Coagulation, Fibrinolysis and the Complement System. New York, London: Cambridge Univ. Press, 1991.

18. Pangburn, M. K., Ferreira, V. P. and Cortes, C.: Discrimination between host and pathogens by the complement system. *Vaccine* 26 (sup8), I 15-21 (2008)

19. Smith, L. C., Azum, K. and Nonaka, M.: Complement systems in invertebrates: The ancient alternative and lectin pathways. *Immunopharmacol* 42 (1-3), 107-120 (1999)

20. Turner, M. W.: The lectin pathway of complement activation (see also pg 115-19, by Matsushita and Fujita) *Res Immunol* 147 (2), 110-115 (1996)

21. Ip, W. K. E., Takahashi, K., Ezekowitz, R. A. and Stuart, L. M.: Mannose-binding lectin and innate immunity. *Immunol Rev* 230 (1), 9-21 (2009)

22. Collard, C. D., Vakeva, A., Morrissey, M. A., Agah, A., Rolins, S. A., Reenstra, W. R., Buras, J. A., Meri, S. and Stahl, G. L.: Complement activation after oxidative stress: role of the lectin complement pathway. *Am J Pathol* 156 (5), 1549-1556 (2000)

23. Wallis, R., Mitchell, D. A., Schmid, R., Schwaeble, W. J. and Keeble, A. H.: Paths reunited: Initiation of the classical and lectin pathways of complement activation. *Immunobiology* 215 (1), 1-11 (2010)

24. Ricklin, D. and Lambris, J. D.: Complement-targeted therapeutics. *Nat Biotchnol* 25 (11), 1265-1275 (2007)

25. Amara, U., Rittirsch, D., Flieri, M., Bruckner, U., Klos, A., Gebhard, F., Labris, J. D. and Huber-Lang, M.: Interaction between the coagulation and complement system. *Adv Exp Med Biol* 632, 71-79 (2008)

26. Amara, U., Flieri, M. A., Rittirsch, D., Klos, A., Chen, H., Acker, B., Bruckner, U. B., Nilsson, B. and etal: Molecular intercommunication between the complement and coagulation systems. *J Immunol* 185 (9), 5628-5636 (2010)

27. Gong, Y., Xi, G. H., Keep, R. F., Hoff, J. T. and Hua, Y.: Complement inhibition attentuates brain edema and neurological deficits induced by thrombin. *Acta Neurochir Suppl* 95, 389-392 (2005)

28. Silverman, G. A., Byrd, P. I., Carrell, R. W. and etal: The serpins are an expanding superfamily of structurally similar but functionally diverse proteins (Supplemental tables online) *J Biol Chem* 276 (36), 33293-33296 (2001)

29. Leung, L. L., Nishimura, T. and Myles, T.: Regulation of tissue inflammation by thrombin-activable carboxypeptidase B (or TAFI) *Adv Exp Med Biol* 632, 61-69 (2008)

30. Deiteren, K., Hendriks, D., Scharpe, S. and Lambier, A. M.: Carboxypeptidase M: Multiple alliances and unknown partners. *Clin Chim Acta* 399 (1-2), 24-39 (2009)

31. Leung, L. L., Myles, T., Nishimura, T., song, J. J. and Robinson, W. F.: Relationship of tissue inflammation by thrombin-activatable carboxypeptidase B (or TAFI) *Mol Immunol* 45, 4080-4083 (2008)

32. Sjoberg, A. P., Trouw, L. A. and Blom, A. M.: Complement activation and inhibition: a delicate balance. *Trends Immunol* 30 (2), 83-90 (2009)

33. Alexander, J. J. and Quigg, R. J.: The simple design of complement factor H: Looks can be deceiving. *Mol Immunol* 44, 123-127 (2007)

34. Skerka, C. and Zipfel, P. F.: Complement factor H related proteins in human diseases. *Vaccine* 26 (sup8), I 9-14 (2008)

35. Skerke, C. and Zipfel, P. F.: Complement factor H related proteins in immune diseases. *Vaccine* 26 (Sup8), I9-I14 (2008)

36. Kemper, C., Atkinson, J. P. and Hourcade, D. E.: Properdin: emerging roles of a pattern recognition molecule. *Annu Rev Immunol* 28, 131-155 (2010)

37. Erdai, A., Isaac, A., Torok, K., Sando, N., Kremlitzka, M., Prechl, J. and Bajtay, Z.: Expression and role of CR1 and CR2 on B and T lymphocytes under physiological and autoimmune conditions. *Mol Immunol* 46 (14), 2767-2773 (2009)

38. Gibson, N. G. and Waxman, F. J.: Relationship between immune complex binding and release and quantitative expression of the complement receptor, Type 1 (CR1, CD35) on human erythrocytes. *Clin Immunol Immunopath* 70 (2), 104-113 (1994)

39. Fearon, D. T.: The CD19/Cr2/TAPA-1 complex of B lymphocytes: Linking natural to acquired immunity. *Annu Rev Immunol* 13, 127-149 (1995)

40. Asokan, R., Hua, J., Young, K. A., Gould, H. J., Hanan, J. P. and etal: Characterization of human complement receptor type 2 (CR2/CD21) as a receptor for IFN-alpha: a potential role in systemic lupus erythematosus. *J Immunol* 177 (1), 383-394 (2006)

41. Lindahl, G., Sjobring, U. and Johnsson, E.: Human complement regulators: a major target for pathogenic microorganisms. *Curr Opin Immunol* 12 (1), 44-51 (2000)

42. Zipfel, P. E. and Skerka, C.: Complement regulatory and inhibitory proteins. *Nat Rev Immunol* 9, 728-740 (2009)

43. McKillop, W. M., Barrett, J. W., Chan, S. H. P. B. M. and Dekaban, G. A.: The extracellular domain of CD11d regulates its cell surface expression. *J Leukoc Biol* 86 (4), 851-862 (2009)

44. Lambris, J. D.: The multifunctional role of C3, the third component of complement. *Immunol Today* 9 (12), 387-393 (1988)

45. vanBruggen, R., Drewniak, A., Jansen, M., vanHoudt, M. and etal: Complement receptor 3, not Dectin-1, is the major receptor on human neutrophils for beta-glucan-bearing particles. *Mol Immunol* 47 (2-3), 575-581 (2009)

46. Kopf, M., Abel, B., Gallimore, A., Carroll, M. and Bachmann, M. E.: Complement component C3 promotes T-cell priming and lung migration to control acute influenza virus infection. *Nat Immunol* 8 (4), 373-378 (2002)

47. Jacobson, A. C., Roundy, K. M., Weis, J. J. and Weis, J. H.: Regulation of murine splenic B cell CR3 expression by complement component 3. *J Immunol* 183 (6), 3963-3960 (2009)

48. Vinay, D. S., Kim, C. H., Choi, B. K. and Kwon, B. S.: Origins and functional basis of regulatory CD11C+CD8+ T cells. *Eur J Immunol* 39 (6), 1552-1563 (2009)

49. Ghebrehiwet, B. and Peerschke, E. I.: cC1q-R (calreticulin) and gC1q-R/p33: unbiquitously expressed multi-ligand binding cellular proteins involved in inflammation and infection. *Mol Immunol* 41 (2-3), 173-183 (2004)

50. Peerschke, E. and Ghebrehiwet, B.: The contribution of gC1qR/p33 in infection and inflammation. *Immunobiology* 212 (4-5), 333-342 (2007)

51. Kittlesen, D. J., ChianesepBullock, K. A., Zai, A. Q., Braciale, T. J. and Hahn, Y. S.: Interaction between complement receptor gC1qR and hepatitis C virus core protein inhibits T-lymphocyte proliferation. *J Clin Invest* 106 (10), 1239-1249 (2000)

52. Yao, Z. Q., Nguyen, D. T., Hiotellis, A. I. and Hahn, Y. S.: Hepatitis C virus core protein inhibits human T lymphocyte responses by a complement-dependent regulatory pathway. *J Immunol* 167 (9), 5264-5272 (2001)

53. Zutter, M. M. and Edelson, B. T.: The alpha2 beta1 integrin: a novel collectin/C1q receptor. *Immunobiology* 212 (4-5), 343-353 (2007)

54. Stano, P., Williams, V., Villani, M., Cymbalyuk, E. S. and etal: App1: an antiphagocytic protein that binds to complement receptors 3 and 2. *J Immunol* 182 (1), 84-91 (2009)

55. Morelli, A. B., Larregina, A. T., Shufesky, W. J., Zahorchalk, A. F. and etal: Internalization of circulating apoptotic cells by splenic marginal zone dendritic cells: dependence on complement receptors and effect on cytokine production. *Blood* 101 (2), 611-620 (2003)

56. Verbovetski, I., Bychkov, H., Trahemberg, U., Shapira, I. and etal: Opsonization of apoptotic cells by autologous iC3b facilitates clearance by immature dendritic cells, down-regulates DR and CD86, and upregulates CC chemokine receptor 7. *J Exp Med* 196 (12), 1553-1561 (2002)

57. Steinberg, P., Szekeres, A., Wille, S., Stockl, J., Selenko, N. and etal: Identification of human CD93 as the phagocytic C1q receptor (C1qRp) by expression cloning. *J Leukoc Biol* 71 (1), 133-140 (2002)

58. Nosworthy, P. J., Fossati-Jimack, L., Vortes-Hernandez, J., Taylor, P. R., Bygrave, A. E., Thompson, R. D., Nourshargh, S., Walport, M. J. and Botto, M.: Murine CD93 (C1qRp) contributes to the removal of apoptotic cells *in vivo* but is not required for C1q-mediated enhancement of phagosytosis. *J Immunol* 172 (6), 3405-3414 (2004)

59. Greenlee, M. C., Sullivan, S. A. and Bohlson, S. S.: CD93 and related family members: their role in innate immunity. *Curr Drug Targets* 9 (2), 130-138 (2008)

60. Lillis, A. P., Greenlee, M. C., Mikhailenko, I., Pizzo, S. V., Tenner, A. J., Strickland, D. K. and Bohlson, S. S.: Murine low-density lipoprotein receptor-relarted protein 1 (LRP) is required for phagocytosis of targets bearing LRP ligands but is not required for C1q-triggered enhancement of phagocytosis. *J Immunol* 181 (1), 364-373 (2008)

61. Chevrier, S., Genton, C., Kallies, A., Karnowski, A. and etal: CD93 is required for maintenance of antibody secretion and persistence of plasma cells in the bonemarrow niche. *Proc Natl Acad Sci USA* 106 (10), 3895-3900 (2009)

62. Fraser, D. A., Laust, A. K., Nelson, E. L. and Tenner, A. J.: C1q differentially modulates phagocytosis and cytokine responses during ingestion of apoptotic cells by human monocytes, macrophages, and dendritic cells. *J Immunol* 183 (10), 175-185 (2009)

63. Gardai, S. J., Xiao, Y. Q., Dickinson, M., Nick, J. A., Voelker, D. R., Greene, K. E. and Henson, P. M.: By binding SIRPalpha or calreticulin/CD91, lung collectins act as dual function surveillance molecules to suppress or enhance inflammation. *Cell* 115 (1), 13-23 (2003)

64. Gold, L. L., Eggleton, P., Sweetwyne, M. E., Van, L. B. and etal: Calreticulin: non-endoplasmic reticulum functions in physiology and disease. *FASEB J* 24, 665-683 (2010)

65. Davitz, M. A. and etal: Release of decay -accelerating factor (DAF) from the cell membrane by phosphatidyl inositol-specific phospholipase C (PIPLC): Selective modification of a complement regulatory protein. *J Exp Med* 163 (May), 1150-1161 (1986)

66. Morgan, B. P. and Meri, S.: Membrane proteins that protect against complement lysis. *Spring Sem Immunopath* 15 (4), 369-396 (1994)

67. Kinoshita, T.: Protection of host from its own complement by membrane-bound complement inhibitors: C3 convertase inhibitors vs membrane attack complex inhibitors. *Res Immunol* 147 (2), 100-103 (1996)

68. Kim, D. D. and Song, W. C.: Membrane complement regulatory proteins. *Clin Immunol* 118 (2-3), 127-136 (2006)

69. Yang, L., Li, R., Meri, S., Rogers, J. and Shen, Y.: Deficiency of complement defense protein CD59 may contribute to neurodegeneration in Alzheimer's disease. *J Neurosci* 20 (20), 7505-7509 (2000)

70. Peng, Q., Li, K., Sacks, S. H. and Zhou, W.: The role of anaphylatoxins C3a and C5a in regulating innate and adaptive immunity. *Inflamm Allergy Drug Targets* 8 (3), 235-246 (2009)

71. Manthey, H. G., Woodruff, T. M., Taylor, S. M. and Monk, P. N.: Complement component 5a (C5a) *Int J Biochem Cell Biol* 41, 2114-2117 (2009)

72. Klos, A., Tenner, A. J., Johswich, K. O., Ager, R. R., Reis, E. S. and Kohl, J.: The role of the anaphylatoxins in health and disease. *Mol Immunol* 46 (14), 2753-2766 (2009)

73. Ward, P. A.: Functions of C5a receptors. *J Mol Med* 87 (4), 375-378 (2009)

74. Rabiet, J., Huet, E. and Boulay, F.: The N-formyl peptide receptors and the analphylatoxin C5a receptors: an overview. *Biochimie* 89 (9), 1089-1106 (2007)

75. Gavrilyuk, V., Kalinin, S., Hilbush, B. S., Middlecamp, A., McGuire, S. and etal: Identification of a complement C5a receptor (C5L2) from astrocytes: characterization of anti-inflammatory properties. *J Neurochem* 92, 1140-1149 (2005)

76. DiScipio, R. G. and Schraufstatter, I. U.: The role of the complement anapylatoxins in the recruitment of eosinophils. *Int Immunopharmacol* 7 (14), 1909-1923 (2007)

77. Fukuoka, Y., Xia, H. Z., Sanchez-Munoz, L. B., Dellinger, A. L., Escribano, L. and Schwartz, L. B.: Generation of anaphylatoxins by human beta-tryptase from C3, C4, and C5. *J Immunol* 180 (9), 6307-6316 (2008)

78. Ganu, V. S., Muller-Eberhard, H. J. and Hugi, T. E.: Factor C3f is a spasmogenic fragment released from C3b by factors I and H: the heptadeca-peptide C3f was synthesized and characterized. *Mol Immunol* 26 (10), 939-948 (1989)

79. Janeway, C. A. and Medzhitov, R.: Innate immune recognition. *Annu Rev Immunol* 20, 197-216 (2002)

80. Waters, P., Vaid, M., Kishore, U. and Madan, T.: Lung surfactant proteins A and D as pattern recognition proteins. *Adv Exp Med Biol* 653, 74-97 (2009)

81. Gil, M., McCormack, F. X. and Levine, A. M.: Surfactant protein A modulates cell surface expression of CR3 on alveolar macrophages and enhances CR3-mediated phagocytosis. *J Biol Chem* 284 (12), 7495-7504 (2009)

82. Endo, Y., Matsushita, M. and Fujita, T.: Role of ficolin in innate immunity and is molecular basis. *Immunobiology* 212 (4-5), 371-379 (2007)

83. Runza, V. L., Schwaeble, W. and Mannel, D. L.: Ficolins: novel pattern recognition molecules of the innate immune system. *Immunobiology* 213, 297-306 (2008)

84. Bottazzi, B., Doni, A., Garlanda, C. and Mantovani, A.: An integrated view of humoral innate immunity: Pentraxins as a paradigm. *Annu Rev Immunol* 28 (157-183) (2010)

85. Basi, N., Zampieri, S., Ghiradello, A., Tonan, M., Zen, M., Cozzi, E. and Doria, A.: Pentraxins, anti-pentraxin antibodies, and atherosclerosis. *Clin Rev Allergy Immunol* 37 (1), 36-43 (2009)

86. Lu, J., Marnell, L. L., Marjon, K. D., Mold, C., DuClos, T. W. and Sun, P. D.: Structural recognition and functional activation of Fc-gammaR by innate pentraxins. *Nature* 456 (Dec18), 989-992 (2008)

87. Szalai, A. J., VanCott, J. L., McGher, J. R., Volanakis, J. E. and BenjaminJr, W. H.: Human C-reactive protein is protective against fatal Salmonella enterica serovar Typhimurium infection in transgenic mice. *Infect Immunity* 68 (10), 5652-5656 (2000)

88. Agrawal, A., Suresh, M. V., Singh, S. K. and FergusonJr, D. A.: The protective functions of human C-reactive protein in mouse models of Streptococcus pheumoniae infection. *Endocr Metab Immun Disord Drug Targets* 8 (4), 231-237 (2008)

89. Castiglioni, M. T., Scavini, M., Cavallin, R., Pasi, F., Rosa, S., Sabbadini, M. G. and Rovere-Querini, P.: Elevation of plasma levels of the long pentraxin 3 precedes preeclampsia in pregnant patients with type 1 diabetes. *Autoimmunity* 42 (4), 296-298 (2009)

90. Robinson, M. J., Sancho, D., Slack, E. C., LeibundGut-Landmann, S. and eSousa, C. R.: Myeloid C-type lectins in innate immunity. *Nat Immunol* 7 (12), 1258-1265 (2006)

91. Kang, Y. S., Do, Y., Lee, H. K., Park, S. H., Cheolho, C. and etal: A dominant complement fixation pathway for pneumoccol polysaccharides initiated by SIGN-R1 interacting with C1q. *Cell* 125 (Apr7), 47-58 (2006)

92. Takagi, H., Numazaki, M., Kajiwara, T., Abe, Y., Ishii, M., Kato, C. and Kojima, N.: Cooperation of specific ICAM-3 grabbing non-integrin-related 1 (SIGNR1) and complement receptor type 3 (CR3) in the uptake of oligomannose-coated liposomes by macrophages. *Glycobiology* 19 (3), 258-266 (2009)

93. Sato, S., StPierre, C., Bhaumik, P. and Nieminen, J.: Galectins in innate immunity: dual functions of host soluble beta-galactoside-binding lectins as damage-associated molecular patterns (DAMPs) and as receptors for pathogen-associated molecular patterns (PAMPs) *Immunological Rev* 230 (172-187) (2002)

94. LeSaux, A., Ng, P. M. L., Koh, J. J. Y., Low, D. H. P., Leong, G. E. L., Ho, B. and Ding, J. L.: The macromolecular assembly of pathogen-recognition receptors is impelled by serine proteases, via their complement control protein modules. *J Mol Biol* 377 (3), 902-913 (2008)

95. Nuutinen, T., Suuronen, T., Kauppinen, A. and Salminen, A.: Clusterin: A forgotten player in Alzheimer's disease. *Brain Res Rev* 61 (2), 89-104 (2009)

96. Hochbrebe, T. T., Humphreys, D., Wilson, M. R. and Esterbrook-Smith, S. B.: A reexamination of the role of clusterin as a complement regulation. *Exp Cell Res* 249 (1), 13-21 (1999)

97. Steinman, L.: A molecular trio in relapse and remission in multiple sclerosis. *Nat Rev Immunol* 9 (Jun), 440-447 (2009)

98. Zheng, W., Li, R., Pan, H., He, D., Xu, R., Guo, T. B., Gun, Y. and Zhang, J. Z.: Role of osteopontin in induction of monocyte chemoattractant protein 1 and macrophage inflammatory protein 1 beta through the NF-kB and MAPK pathwayas in rheumatoid arthritis. *Arthritis Rheum* 60 (7), 1957-1965 (2009)

99. Jain, A., Karadag, A., Fohr, B. and etal: Three SIBLINGs (Small Integrin-Binding LIgand, N-linked glycoproteins) enhance factor H's cofactor activity enabling MCP-like cellular evasion of complement-mediated attack. *J Biol Chem* 277 (Apr19), 13700-13708 (2002)

100. Fedarko, N. S., Fohr, B., Robey, P. G. and etal: Factor H binding to bone sialoprotein and osteopontin enables tumor cell evasion of complement-mediated attack. *J Biol Chem* 275 (22), 16666-16672 (2000)

101. Yan, Y. P., Lang, B. T., Vemuganti, R. and Dempsey, R. J.: Persistent migration of neuroblasts from the subventricular zone to the injured stratum mediated by osteopontin following intracranial hemorrhage. *J Neurochem* 109 (6), 1624-1635 (2009)

102. Attia, A. S., Ram, S., Rice, P. A. and Hansen, E. J.: Binding of vitronectin by the Moraxella catarrhalis UspA2 protein interferes with late stages of the complement cascade. *Infect Immun* 74 (3), 1597-1611 (2006)

103. Hallstrom, T., Blom, A. M., Zipfel, P. F. and Riesbeck, K.: Nontypeable Haemophilus influenzae protein E binds vitronectin and is important for serum resistance. *J Immunol* 183 (4), 2593-2601 (2009)

104. Schwartz, I., Seger, D. and Shaltiel, S.: Vitronectin. *Int J Biochem Cell Biol* 31 (5), 539-544 (1999)

105. Bargoma, E. M., Mitsuyoso, J. K., Larkin, S. K., Styles, L. A., Kuypers, F. A. and Test, S. T.: Serum C-reactive protein parallels secretory phopholipase A2 in sickle cell disease patients with vasoocclusive crisis or acute chest pain (Letter) *Blood* 105, 3384-3385 (2005)

106. Hack, C. E., Wolbink, G. J., Schalkwijk, C. and etal: A role for secretory phospholipase A2 and C-reactive protein in the removal of injured cells. *Immunol Today* 18 (3), 111-115 (1997)

107. Birts, C. N., Barton, C. H. and Wilton, D. C.: A catalytically independent physiological function for human acute phase protein group IIA phospholipase A2: cellular uptake facilitates cell debris removal. *J Biol Chem* 283 (8), 5034-5045 (2008)

108. Gronroos, J. O., Salonen, J. H., Viander, M., Nevalainen, T. J. and Laine, V. J.: Roles of group IIA phospholipse A2 and complement in killing of bacteria by acute phase serum. *Scand J Immunol* 62 (4), 413-419 (2005)

109. Billy, D., Speijer, H., Zwaal, R. F. A., Hack, E. C. and Hermens, W. T.: Anticoagulant and membrane degrading effects of secretory (non-pancreatic) phospholipase A2 are inhibited in plasma. *Thromb Haemost* 87 (6), 978-984 (2002)

110. Payne, S. G., Oskeritzian, C. A., Griffiths, R., Subramanian, P. and ETAL: The immunosuppressant drug FTY720 inhibits cytosolic phospholipase A2 indendently of sphingosine-1-phosphate receptors. *Blood* 109 (3), 1077-1085 (2007)

111. Farooqui, A. A., Ong, W. Y. and Horrocks, L. A.: Inhibitors of brain phospholipase A2 activity: their neuropharmacological effects and therapeutic importance for the treatment of neurologic disorders. *Pharm Rev* 58 (3), 591-620 (2006)

112. Sanchez-Mejia, R. O. and Mucke, L.: Phospholipase A2 and arachadonic acid in Alzheimer's disease. *Biochim Biophys Acta* 1801 (8), 784-790 (2010)

113. Kihara, Y., Yanagida, K., Masago, K., Kita, Y., Hishikawa, D., Shindou, H., Ishii, S. and Shimizu, T.: Platelet-activating factor production in the spinal cord of experimental allergic encephalomyelitis mice via the group IVA cytosolic phospholipase A2-lyso-PAFAT axis. *J Immunol* 181 (7), 5008-5014 (2008)

114. Carro, E.: Gelsolin as therapeutic target in Alzheimer's disease. *Expert Opin Ther Targets* 14 (6), 585-592 (2010)

115. Osborn, T. M., Dahlgren, C., Hartwig, J. H. and Stossel, T. P.: Modifications of cellular responses to lysophosphatidic acid and platelet-activating factor by plasma gelsolin. *Am J Physiol Cell Pysiol* 292 (4), C1323-C1330 (2007)

116. Hill, J. M., Zhang, Y., Clement, C., Neumann, D. M. and Lukiw, W. J.: HSV-1 infection of human brain cells induces miRNA-146a and Alzheimer-type inflammatory signaling. *Neuroreport* 20 (16), 1500-1506 (2009)

117. Steel, D. M. and Whitehead, A. S.: The major acute phase reactants: C-reactive protein, serum amyloid P component and serum amyloid A protein (see also pg 74-80 this issue) *Immunol Today* 15 (2), 81-88 (1994)

118. Ambrus, G., Gal, P., Kojima, M., Szilagy, K., Balczer, J., Antal, J., Graf, L., Lalch, A., Moffatt, B. E., Schwaeble, W., Sim, R. B. and Zavodszky, P.: Natural substrates and inhibitors of mannan-binding lectin-associated serine protease-1 and -2: a study on recombinant catalytic fragments. *J Immunol* 170 (3), 1374-1382 (2003)

119. Scharfstein, J.: Parasite cysteine proteinase interactions with alpha 2-macroglobulin or kininogens: differential pathways modulating inflammation and innate immunity in infection by pathogenic trypanosomatids. *Immunobiology* 211 (1-2), 117-125 (2006)

120. Salvesen, G. and Pizzo, S. V. Proteinase inhibitors: Alpha-macroglublins, serpins and kinins. In: Colman R, Hirsh J, Marder VJ, Salzman EW, eds. Hemostasis and Thrombosis: Basic Principles and Clinical Practice (Ch 12) Philadelphia: J B Lippincott, pp. 241-259, 1994.

121. Mocchegiani, E. and Malavolta, M.: Zinc dyshomeostasis, ageing and neurodegeneration: implications of A2M and inflammatory gene polymorphisms. *J Alzheimers* 12 (1), 101-109 (2007)

122. Stebbing, J., Bower, M., Gazzard, B., Wildfire, A., Pandha, H., Dalgleish, A. and Spicer, J.: The common heat shock protein receptor CD91 is up-regulated on monocytes of advanced melanoma slow progressors. *Clin Exp Immunol* 138, 312-316 (2004)

123. Tarr, J. and Eggleton, P.: Immune function of C1q and its modulators CD91 and CD93. *Crit Rev Immunol* 25 (4), 305-330 (2005)

124. Gorgani, N. N. and Theofilopoulos, A. N.: Contribution of histidine-rich glycoprotein in clearance of immune complexes and apoptotic cells: implications for ameliorating autoimmune diseases. *Autoimmunity* 40 (4), 260-266 (2007)

125. Sjoberg, A. P., Manderson, G. A., Morgelin, M., Day, A. J., Heinegard, D. and Bloom, A. M.: Short leucine-rich glycoproteins of the extracellular matrix display diverse patterns of complement interaction and activation. *Mol Immunol* 46, 830-839 (2008)

126. Iozzo, R. V. and Schaefer, L.: Proteoglycans in health and disease: novel regulatory signaling mechanisms evoked by the small leucine-rich proteoglycans. *FEBS J* 277, 3864-3875 (2010)

127. Miwa, T. and Song, W. C.: Membrane complement regulatory proteins: insights from animal studies and relevance to human diseases. *Int J Immunopharmacol* 1 (3), 445-459 (2001)

128. Miwa, T., Zhou, L., Hilliard, B. and etal: Crry, but not CD59 and DAF, is indispensible for murine erythrocyte protection *in vivo* from spontaneous complement attack. *Blood* 99 (10), 3707-3716 (2002)

129. Blanchong, C. A., Chung, E. K., Rupert, K. L., Yang, Y. and etal: Genetic, structural and functional diversities of human complement components C4A and C4B and their mouse homologues, S1p and C4. *Int Immunopharmacol* 1, 365-392 (2001)

130. Wasowska, B. A., Lee, C. Y., Halushka, M. K. and BaldwinIII, W. M.: New concepts of complement in allorecognition and graft rejection. *Cell Immunol* 248, 18-30 (2007)

131. Schwab, C., Klegeris, A. and McGeer, P. L.: Inflammation in transgenic mouse models of neurodegenerative disorders. *Biochim Biophys Acta* Epub preprint (2009)

132. Reichwald, J., Danner, S., Wiedenhold, K. H. and Staufenbiel, M.: Expression of complement system components during aging and amyloid deposition in APP transgeneic mice. *J Neuroinflammation* 17 (6), 35 (2009)

133. Ming, L., Ager, R. R., Fraser, D. A., Tjokro, N. O. and Tenner, A. J.: Development of a humanized C1q A chain knock-in mouse: Asssessment of antibody independent beta-amyloid induced complement activation. *Mol Immunol* 45 (11), 3244-3252 (2008)

134. Rahpeymai, Y. and al, e.: Complement: a novel factor in basal and ischemia-induced neurogenesis. *EMBO J* 25, 1364-1374 (2006)
135. Kimberley, F. C., Sivasankar, B. and Morgan, B. P.: Alternative roles for CD59. *Mol Immunol* 44, 73-81 (2007)

136. Ratajczak, M. Z., Wysoczynski, M., Reca, R., Wan, W., Zuba-Suma, E. K., Kucia, M. and Ratajczak, J.: A pivotal role of activation of complement cascade (CC) in mobilization of hematopoietic stem / progenitor cells. *Adv Exp Med Biol* 632, 47-60 (2008)

137. Lee, H. and Ratajczak, M. Z.: Innate immunity: a key player in the mobilization of hematopoietic stem / progenitor cells. *Arch Immunol Ther Exp* 57 (4), 269-278 (2009)

138. Monje, M. J., Toda, H. and Palmer, T. D.: Inflammatory blockade restores adult hippocampal neurogenesis (with editorial, p1689) *Science* 302 (Dec 5), 1760-1763 (2003)

139. Esteban, M. A., Wang, T., Qin, B., Yang, J., Qin, D. and etal: Vitamin C enhances the generation of mouse and human induced pluripotent stem cells (with editorial pg 1-2) *Cell Stem Cell* 6 (1), 71-79 (2010)

140. Smith, A. R., Visioli, F. and Hagen, T. M.: Vitamin C matters: increased oxidative stress in cultured human aortic endothelial cells without supplemental ascorbic acid. *FASEB J* 16, 1102-1104 (2002)

141. Tegla, C. A., Cudrici, C., Rus, V., Ito, T., Vlaicu, S., Singh, A. and Rus, H.: Neuroprotective effects of the complement terminal pathway during demyelination: implications for oligodendrocyte survival. *J Neuroimmunol* 213 (1-2), 3-11 (2009)

142. Scolding, N. J., Morgan, B. P., Houston, W. A. J., Linington, C., Campbell, A. K. and Compston, D. A. S.: Vesicular removal by oligodendrocytes of membrane attack complexes formed by activated complement. *Nature* 339 (22 Jun), 620-622 (1989)

143. Hamilton, K. K., Hattori, R., Esmon, C. T. and Sims, P. J.: Complement proteins C5b-9 induce vesiculation of the endothelial plasma membrane and expose catalytic surface for assembly of the prothrombinase enzyme complex. *J Biol Chem* 265 (7), 3809-3814 (1990)

144. Sims, P. J. and Wiedmer, T.: The response of human platelets to activated components of the complement system. *Immunol Today* 12 (9), 338-341 (1991)

145. Scolding, N. J., Morgan, B. P., Houston, A., Campbell, A. K., Linington, C. and Compston, D. A.: Normal rat serum cytotoxicity against syngeneic oligodendrocytes. Complement activation and attack in the absence of anti-myelin antibodies. *J Neurol Sci* 89 (2-3), 289-300 (1989)

146. Wing, M. G., Zajicek, J., Seilly, D. J., Compston, D. A. and Lachmann, P. J.: Oligodendrocytes lack glycolipid anchored proteins which protect them against complement lysis. *Immunology* 76, 140-145 (1992)
147. Cudrici, C., Ito, T., Zatfranskaia, E., Weerth, S., Rus, V. and etal: Complement C5 regulates the expression of insulin-like growth factor binding proteins in chronic experimental allergic encephalomyelitis. *J Neuroimmunol* 203 (1), 94-103 (2008)

148. Wyss-Coray, T., Yan, F., Lin, A. H., Labris, J. D., Alexander, J. J., Quigg, R. J. and Masilah, E.: Prominent neurodegeneration and increased plaque formation in complement-inhibited Alzheimer's mice. *Proc Natl Acad Sci USA* 99 (16), 10837-10842 (2002)

149. Maier, M., Peng, Y., Jiang, L., Seabrook, T. J., Carroll, M. C. and Lemere, C. A.: Complement C3 deficiency leads to accelerated amyloid beta plaque deposition and neurodegeneration and modulation of the microglia / macrophage phenotype in amyloid precursor protein transgenic mice. *J Neurosci* 28 (25), 6333-6341 (2008)

150. Pisalyaput, K. and Tenner, A. J.: Complement component C1q inhibits beta-amyloid- and serum amyloid P-induced neurotoxicity via caspase- and calpain-independent mechanisms. *J Neurochem* 104 (3), 696-707 (2008)

151. Mukherjee, P., Thomas, S. and Pasinetti, G. M.: Complement anaphylatoxin C5a neuroprotects through regulation of glutamate receptor subunit 2 *in vitro* and *in vivo*. *J Neuroinflammation* 29 (5), 5 (2008)

152. Ager, R. R., Fonseca, M. I., Chu, S. H., Sanderson, S. D., Taylor, S. M., Woodruff, T. M. and Tenner, A. J.: Microglial C5aR (CD88) expression correlates with amyloid-beta deposition in murine models of Alzheimer's disease. *J Neurochem* 113 (2), 389-401 (2010)

153. Reiter, Y., Ciobotariu, A. and Hishelson, Z.: Sublytic complement attack protects tumor cells from lytic does os antibody and complement. *Eur J Immunol* 22 (5), 1207-1213 (1992)

154. Dashiell, S. M., Rus, H. and Koski, C. L.: Terminal complement complexes concommitantly stimulate

proliferation and rescue of Schwann cells from apoptosis. *Glia* 30 (2), 187-198 (2000)

155. Koch, C. A., Khalpey, Z. I. and Platt, J. L.: Accomodation: preventing injury in transplantation and disease. *J Immunol* 172 (Aug24), 5143-5148 (2004)

156. Manderson, A. P., Botto, M. and Walport, M. J.: The role of complement in the development of systemic lupus erythematosus. *Annu Rev Immunol* 22, 431-456 (2004)

157. Veerhuis, R., VanBreeman, M. J., Hozemans, J. M., Morbin, M., Ouladhadj, J., Tagliavini, F. and Eikelenboom, P.: Amyloid beta plaque-associated proteins C1q and SAP enhance the Abeta1-42 peptide-induced cytokine secretion by adult human microglia *in vitro*. *Acta Neuropathol* 105 (2), 135-144 (2003)

158. Rogers, J., Li, R., Mastroeni, D., Grover, A. and etal: Peripheral clearance of amyloid beta peptide by complement C3-dependent adherence to erythrocytes. *Neurobiol Aging* 27, 1733-1739 (2006)

159. Tarr, Z. S. and Seshadri, S.: Inflammation in the Alzheimer's disease cascade: culprit or innocent bystander? *Alzheimers Res Ther* 2, 6 (2010)

160. Lu, J., Goh, S. G., Tng, P. Y. L., Deng, Y. Y., Ling, E. and Moochhala, S.: Systemic inflammatory response following acute brain injury. (2009)

161. Soriano, A. O., Jy, W., Chirinos, J. A., Valdivia, M. A., Velasquez, H. S., Jimenez, J. J., Horstman, L. L., Kett, D. H., Schein, R. M. H. and Ahn, Y. S.: Levels of endothelial and platelet microparticles and their interactions with leukocytes correlate with organ dysfunction and predict mortality in severe sepsis. *Crit Care Med* 33 (11), 2540-2546 (2005)

162. Gendre, R., Rapti, G., Richmond, J. E. and Bessereau, J. L.: A secreted complement control protein ensures acetylcholine receptor clustering. *Nature* 461 (Oct15), 992-999 (2009)

163. Kushkal, J., Kemper, C. and Gigli, I.: Ancient origins of human complement factor H. *J Mol Evol* 47 (5), 625-630 (1998)

164. Schikorski, D., Cuvillier-Hot, V., Leippe, M., Boidin-Wichlacz, C., Slomianny, C., Macagno, E., Salzer, M. and Tasiemski, A.: Microbial challenge promotes the regenerative process of the injured central nervous system of the medicinal leech by inducing the synthesis of antimicrobial peptides in neurons and microglia. *J Immunol* 181, 1083-1095 (2008)

165. Carroll, M. C.: A protective role for innate immunity in systemic lupus erythematosus. *Nat Rev Immunol* 4 (Oct), 825-831 (2004)

166. Baruah, P., Simpson, E., Dumitriu, I. E., Derbyshire, K., Coe, D. and etal: Mice lacking C1q or C3 show accelerated rejection of minor H disparate skin grafts and resistence to inducation of tolerance. *Eur J Immunol* 40 (6), 1758-1767 (2010)

167. Lien, Y. H. H., Lai, L. W. and Silva, A. L.: Pathogenesis of renal ischmia/reperfusion injury: lessons from knockout mice. *Life Sci* 74, 543-552 (2003)

168. Griffiths, M. R., Gasque, P. and Neal, J. W.: The multiple role of the innate immune system in the regulation of apoptosis and inflammation in the brain. *J Neuropathol Exp Neurol* 68 (3), 217-226 (2009)

169. Munoz, L. E., Lauber, K., Schiller, M., Manfredi, A. A. and Hermann, M.: The role of defective clearance of apoptotic cells in systemic autoimmunity. *Nat Rev Rheumatol* 6 (5), 280-289 (2010)

170. O'Brien, B. A., Geng, X., Orteu, C. A., Huang, Y., Ghoreishi, M., Zhang, Y. Q., Bush, J. A., Li, G., Finegood, D. T. and Dutz, I. P.: A deficiency in the *in vivo* clearance of apoptotic cells is a feature of the NOD mouse. *J Autoimm* 104 (2), 104-115 (2006)

171. Carroll, M. C.: The role of complement and complement receptors in induction and regulation of immunity. *Ann Rev Immunol* 16, 545-568 (1998)

172. Dempsey, P. W. and Fearon, D. T.: Complement: instructing the acquired immune system through the CD21/CD19 complex. *Res Immunol* 147 (2), 71-75 (1996)

173. Dempsey, P. W., Allison, M. E., Akkaraju, S., Goodnow, C. C. and Fearon, D. T.: C3d of complement as a molecular adjuvant: bridging innate and acquired immunity. *Science* 271 (5247), 348-350 (1996)

174. Stager, S., Alexander, J., Kirby, A. C., Botto, M. and etal: Natural antibodies and complement are endogenous adjuvants for vaccine-induced CD8+ T cell responses. *Nat Med* 9 (10), 1287-1292 (2003)

175. Holers, V. M. and Kulik, L.: Complement receptor 2, natural antibodies and innate immunity: Inter-relationships in B cell selection and activation. *Mol Immunol* 44, 64-72 (2007)

176. Gonzalez, S. F., Jayasekera, J. P. and Carroll, M. C.: Complement and natural antibody are required in the long-term memory response to influenza virus. *Vaccine* 26 (sup8), I 85-93 (2008)

177. Kemper, C. and Atkinson, J. P.: T-cell regulation: with complements from innate immunity. *Nat Rev Immunol* 7 (Jan), 9-18 (2007)

178. Jima, D. D., Shah, R. N., Orcutt, T. M., Joshi, D., Law, J. M., Litman, G. W., Trede, N. S. and Yoder, J. A.: Enhanced transcription of complement and coagulation genes in the absence of adapative immunity. *Mol Immunol* 46 (7), 1505-1516 (2009)

179. Blajchman, M. A. and Ozge-Anwar, A. H.: The role of the complement system in hemostasis. *Prog Hemat* XIV, 149-182 (1986)

180. DeLaCadena, P. A., Wachtfogel, Y. T. and Colman, R. W. Ch 11: Contact activation pathway: Inflammation and coagulation. In: Colman R, Hirsh J, Marder VJ, Salzman EW, eds. Hemostasis and Thrombosis. Philadelphia: J B Lippincott, pp. 219-240, 1994.

181. Lupia, E., DelSorbo, L., Bergerone\, S., Emanuelli, G. and etal: The membrane attack complex of complement contributes to plasmin-induced synthesis of platelet activating factor by endothelial cells and neutrophils. *Immunology* 109 (4), 557-563 (2003)

182. Scarisbrick, I. A., Linbo, R., Vandell, A. G., Keegan, M., Blaber, S. I., Blaber, M., Sneve, D., Lucchinetti, C. F., Rodriguez, M. and Diamandis, E. P.: Kallikreins are associated with secondary progressive multiple sclerosis and promote neurodegeneration. *Biol Chem* 389 (6), 739-745 (2008)

183. Cugno, M., Zanichelli, A., Foieni, F., Caccia, S. and Cicardi, M.: C1-inhibitor deficiency and angioedema: molecular mechanisms and clinical progress. *Trends Mol Med* 15 (2), 69-78 (2009)

184. Bossi, F., Bulla, R. and Tedesco, F.: Endothelial cells are a target of both complement and kinin system. *Int Immunopharmacol* 8 (2), 143-147 (2008)

185. vanderLinden, P. W., Hack, C. E., Eerenberg, A. J., Struyvenberg, A. and vanderZwan, J. K.: Activation of the contact system in insect-sting anaphylaxis: association with the development of angioedema and shock. *Blood* 82 (6), 1732-1739 (1993)

186. Girgis, N. M., Dehaven, B. C., Fan, X., Viner, K. M., Shamim, M. and Isaacs, S. N.: DUPE = 1707; these authors = 1236; the cited ref is not Girgis but = 1707. *J Immunol* 180 (9), 6307-6315 (2008)

187. Ritis, K., Doumas, M., Mostellos, D. and etal: A novel C5a receptor-tissue factor cross-talk in neutrophils links innate immunity to coagulation pathways. *J Immunol* 177 (7), 4794-4802 (2006)

188. Redecha, P., Tilley, R., Tencati, M., Salmon, J. E. and etal: Tissue factor: a link between C5a and neutrophil activation in antiphospholipid antibody induced fetal injury. *Blood* 110 (7), 2423-2431 (2007)

189. VanDePoel, R. H. L., Meijers, J. C. M. and Bouma, B. N.: C4b-binding protein inhibits the factor V-dependent but not the factor V-independent cofactor activity of protein S in the activated protein C-mediated inactivation of factor VIIIa. *Thromb Haemost* 85, 761-765 (2001)

190. Kohn, M.: VT study dissociates C4BP from protein S (Editorial on Buil *et al*, p4644-50) *Blood* 115 (23), 4623-4624 (2010)

191. VanDeWouwer, M., Plaisance, S., DeVries, A., Waelkens, E. and etal: The lectin-like domain of thrombomodulin interferes with complement activation and protects against arthritis. *J Thromb Haemost* 4 (8), 1813-1824 (2006)

192. Wang, L., Tran, N. D., Kittaka, M., Fisher, M. J., Schreiber, S. S. and Zlokovic, B. V.: Thrombomodulin expression in bovine brain capillaries: Anticoagulant function of the blood-brain barrier, regional differences, and regulatory mechanisms. *Arterioscler Thromb Vasc Biol* 17, 3139-3146 (1997)

193. Ryu, J. K., Davalos, D. and Akassoglou, K.: Fibrinogen signal transduction in the nervous system. *J Thromb Haemost* Supl 1 (Jul 7), 151-154 (2009)

194. Taoka, Y., Okajima, K., Uchiba, M. and Masayoski, J.: Neuroprotection by recombinant thrombomodulin. *Thromb Haemost* 83, 462-468 (2000)

195. Tei, R., Kaido, T., Nakase, H. and Sakaki, T.: Protective effect of C1 esterase inhibitor on acute traumatic spinal cord injury in the rat. *Neurol Res* 30 (7), 761-767 (2008)

196. Sims, P. J. Interaction of human platelets with the complement system (Ch 18) In: Kunicki TJ, George JN, eds. Platelet Immunobiology. Philadelphia, PA: J B Lippincott, pp. 354-383, 1989.

197. Houle, J. J., Leddy, J. P. and Rosenfeld, S. I.: Secretion of the terminal complement proteins C5-C9 by human platelets. *Clin Immunol Immunopath* 50, 385-393 (1989)

198. Peerschke, E. I., Yin, W. and Ghebehiwet, B.: Platelet mediated complement activation. *Adv Exp Med Biol* 632, 81-91 (2008)

199. Festoff, B. W., Smirnova, I. V. and Citron, B. A.: Thrombin, its receptor and protease nexin I, its potent serpin, in the nervous system. *Semin Thromb Hemost* 22 (3), 267-271 (1996)

200. Bornsen, L., Khademi, M., Olsson, T., Sorensen, P. S. and Sellebjerg, F.: Osteopontin concentrations are increased in cerebrospinal fluid during attacks of multiple sclerosis. *Mult Scler* epub preprint (2010)

201. Christensen, B., Schack, L., Kianing, E. and Sorensen, E. S.: Osteopontin is cleaved at multiple sites close to its integrin-binding motifs in milk and is a novel substrate for plasmin and cathepsin D. *J Biol Chem* 285 (11), 7929-7937 (2010)

202. Chinata, K. and Yoshikawa, M.: Food intake regulation by central complement system. *Adv Exp Med Biol* 632, 35-48 (2008)

203. MacLaren, R., Cui, W. and Cianflone, K.: Adipokines and the immune system: an adipocentric view. *Adv Exp Med Biol* 632, 1-21 (2008)

204. Baciu, I.: Nervous control of the phagocytic system. *Int J Neurosci* 41 (1-2), 127-141 (1988)

205. Ulloa, L.: The vagus nerve and the nicotinic anti-inflammatory pathway. *Nat Rev Drug Discov* 4 (8), 673-684 (2005)

206. Sternberg, E. M.: Neural regulation of innate immunity: a coordinated nonspecific host response to pathogens. *Nat Rev Immunol* 6 (Apr), 318-328 (2006)

207. Rosas-Ballina, M. and Tracey, K. J.: Colinergic control of inflammation. *J Intern Med* 265 (5), 663-679 (2009)

208. Flierl, M. A., Rittirsch, D., Sama, J. V., Huber-Lang, M. and War, P. A.: Adrenergic regulation of complement-induced acute lung injury. *Adv Exp Med Biol* 632, 93-103 (2008)

209. Yuzaki, M.: Cb1n and C1q family proteins: new transneuronal cytokines. *Cell Mol Life Sci* 65 (11), 1698-1705 (2008)

210. Sehic, E. C., Li, S., Ungar, A. L. and Blatteis, C. M.: Complement reduction impairs the febrile response of guinea pigs to endotoxin. *Am J Physiol* 274 (6,Prt2), R 1594-1603 (1998)

211. Sehic, E. C. and Blatteis, C. M.: Blockade of lipopolysaccharide-induced fever by subdiaphragmatic vagotomy in guinea pigs. *Brain Res* 726 (1-2), 160-166 (1996)

212. Kawai, T. and Akira, S.: Toll-like receptors and RIG-1-like receptor signalling. *Ann NY Acad Sci* 1143, 1-20 (2008)

213. Millard, A., Spirig, R., Mueller, N. J., Seebach, J. D. and Rieben, R.: Inhibition of direct and indirect TLR-mediated activation of human NK cells by low molecular wqeight dextran sulfate. *Mol Immunol* 47, 2349-2358 (2010)

214. Liu, P. T., Stenger, S., Li, H., Wenzel, L. and etal: Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response. *Science* 311 (Mar24), 1770-1773 (2006)

215. Hong, M. H., Jin, C. H., Saito, T., Ishimi, Y., Abe, E. and Suda, T.: Transcriptional regulation of the production of the third component of complement (C3) by 1 alpha,25-hydroxy vitamin D3, in mouse marrow-derived stromal cells (ST2) and primary osteoblastic cells. *Endocrinology* 129 (5), 2774-2779 (1991)

216. Chiavolini, D., Weir, S., Murphy, J. R. and Wetzler, L. M.: Neisseria meningitidis PorB, a Toll-like receptor 2 ligand, improves the capacity of Francisella tularensis lipopolysaccharide to protect mice against experimental tularemia. *Clin Vaccine Immunol* 15 (9), 1322-1329 (2008)

217. Zhang, X., Kimura, Y., Fang, C., Zhou, L., Sfyroera, G., Labris, J. D., Wetsel, B. A., Miwa, T. and Song, W. C.: Regulation of Toll-like receptor-mediated inflammatory response by complement *in vivo*. *Blood* 110, 228-236 (2007)

218. Pettigrew, H. D., Teuber, S. S. and Gershwin, M. E.: Clinical significance of complement deficiencies. *Ann N Y Acad Sci* 1173, 108-123 (2009)

219. Welsch, J. A. and Ram, S.: Factor H and Neisserial pathogenesis. *Vaccine* 265 (Supl 8), I 40-45 (2008)

220. Tedesco, F.: Inherited complement deficiencies and bacterial infections. *Vaccine* 26-S, 13-18 (2008)

221. Orihuela, C. J., Mahdavi, J., Thornton, J., Mann, B. and etal: Laminin receptor initiates bacterial contact with the blood brain barrier in experimental meningitis models. *J Clin Invest* 119 (6), 1638-1646 (2009)

222. Marx, J.: A clearer view of macular degeneration. *Science* 311 (Mar24), 1704-1705 (2006)

223. Gold, B., Merriam, J. E., Zernant, J., Hancox, L. S. and etal: Variation in factor B (BF) and complement component 2 (C2) genes is associated with age-related macular degenerationq. *Nat Genet* 38 (4), 458-462 (2006)

224. Patel, M. and Chan, C. C.: Immunopathological aspects of age-related macular degeneration. *Sem Immunopathol* 30, 97-110 (2008)

225. Nussenblatt, R. B., Liu, B. and Li, Z.: Age-related macular degeneration: an immunologically driven disease. *Curr Opin Investig Drugs* 10 (5), 434-442 (2009)

226. Graus, Y. M. and DeBaets, M. H.: Myasthenia gravis: an autoimmune response against the aceylcholine receptor. *Immunol Res* 12 (1), 78-100 (1993)

227. Liu, A., Lin, H., Liu, Y., Cao, X., Wang, X. and Li, Z.: Correlation of C3 level with severity of generalized myasthenia gravis. *Muscle Nerve* 40 (5), 801-808 (2009)

228. Heckmann, J. M., Uwimpuhwe, H., Ballo, R., Kaur, M., Bajic, V. B. and Prince, S.: A functional SNP in the regulatory region of the decay accelerating factor gene associates with extraocular muscle paresis in myasthenia gravis. *Genes Immunol* 11 (1), 1-10 (2010)

229. Soltys, J., Kusner, L. L., Young, A., Richmonds, C., Hatala, D., Gong, B., Shanmugavel, V. and Kaminsky, H. J.: Novel complement inhibitor limits severity of experimentally myasthenia gravis. *Ann Neurology* 65 (1), 67-75 (2009)

230. Sheng, J. R., Li, L. C., Prabhakar, B. S. and Meriggioli, M. N.: Acetylcholine receptor-alpha subunit expression in myasthenia gravis: a role for the autoantigen in pathogenesis? *Muscle Nerve* 40 (2), 279-286 (2009)

231. Graus, Y. M., Verschuuren, J. J., Spaans, F. and etal: Age-related resistence to experimental autoimmune myasthenia gravis in rats. *J Immunol* 150 (9), 4093-3103 (1993)

232. Veerhuis, R., Boshuizen, R. S. and Familian, A.: Amyloid associated proteins in Alzheimer's and prion diseases (and Editorial pg 221) *Curr Drug Targets CNS Neurol Disord* 4 (3), 235-248 (2005)

233. McGeer, P. L., Akiyama, H., Itagaki, S. and McGeer, E. G.: Immune system response in Alzheimer's disease. *Can J Neurol Sci* 16 (Supl4), 516-527 (1989)

234. McGeer, P. L. and McGeer, E. G.: The possible role of complement activation in Alzheimer's disease. *Trends Mol Med* 6 (11), 519-523 (2002)

235. Rodgers, J., Cooper, N. R., Webster, S., Schultz, J., McGeer, P. L., Styren, S. D., Civin, W. H., Brachova, L., Brady, B., Ward, P. and Lieberburg, I.: Complement activation by beta-amyloid in Alzheimer disease. *PNAS USA* 89, 10016-10020 (1992)

236. Salminen, A., Ojala, J., Kauppinen, A., Kaarniranta, K. and Suuronen, T.: Inflammation in Alzheimer's disease: amyloid-beta oligomers trigger innate immunity defense via pattern recognition receptors. *Prog Neurobiol* 87 (3), 181-194 (2009)

237. Lambert, J. C., Heath, S., Even, G., Campion, D., Sleegers, K., Hiltunen, M., Combarros, O., Zelenika, D., Bullido, M. J., Tavernier, B., Letenneur, L., Hiltunen, M. and etal: Genome-wide association study identifies variants at CLU and CR1 associated with Alzheimer's disease (with editorial pg 1047-8, "Beyond APOE") *Nature Genetics* 41 (10), 1094-1099 (2009)

238. Consortium: Meta-analysis confirms CR1, CLU, and PICALM as Alzheimer disease risk loci and revealas interaction with APOE genotype. *arch Neurol* Pre-pub (2010)

239. Harold, D., Abraham, R., Hollingworth, P., Sims, R., Gerrish, A., Hamshere, M. L., Pahwa, J. S., Moskvina, V., Dowzell, K., Williams, A., Jones, N., Thomas, C. and etal: Genome-wide association study identifies variants at CLU and PICALM associated with Alzheimer's disease *Nat Genetics* 41 (10), 1088-1093 (2009)

240. Flaschabart, F., Caliebe, A., Nothnagel, M., Kleindorp, R., Nikolaus, S., Schreiber, S. and Nebel, A.: Depletion of potential A2M risk haplotype for Alzheimer's disease in long-lived individuals. *Eur J Hum Genet* 18 (1), 59-61 (2010)

241. Holmes, C., Cunningham, C., Zotova, E., Woolford, J., Dean, C., Kerr, S., Culliford, D. and Perry, V. H.: Systemic inflammation and disease progression in Alzheimer disease. *Neurology* 73 (10), 768-774 (2009)

242. Emmerling, M. R., Watson, M. D., Raby, C. A. and Spieger, K.: The role of complement in Alzheimer's disease pathology. *Biochim Biophys Acta* 1502 (1), 158-171 (2000)

243. Erlich, P., Dumestre-Perard, C., Ling, W. L., Lemaire-Vieille, C. and etal: Complement protein C1q forms a complex with with cytotoxic prion protein oligomers. *J Biol Chem* 285 (25), 19267-19276 (2010)

244. Woodruff, T. M., Constantini, K. J., Taylor, S. M. and Noakes, P. G.: Role of complement in motor neuron disease: animal models and therapeutic potential of complement inhibitors. *Adv Exp Med Biol* 632, 143-158 (2008)

245. Chiu, I. M., Pfatman, H., Kuligowski, M., Tapia, J. C., Carrasco, M. A., Zhang, M., Maniatis, T. and Carroll, M. C.: Activation of innate and humoral immunity in the peripheral nervous system of ALS transgenic mice. *PNAS USA* 106 (49), 20960-20965 (2009)

246. Ciz, M., Komrskova, D., Pracharova, L., Okenkova, K., Cizova, H., Moravcova, A., Jancinova, V., Petrikova, M., Lojek, A. and Nosal, R.: Serotonin modulates the oxidative burst of human phagocytes via various mechansisms. *Platelets* 18 (8), 583-590 (2007)

247. Pinter, C., Beltrami, S., Caputo, D., Ferrante, P. and Clivio, A.: Presence of autoantibodies against complement regulatory proteins in relapsing-remitting multiple sclerosis. *J Neurovirol* 6 (supl2), S 42-46 (2000)

248. Cassiani-Ingoni, R., Greenstone, H. L., Donati, D., Fogdell-Hahn, A., Martinelli, E., Refai, D., Martin, R., Berger, E. A. and Jacobson, S.: CD46 on glial cells can function as a receptor for viral glyco-protein-mediatred cell-cell-fusion. *Glia* 52 (3), 252-258 (2005)

249. Nielsen, T., Rostgaard, K. and etal: Effects of infectious mononucleosis and HLA-DRB1*15 in multiple sclerosis. *Mult Scler* 15 (4), 431-436 (2009)

250. Ferndando, M. M., Stevens, C. R., Walsh, E. C., DeJager, P. L., Goyette, P., Plenge, R. M., Vyse, T. J. and Rioux, J. D.: Defining the role of the MHC in autoimmunity: a review and pooled analysis. *PLoS Genet* 4 (4), e1000024 (2008)

251. Ingram, G., Hakobyan, S., Robertson, N. P. and Morgan, B. P.: Complement in multiple sclerosis: its role in disease and potential as a biomarker. *Clin Exp Immunol* 155 (2), 128-139 (2009)

252. Piddlesden, S. J., Lassmann, H., Zimprich, F., Morgan, B. P. and Linington, C.: The demyelinating potential of antibodies to myelin oligodedrocyte glycoprotein is related to their ability to fix complement. *Am J Pathol* 143 (2), 555-564 (1993)

253. Li, H., Mei, Y., Wang, Y. and Xu, L.: Vasoactive intestinal peptide suppressed experimental autoimmune encepalomyelitis by inhibiting T helper-1 responses. *J Clin Immunol* 26 (5), 430-437 (2006)

254. Zein, N. E., Badran, B. and Sariban, E.: VIP differentially activates beta2 integrins, CR1, and matrix metalloproteinase-9 in human monocytes through

cAMP/PKA, and PI-3K signaling pathways via VIP receptor type 1 and FPRL1. *J Leukoc Biol* 83 (4), 972-981 (2008)

255. Pappaworth, I. Y., Kulik, L., Haluszczak, C., Reuter, J. W., Holers, V. M. and Marchbank, K. J.: Increased B cell deletion and significantly reduced auto-antibody titre due to premature expression of human complement receptor 2 (CR2, CD21) *Mol Immunol* 46 (6), 1042-1049 (2009)

256. Egg, R., Reindl, M., Deisenhammer, F., Linington, C. and Berger, T.: Anti-MOG and anti-MBP antibody subclasses in multiple sclerosis. *Multiple Sclerosis* 7, 285-289 (2001)

257. Bidot, C. J., Horstman, L. L., Jy, W., Jimenez, J. J., BidotJr, C., Ahn, Y. S., Alexander, J. S., Gonzalez-Toledo, E., Kelley, R. E. and Minagar, A.: Clinical and neuroimaging correlates of antiphospholipid antibodies in multiple sclerosis. *JCM Neurol* 7, 36 (2007)

258. Johnson, A. M., Alper, C. A., Rosen, F. S. and Craig, J. M.: C1 inhibitor: evidence for decreased hepatic synthesis in hereditary angioneurotic edema. *Science* 173 (Aug6), 553-554 (1971)

259. Axelsson, U. and Laurell, A. B.: A case of angioneurotic aedema with a high content of non-functioning, double peaked C1 esterase inhibitor. *Clin Exp Immunol* 8 (3), 511-566 (1971)

260. Zuraw, B. L.: Hereditary angioedema. *New Engl J Med* 359 (10), 1027-1036 (2008)

261. Mukeba, D., Chandrikakumari, K., Giot, J. B., Leonard, P. and etal: Autoimmune angioneurotic edema in a patient with Helicobacter pylori infection. *Helicobacter* 14 (1), 9-11 (2009)

262. Cugno, M., Castelli, R. and Cicardi, M.: Angioedema due to acquired C1-inhibitor deficiency: a bridging condition between autoimmunity and lymphoproliferation. *Autoimmun Rev* 8 (2), 156-159 (2008)

263. Blanch, A., Roche, O., Urrutia, I., Gamboa, P., Fontan, G. and Lopez-Trascasa, M.: First case of homozygous C1 inhibitor decificiency (with editorial pg 1327-9) *J Allergy Clin Immunol* 118 (6), 1330-1335 (2006)

264. Bork, K., Wulff, K., Hardt, J., Witzke, G. and Staubach, P.: Hereditary angioedema caused by missense mutations in the factor XII gene: clinical features, trigger factors, and therapy. *J Allergy Clin Immunol* 124 (1), 129-134 (2009)

265. DavisIII, A. E., Cai, S. and Liu, D.: C1 inhibitor: biologic activities that are independent of protease inhibition. *Immunobiology* 212 (4-5), 313-323 (2007)

266. Thorgersen, E. B., Ludviksen, J. K., Lambris, J. D. and etal: Anti-inflammatory effects of C1-inhibitor in porcine and human whole blood are independent of its protease inhibition activity. *Innate Immun* Aug (Epub Preprint), 1-11 (2009)

267. Kagiyama, A., Savage, H. E., Michael, L. H., Hanson, G., Entman, M. L. and Rossen, R. D.: Molecular basis of complement activation in ischemic myocardium: Identification of the specific molecules of mitochondrial origin that bind human C1q and fix complement. *Circ Res* 64, 607-615 (1989)

268. Semb, A. G., Vaage, J., Sorlie, D., Lie, M. and Mjos, O. D.: Coronary trapping of a complement activation product (C3a desArg) during myocardial reperfusion in open-heart surgery. *Scand J Thorac Cardiovasc Surg* 24 (3), 223-227 (1990)

269. Collard, C. D., Vakeva, A., Bukusoglu, C., Zund, G., Sperati, C. J., Colgan, S. P. and Stahl, G. L.: Reoxygenation of hypoxis human umbilical vein endothelial cells activates the classic complement pathway. *Circulation* 96, 326-333 (1997)

270. Bishop, M. J., Giclas, P. C., Guidotti, S. M. and etal: Complement activation is a secondary rather than a causative factor in rabbit pulmonary artery ischemia / reperfusion injury. *Am Rev Resp Dis* 143 (2), 386-390 (1991)

271. Rosse, W. F.: Phosphatidylinositol-linked proteins and paroxysmal nocturnal hemoglobinuria (Review) *Blood* 75 (8), 1595-1601 (1990)

272. Almeida, A. M., Murakami, Y., Layton, D. M., Hillmen, P., Selleck, G. S. and etal: Hypomorphic promoter mutations in PIGM causes inherited clycosyl phosphatidyl inositol deficiency. *Nat Med* 12 (7), 846-851 (2006)

273. Samadder, N. J., Casaubon, L., Silver, F. and Cavalcant, R.: Neurological complications of paroxysmal nocturnal hemoglobinuria. *Can J Neurol Sci* 34 (3), 368-371 (2007)

274. Rosse, W. F. and Ware, R. E.: The molecular basis of paroxysmal nocturnal hemoglobinura. *Blood* 86 (9), 3277-3286 (1995)

275. VanL:andingham, J. W., Cekic, M., Cutler, S., Hoffman, S. W. and Stein, D. G.: Neurosteroids reduce inflammation after TBI through CD55 induction. *Neurosci Lett* 425 (2), 94-98 (2007)

276. Bellander, B., Olafsson, I. H., Ghatan, P. H., Skejo, H. P. B., Hansson, L., Wanacek, M. and Svensson, M. A.: Secpondary insults following traumatic brain injury enhance complement activation in the human brain and release of the tissue damage marker S100B. *Acta Neurochir* E Pub Preprint August (2010)

277. Leinhase, I., Rozanski, M., Harhausen, D., Thurman, J. M., Schmidt, O. I., Hosini, A. M., Taha, M. E., Rittirsch, D., Ward, P. A., Holers, V. M., Ertel, W. and Stahel, P. E.: Inhibition of the alternative complement activation pathway

in traumatic brain injury by a monoclonal anti-factor B antiobdy: a randomized placebo-controlled study in mice. *J Neuroinflammation* 4 (13), 1-12 (2007)

278. Yager, P. H., You, Z., Qin, T., Kin, H. H., Takahashi, K., Ezekowitz, A. B., Stahl, G. L., Carroll, M. C. and Whalen, M. J.: Mannose binding lectin gene deficiency increases susceptibility to traumatic brain injury in mice. *J Cereb Blood Flow Metab* 28 (5), 1030-1039 (2008)

279. Xi, G., Hua, Y., Keep, R. F., Younger, J. G. and Hoff, J. T.: Systemic complement depletion diminishes perihematomal brain edema in rats. *Stroke* 32, 162-167 (2001)

280. Nguyen, H. X., Galvan, M. D. and Anderson, A. J.: Characterization of early and terminal complement proteins associated with polymorphonuclear leukocytes *in vitro* and *in vivo* after spinal cord injury. *J Neuroinflammation* 25 (5), 1-13 (2008)

281. Tasi, H. M.: The molecular biology of thrombotic microangiopathy. *Kidney Int* 70 (1), 16-23 (2006)

282. Yamamoto, T., Satomura, K., Okada, S. and Ozono, K.: Risk factors for neurological complications in complete hemolytic uremic syndrome caused by Escherichia coli O157. *Pediatr Int* 51 (2), 216-219 (2009)

283. McCrae, K. R. and Cines, D. Thrombotic thrombocytopenic purpura and hemolytic uremic syndrome (Ch 128) In: Hoffman R, Benz EJ, Shattil SJ, Furie B, Cohen HJ, Silberstein LE, McGlave P, eds. Hematology: Basic Principles and Practice (3rd Ed'n) Philadelphia: Elsevier, Churchill, Livingstone, pp. 2126-2137, 2000.

284. Lofling, J. C., Paton, A. W., Varki, N. M., Paton, J. C. and Varki, A.: A dietary non-human sialic acid may facilitate hemolytic uremic syndrome. *Kidney Int* 76 (2), 140-144 (2009)

285. Orth, D., Khan, A. B., Naim, A., Grif, K. and etal: Shiga toxin activates complement and binds factor H: evidence for an active role of complement in hemolytic uremic syndrome. *J Immunol* 182 (10), 6394-6400 (2009)

286. Ling, L., Katz, Y., Schlesinger, M., Carmi, R. and etal: Complement factor H gene mutation associated with autosomal recessive atypical hemolytic uremic syndrome. *Am J Hum Genet* 65 (6), 1538-1546 (1999)

287. Nilsson, S. C., Kalchishkova, N., Trouw, L. A. and etal: Mutations in complement factor I as found in atypical hemolytic uremic syndrome lead to either altered secretion or altered function of factor I. *Eur J Immunol* 40, 172-185 (2009)

288. Stahl, A. L., Kristoffersson, A., Olin, A. I., Olsson, M. L. and etal: A novel mutation in the complement regulator clusterin in recurrent hemolytic uremic syndrome. *Mol Immunol* 46 (11-12), 2236-2243 (2009)

289. Jozsi, M., Strobel, S., Dahse, H. M., Liu, W. S., Hoyer, P. F., Oppermann, M., Skerka, C. and Zipfel, P. F.: Anti-factor H autoantibodies block C-terminal recognition function of factor H in hemolytic uremic syndrome. *Blood* 110 (5), 1516-1518 (2007)

290. Skerka, C., Jozsi, M., Zipfel, P. F. and etal: Autoantibodies in haemolytic uremic syndrome (HUS) (Theme issue; see editorial pg 225) *Thromb Haemost* 101 (2), 227-232 (2009)

291. Moore, I., Strain, L., Pappworth, I. and etal: Association of factor H autoantibodies with deletions of CFHR1, CFHR3, CFHR4 and with mutations in CFH, CFI, CD46, and C3 in patients with hemolytic uremic syndrome. *Blood* 115, 379-387 (2010)

292. Tsai, H. M., Li, A. and Rock, G.: Inhibitors of von Willebrand factor-cleaving protease in thrombotic thrombocytopenic purpura. *Clin Lab* 47, 387-392 (2001)

293. Dong, J. F., Moake, J. L., Nolasco, L., Bernardo, A., Arceneaux, W., Shrimpton, C. N., Schade, A. J., McIntire, L. V., Fujikawa, K. and Lopez, J. A.: ADAMTS-13 rapidly cleaves newly secreted ultralarge von Willebrand factor multimers on the endothelial surface under flowing conditions. *Blood* 100, 4033-4039 (2002)

294. Garvey, M. B. and Freedman, J.: Complement in thrombotic thrombocytopenic purpura. *Am J Hematol* 15, 397-398 (1983)

295. Ren, G., Hack, B. K., Cunningham, P. N., Alexander, J. J., Haas, M. and Quigg, R. J.: A complement-dependent model of thrombotic thrombocytopenic purpura induced by antibodies reactive with endothelial cells. *Clin Immunol* 103 (1), 43-53 (2002)

296. Ruiz-Torres, M. P., Casiraghi, F., Galbusera, M., Macconi, D., Gastoldi, S., Todeschini, M., Porrati, F., Belotti, D., Pogliani, E. M., Noris, M. and Remuzzi, G.: Complement activation: the missing link between ADAMTS-13 deficiencty and microvascular thrombosis of thrombotic microangiopathies. *Thromb Haemost* 93 (3), 443-452 (2005)

297. Rock, G., Chauhan, K., Jamieson, G. A. and Tandon, N. N.: Anti-CD36 antibodies in patients with lupus anticoagulant and thrombotic complications. *Br J Haematol* 88, 878-880 (1994)

298. Schultz, D. A., Arnold, P. I., Jy, W., Valant, P., Gruber, J., Ahn, Y. S., Mao, F. W. and Horstman, L. L.: Anti-CD36 autoantibodies in thrombotic thrombocytopenic purpura and other thrombotic disorders: identification of an 85kd form of CD36 as a target antigen. *Br J Hematol* 103, 849-857 (1998)

299. Scheiflinger, F., Knobl, P., Trattner, B., Plaimauer, B., Mohr, G., Dockal, M., Dorner, F. and Rieger, M.: Nonneutralizing IgM and IgG antibodies to von Wilebrand factor cleaving protease (ADAMTS-13) in a patient with thrombotic thrombocytopenic purpura. *Blood* 102 (9), 3241-3243 (2003)

300. Praprotnik, S., Blank, M., Levy, Y., Tavor, S. and etal: Anti-endothelial cell antibodies from patients with thrombotic thrombocytopenic purpura specifically activate small vessel endothelial cells. *Int Immunol* 13 (2), 203-210 (2001)

301. Kotzin, B. L.: Systemic lupus erythematosus. *Cell* 85, 303-306 (1996)

302. Cervera, R., Kamashta, M. A. and Hughes, G. R. V.: The Euro-lupus project: epidemiology of systemic lupus erythematosus in Europe. *Lupus* 18, 869-874 (2009)

303. Mills, J. A.: Systemic lupus erythematosus. *N Engl J Med* 330 (26), 1871-1879 (1994)

304. Douglas, K. B., Windels, D. C., Zhao, J., Gadeliya, A. V. and etal: Complement receptor 2 polymorphisms associated with systemic lupus erythematosus modulate alternative splicing. *Genes Immunol* 10 (5), 457-469 (2009)

305. Douglas, M. C., Lamberg, S. I., Loincz, A. L., Good, R. A. and Day, N. K.: Lupus erythematosus-like syndrome with a family deficiency of C2. *Arch Dermatol* 112 (5), 671-674 (1976)

306. Wild, J. H., Zvaifler, N. J., Muller-Eberhard, H.-J. and Wilson, C. B.: C3 metabolism in a patient with deficiency of the second component of complement (C2) and discoid lupus erythematosus. *Clin Exper Immunol* 24 (2), 238-248 (1976)

307. Moser, K. L., Kelly, J. A., Lessard, C. J. and Harley, J. B.: Recent insights into the genetic basis of systemic lupus erythematosus. *Genes Immunity* 10, 373-379 (2009)

308. Castro, J., Balada, E., Ordi-Ros, J. and Vilardell-Tarres, M.: The complex immunogenetic basis of systemic lupus erythematosus. *Aurtoimmune Rev* 7 (5), 345-351 (2008)

309. Lood, C., Gullstrand, B., Truedsson, L., Olin, A. I., Alm, G. V., Ronnblom, L., Sturfelt, G., Eloranta, M. L. and Bengtsson, A. A.: C1q inhibits immune complex-induced interferon-alpha production in plasmacytoid dentritic cells: a novel link between C1q deficiency and systemic lupus erythematosus pathogenesis. *Arthritis Rheum* 60 (10), 3081-3090 (2009)

310. Javierre, B. M., Fernandez, A. F., Richter, J. and etal: Changes in the pattern of DNA methylation associate with twin discordance in systemic lupus erythematosus. *Genome Res* Epub Preprint (Dec) (2009)

311. DeGiorgio, L. A., Konstantinov, K. N., Lee, S. C. and etal: A subset of lupus anti-DNA antibodies cross-reacts with NR2 glutamate receptor in systemic lupus erythematosus (with commentary pg 1175-6) *Nat Med* 7 (11), 1189-1193 (2001)

312. Zandman-Goddard, G., Berkun, Y., Barzilia, O., Boaz, M., Blank, M., Ram, M., Sherer, Y., Anaya, J. M. and Shoenfeld, Y.: Exposure to Epstein-Barr virus infection is associated with mild systemic lupus erythematosus disease. *Ann N Y Acad Sci* 1173, 658-663 (2009)

313. Goldblatt, F., Yuste, J., Isenberg, D. A., Rahman, A. and Brown, J.: Impaired C3b/iC3b deposition on Streptococcus pheumoniae in serum from patients with systemic lupus eryhematosus. *Rheumatology* 48 (12), 1498-1501 (2009)

314. Navratil, J. S., Manzi, S., Kao, A. H., Krishnaswami, S., Liu, C. C., Ruffing, M. J., Shaw, P. S., Nilson, A. C., Dryden, E. R., Johnson, J. J. and Ahearn, J. M.: Platelet C4d is highly specific for systemic lupus erythematosus. *Athritis Rheum* 54 (2), 670-674 (2008)

315. Shoenfeld, Y., Meroni, P. L. and Toubi, E.: Antiphospholipid syndrome and systemic lupus erythematosus: are they separate entities or just clinical presentations on the same scale? *Curr Opin Rheumatol* 21 (5), 495-500 (2009)

316. Hughes, G. R. V.: The antiphospholipid syndrome and 'multiple sclerosis' (with editorial, pg 109-15) *Lupus* 8 (2), 89 (1999)

317. Ijdo, J. W., Conti-Kelly, A. M., Greco, P., Abedi, M., Amos, M., Provenzale, J. M. and Greco, T. P.: Anti-phospholipid antibodies in patients with multiple sclerosis and MS-like illnesses: MS or APS? *Lupus* 8, 109-115 (1999)

318. Horstman, L. L., Jy, W., Bidot, C. J., Ahn, Y. S., Kelley, R. E., Zivadinov, R., Maghzi, A. H., Etemadifar, M., Mousavi, A. S. and Minagar, A.: Antiphospholipid antibodies: Paradigm in transition. *J Neuroinflammation* 6 (3), 1-21 (2009)

319. Giannakopoulos, Passam, F., Rahgozar, S. and Krilis, S. A.: Current concepts on the pathogenesis of the antiphospholipid syndrome. *Blood* 109, 422-430 (2007)

320. Shoenfeld, Y.: Etiology and pathogenetic mechanisms of the anti-phosphospholipid syndrome unraveled. *Trends Immunol* 24 (1), 2-4 (2003)

321. Avalos, I. and Tsokos, G. C.: The role of complement in the antiphospholipid syndrome-associated pathology. *Clin Rev Allergy Immunol* 36 (2-3), 141-144 (2009)

322. Munakata, Y., Saito, T., Mutsada, K., Seino, J., Shibata, S. and Sasoki, T.: Detection of complement-fixing antiphospholipid antibodies in associated with thrombosis. *Thromb Haemost* 83, 728-731 (2000)

323. Ornoy, A., Matalon, S. Y. T., Blank, M., Blumenfeld, Z., Miller, R. K. and Shoenfeld, Y.: The effects of antiphospholipid antibodies obtained from women with SLE/APS and associated pregnancy loss on rat embryos and placental explants in culture. *Lupus* 12, 573-578 (2003)

324. Salmon, J. E. and Girardi, G.: Antiphospholipid antibodies revisited: A disorder initiated by inflammation

(Theodore E Woodward Award) *Trans Am Clin Climatol Assoc* 118, 99-114 (2007)

325. Lynch, A. M., Gibbs, R. S., Murphy, J. R., Byers, T., Neville, M. C., Giclas, P. C., Salmon, J. E., VanHecke, T. M. and Holers, V. M.: Complement activation fragment Bb in early pregnancy and spontaneous preterm birth (with editorial pg 327-8) *Am J Obset Gynecol* 199 (4), 354.e351-358 (2008)

326. Lynch, A. M., Murphy, J. R., Byers, T., Gibbs, R. S., Neville, M. C., Gicias, P. C., Salmon, J. E. and Holers, V. M.: Alternative complement pathway activation fragment Bb in early pregnancy as a predictor of preeclampsia. *Am J Obstet Gynecol* 199 (4), 385 (e381-389) (2008)

327. Ahn, Y. S., Horstman, L. L., Jy, W., Jimenez, J. J. and Bowen, B.: Vascular dementia in patients with immune thrombocytopenic purpura (ITP) *Thromb Res* 107, 337-344 (2002)

328. Harrington, W. J., Minnich, V., Hollingsworth, J. W. and Moore, C. V.: Demonstration of a thrombocytopenic factor in the blood of patients with thrombocytopenic purpura. *J Lab Clin Med* 38, 1-10 (1951)

329. Winiarski, J. and Holm, G.: Platelet associated immunoglobulins and complement in idiopathic thrombocytopenic purpura. *Clin Exp Immunol* 53, 201-207 (1983)

330. Hegde, U. M., Bowes, A. and Roter, B. L. T.: Platelet associated complement components (PAC3c and PAC3d) in patients with autoimmune thrombocytopenia. *Brit J Haem* 60, 49-55 (1985)

331. Lehman, H. A., Lehman, L. O., Rustagi, P. K., Rustagi, R. N., Plunkett, R. W., Farolino, D. L., Conway, J. and Logue, G. L.: Complement mediated autoimmune thrombocytopenia. N Engl J Med 316 (4), 194-198 (1987)

332. Jy, W., Horstman, L. L., Lin, A., Bidot-Jr, C. and Ahn, Y. S.: Elevated Complement (C) and IgG Bound Microparticles (MP) in Immune Thrombocytopenic Purpura (ITP) and Hemolytic Anemia (HA) Blood, Ab#1313 (2009)

333. Sims, P. J., Rollins, S. A. and Wiedmer, T.: Regulatory control of complement on blood platelets: Modulation of platelet procoagulant responses by a membrane inhibitor of the C5b-9 complex. J Biol Chem 264 (32), 19228-19235 (1989)

334. Biro, E., Nieuwland, R., Tak, P. P., Pronk, M., Schaap, M. C. L., Sturk, A. and Hack, C. E.: Activated complement components and complement activated molecules on the surface of cell-derived microparticles in patients with rhrumatoid arthritis and healthy individuals. *Ann Rheum Dis* 66, 1085-1092 (2008)

335. Cies, C. P. and Maas, S.: Conserved recoding RNA editing of vertebrate C1q-related factor C1QL1. *FEBS Lett* 583 (7), 1171-1174 (2009)

336. Saxena, K., Kitzmiller, K. J., Wu, Y. L., Zhou, B., Esack, N. and etal: Great genotypic and phenotypic diversities associated with copy-number variations of complement C4 and RP-C4-CYP21-TNX (RCCX) modules: A comparison of Asian-Indian and European American populations. *Mol Immunol* 46 (7), 1289-1303 (2009)

337. Lachmann, P. J. and Smith, R. A.: Taking complement to the clinic - has the time finally come? (Editorial) *Scand J Immunol* 69 (6), 471-478 (2009)

338. Nilsson, B., Ekdahl, K. N., Mollnes, T. E. and Lambriss, J. D.: The role of complement in biomaterial-induced inflammation. *Mol Immunol* 44, 87-94 (2007)

339. Wagner, E. and Frank, M. M.: Therapeutic potential of complement modifiers. *Nat Rev Drug Discov* 9 (Jan), 43-56 (2010)

340. Perasidis, A.: Complement inhibitors. *Nat Biotech* 16 (Sep), 882-883 (1998)

341. Liszewski, M. K. and Atkinson, J. P.: Novel complement inhibitors. *Expert Opin Investig Drugs* 7 (3), 323-331 (1998)

342. Brodsky, R. A., Young, N. S., Antolioli, E. and etal: Multicenter phase 3 study of the complement inhibitor eculizumab for the treatjment of parazoysmal nocturnal hemoglobinuria. *Blood* 111, 1840-1847 (2008)

343. Hill, A., Hillman, P., Richards, S. J. and etal: The complement inhibitor eculizumab in paroxysmal nocturnal hemoglobinuria. *New Engl J Med* 355 (Sep21), 1233-1243 (2006)

344. Sahu, A., Morikis, D. and Labris, J. D.: Compstatin, a peptide inhibitor of complement, exhibits species-specific binding to complement component C3. *Mol Immunol* 39 (10), 557-566 (2008)

345. Ricklin, D. and Lambris, J. D.: Compstatin: a complement inhibitor on its way to clinical application. *Adv Exp Med Biol* 632, 273-292 (2008)

346. Mollnes, T. E., Brekke, O. L., Fung, M., Fure, H., Christiansen, D., Bergstein, G., Videm, V., Lappegard, K. T., Kohl, J. and Lambris, J. D.: Essential role of the C5a receptor in E coli-induced oxidative bursr and phagocytosis revealed by a novel lepirudin-based human whole blood model. *Blood* 100 (5), 1869-1877 (2002)

347. Markiewski, M. M. and Lambris, J. D.: Unwelcome complement. *Cancer Res* 69 (16), 6367-6370 (2009)

348. Jacobson, A. C., Weis, J. J. and Weis, J. H.: CD21 signaling via C3 regulates Purkinje cell protein 4 (Pcp4) expression. *Mol Immunol* 46 (7), 1488-1493 (2009)

349. Barrington, R. A., Schneider, T. J., Pitcher, L. A. and etal: Uncoupling CD21 and CD19 of the B cell coreceptor. *PNAS USA* 106 (34), 14490-14495 (2009)

350. Proctor, L. M., Woodruff, T. M., Sharma, P., Shiels, I. A. and Taylor, S. M.: Transdermal pharmacology of small molecule cyclic C5a antagonists. *Adv Exp Med Biol* 586, 329-345 (2006)

351. Li, Q., Nacion, K., Bu, H. and Lin, F.: The complement inhibitor FUT-175 suppresses T cell autoreactivity in experimental autoimmune encephalomyelitis. *Am J Pathol* 175 (2), 661-667 (2009)

352. Vogel, C. W. and Fritzinger, D. C.: Humanized cobra venom factor: Experimental therapeutics for targeted complement activation and complement depletion. *Curr Pharm Des* 13 (28), 16-26 (2007)

353. Liu, D., Lu, F., Qin, G., Fernandes, S. M., Li, J. and Davis, A. E.: C1 inhibitor-mediated protection from sepsis. *J Immunol* 179 (6), 3966-3972 (2007)

354. Beinrohr, L., Dobo, J., Zavodszky, P. and Gal, P.: C1, MBL-MASPs and C1-inhibitor: novel approaches for targeting complement-mediated inflammation. *Trends Mol Med* 14 (12), 511-521 (2008)

355. Weisman, H. F., Bartowe, T., Leppo, M. K., MarchJr, H. C., Roux, K. H., Weisfeldt, M. L. and Fearon, D. T.: Soluble human complement receptor type 1: inhibitor of complement suppressing post-ischemic myocardial inflammation and necrosis. *Science* 249, 146-151 (1990)

356. Eror, A. T., Stojadinovic, A., Starnes, B. W., Macrides, S. C., Tsokos, G. C. and Shea-Donohue, T.: Antiinflammatory effects of soluble complement receptor type1 promote rapid recovery of ischemia / reperfusion injury in rat small intestine. *Clin Immunol* 90 (2), 266-275 (1999)

357. Shandelya, S. M., Kuppusamy, P., Herskowitz, A., Weisfeldt, M. L. and Zweier, J. L.: Soluble complement receptor type 1 inhibits the complement pathway and prevents contractile failure in the post-ischemic heart: Evidence that complement activation is required for neutrophil-mediated reperfusion injury. *Circulation* 88 (6), 2812-2826 (1993)

358. Huang, J., Kim, L. J., Mealey, R., Marsh, H. C., Zhang, Y., Tenner, A. J., Connolly, E. S. and Pinsky, D. J.: Neuronal protection in stroke by in sLex-glycosylated complement inhibitory protein. *Science* 285, 595-599 (1999)

359. Jha, P. and Kolwal, G. J.: Vaccinia complement control protein: multi-functional protein and a potential wonder drug. *J Biosci* 28 (3), 265-271 (2003)

360. Ghberemariam, Y. T., Odunuga, O. O., Janse, K. and Kotwal, G. J.: Humanized recombinant vaccinia virus complement control protein (hrVCP) with three amino acid changes, H98Y, E102K, and E120K, creating an additional putative heparin binding site, is 100-fold more active than rVCP in blocking both classical and alternative complement pathways. *Ann N Y Acad Sci* 1056 (Nov), 113-122 (2005)

361. Girgis, N. M., Dehaven, B. C., Fan, X., Viner, K. M., Shamim, M. and Isaacs, S. N.: Cell surface expression of the vaccinia virus complement control protein is mediated by interaction with the viral A56 protein and protects infectected cells from complement attack. *J Virol* 82 (9), 4205-4214 (2008)

362. Liszewski, M. K., Leung, M. K., Hauhart, R., Fang, C. J., Bertram, P. and Atkinson, J. P.: Smallpox inhibitor of complement enzymes (SPICE): dissecting functional sites and abrogating activity. *J Immunol* 183 (5), 3150-3159 (2009)

363. Okroj, M., Mark, L., Stokowska, A., Wong, S. W., Rose, N., Blackbourn, D. J. and Etal: Characterization of the complement inhibitory function of rhesus rhadinovirus complement control protein (RCP) *J Biol Chem* 284 (1), 505-514 (2008)

364. Blom, A. M., Mark, A. L. and Spiller, O. B.: Viral heparin-binding complement inhibitors - a recurring theme. *Adv Exp Med Biol* 598, 105-125 (2007)

365. Hostetter, M. K.: The iC3b receptor of Candida albicans and its roles in pathogenesis. *Vaccine* 26 (sup8), I 8-12 (2008)

366. Zipfel, P. F.: Complement and immune defense: from innate immunity to human diseases. *Immunology Letters* 126, 1-7 (2009)

367. Rossmann, E., Kraiczy, P., Herzherger, P., Skerka, C. and etal: Dual binding specificity of a Borrelia hermsii-associarted complement regulator-acquiring surface protein for factor H and plasminogen discloses a putative virulence factor of relapsing fever spirochetes. *J Immunol* 178, 7292-7301 (2007)

368. Kunert, A., Losse, J., Gruszin, C., Huhn, M. and Etal: Immune evasion of the human pathogen Pseudomonas areuginosa: Elongation factor Tuf is a factor H and plasminogen binding protein. *J Immunol* 179 (2979-2988) (2007)

369. Rooijakkers, S. H. M., vanWamel, W. J. B., Ruyken, M., vanKessel, P. M. and etal: Anti-opsonic properties of staphylokinase. *Microbes Infect* 7, 476-484 (2005)

370. Zipfel, P. F., Hallstrom, T., Hammerschmidt, S. and Skerka, C.: The complement fitness factor H: role in human diseases and for immune escape of pathogens like pneumocci. *Vaccine* 26 (Sup8), 167-174 (2008)

371. Brockman, M. A. and Knipe, D. M.: Herpes virus as a tool to define the role of complement in the immune response to peripheral infection. *Vaccine* 26 (Sup8), I 94-99 (2008)

372. Avirutnan, P., Mehlhop, E. and Diamond, M. S.: Complement and its role in protection and pathogenesis of flavivirus infections. *Vaccine* 26 (Sup8), I100-107 (2008)

373. Stetson, D. B.: Connection between antiviral defense and autoimmunity. *Curr Opin Immunol* 241 (3), 244-250 (2009)

374. Rehwinkel, J. and eSousa, C. R.: RIGorous detection: Exposing virus through RNA sensing. *Science* 327 (Jan15), 284-286 (2010)

375. Cantorna, M. T.: Vitamin D and multiple sclerosis: an update. *Nutr Rev* 66 (10sup2), S135-S138 (2008)

376. Myhr, K. M.: Vitamin D treatment in multiple sclerosis. *J Neurol Sci* 286 (1-2), 104-108 (2009)
377. Nino, M., Fukazawa, T., Kikuchi, S. and Sasaki, H.: Therapeutic potential of vitamin D for multiple sclerosis. *Curr Med Chem* 15 (5), 499-505 (2008)

378. Smolders, J., Damoiseaux, J., Menheere, P. and Hupperts, R.: Vitamin D as an immune modulator in multiple sclerosis, a review. *J Neuroimmunol* 194 (1-2), 7-17 (2008)

379. Holick, M. F.: Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular diseas. *Am J Clin Nutr* 80 (Supl), S 1678-1688 (2004)

380. Cannell, J. J., Viete, R., Umhau, J. C., Hollick, M. F. and etal: Epidemic influenza and vitamin D. *Epidemiol Infect* 134 (6), 1129-1140 (2006)

381. Gombart, A. F., Borregaard, N. and Koeffler, H. P.: Human cathelicidin antimicrobial peptide (CAMP) gene is a direct target of the vitamin D receptor and is strongly u-regulated in myeloid cells by 1,25-dihydroxy vitamin D3. *FASEB J* 19 (9), 1067-1077 (2005)

382. Cutolo, M. and Otsa, K.: Review: vitamin D, immunity and lupus. *Lupus* 17 (1), 6-10 (2008)

383. Cutolo, M., Otsa, K., Uprus, M., Paolino, S. and Seriolo, B.: Vitamin D in rheumatoid arthritis. *Autoimmune Rev* 7 (1), 59-64 (2007)

384. Haddad, J. G.: Plasma vitamin D-binding protein (Gc-globulin): multiple tasks. *J Steroid Biochem Mol Biol* 53 (1-6), 579-582 (1995)

385. Trujillo, G. and Kew, R. R.: Platelet-derived thrombospondin-1 is necessary for the vitamin D-binding protein (Gc-globulin) to function as a chemotactic cofactor for C5a. *J Immunol* 173 (6), 4130-4136 (2004)

386. Zhang, J. and Kew, R. R.: Identification of a region in the vitamin D-binding protein that mediates its C5a chemotactic cofactor function. *J Biol Chem* 279 (51), 53282-53287 (2004)

387. Gressner, O., Meier, U., Hillebrandt, S., Wasmuth, H. E. and etal: Gc-globulin concentrations and C5 haplotype-tagging polymorphisms contribute to variations in serum activity of complement factor C5. *Clin Biochem* 40 (11), 771-775 (2007)

388. Bouillon, R., Carmeliet, G., Verlinden, L., vanEtten, E. and etal: Vitamin D and human health: lessons from vitamin D receptor null mice. *Endocr Rev* 29 (6), 726-776 (2008)

389. Tsukamoto, H., Nagasawa, K., Ueda, Y. and etal: Effects of cell differentiation on the synthesis of the third and fourth component of complement (C3, C4) by the human monocytic cell line U937. *Immunology* 77 (4), 621-623 (1992)

390. Creemers, P. C., DuToit, E. D. and Kriel, J.: DBP (vitamin D binding protein) and BF (properdin factor B) allele distribution in Namibian San and Khoi and in other South African Populations. *Gene Geogr* 9 (3), 185-189 (1995)

391. Zipplies, J. K., Hauck, S. M., Schoeffmann, S., Amann, B. and etal: Serum PEDF levels are decreased in a spontaneous animal model for human autoimmune uveitis. *J Proteome Res* 8 (2), 992-998 (2009)

392. Rithidech, K. N., Honikel, L., Milazzo, M., Madigan, D., Troxell, R. and Krupp, L. B.: Protein expression profiles in pediatric multiple sclerosis: potential biomarkers. *Mult Scler* 15 (4), 455-464 (2009)

393. Roach, I. T., Rebres, R. A., Fraser, I. D., Decamp, D. L., Lin, K. M., Sternweis, P. C., Simon, M. I. and Seaman, W. E.: Signaling and cross-talk by C5a and UDP in macrophages selectively use PLC beta3 to regulate intracellular free calcium. *J Biol Chem* 283 (25), 17351-17361 (2008)

394. Weiler, J. M., Edens, R. E., Linhardt, R. J. and Kapelanksi, D. P.: Heparin and modified heparin inhibit complement activation *in vivo*. *J Immunol* 148, 3210-3215 (1992)

395. Salzman, E. W., Hirsh, J. and Marder, V. J. Clinical use of heparin (Ch 83) In: Colman R, Hirsh J, Marder VJ, Salzman EW, eds. Hemostasis and Thrombosis. Philadelphia: J B Lippincott, pp. 1584-1591, 1994.

396. Lindahl, U., Lidholt, K., Spillman, D. and Kjellen, L.: More to "heparin" than anticoagulation. *Thromb Res* 75, 1-32 (1994)

397. Ludwig, R. J.: Therapeutic use of heparin beyond anticoagulation. *Curr Drug Discov Technol* 6 (4), 281-289 (2009)

398. Gorski, A., Wasik, M., Nowaczyk, M. and Korczak-Kowalska, G.: Immunomodulating activity of heparin. *FASEB J* 5, 2287-2291 (1991)

399. Ludwig, R. J., Alban, S. and Boehncke, W. H.: Structural requirements of heparin and related molecules to exert a multitude of anti-inflammatory activities. *Mini Rev Med Chem* 6 (9), 1009-1029 (2006)

400. Saito, A. and Munakata, H.: Analysis of plasma proteins that bind to glycosaminoglycans. *Biochim Biophys Acta* 1770 (2), 241-246 (2007)

401. Volpi, N., Cusmano, M. and Venturelli, T.: Qualitative and quantitative studies of heparin and chondroitin sulfates in normal human plasma. *Biochim Biophys Acta* 1243 (1), 49-58 (1995)

402. Urbanyi, Z., Forrai, E., Sarvan, M., Liko, I., Illes, J. and Pazmany, T.: Glycosaminoglycans inhibit neurodegenerative effecrts of serum amyloid P component *in vitro*. *Neurochem Int* 46 (6), 471-477 (2005)

403. Kilgore, K. S., Tanhehco, K. B. N. J., Park, J. L., Booth, E. A., Washington, R. A. and Lucchesi, B. R.: The semisynthetic polysaccharide pentosan polysulfate prevents complement-mediated myocardial injury in the rabbit perfused heart. *J Pharmacol Exp Ther* 285 (3), 987-994 (1998)

404. Spring, R., vanKooten, G., Obregon, C., Nicod, L., Daha, M. and Rieben, R.: The complement inhibitor low molecular weight dextran sulfate prevents TLR4-induced phenotypic and functional maturation of human dendritic cells. *J Immunol* 181 (2), 878-890 (2008)

405. Mannari, D., Liu, C., Hughes, D. and Mehta, A.: The role of heparin in alleviating complement-mediated acute intravascular hemolysis. *Acta Haematol* 119 (3), 166-168 (2008)

406. Dendrinos, S., Sakkas, E. and Makrakis, E.: Low-molecular-weight heparin versus intravenous immunoglobulin for recurrent abortion associated with antiphospholipid antibody syndrome. *Int J Gynaecol Obstet* 104 (3), 223-225 (2009)

407. Oberkersch, R., Attorresi, A. and Calabrese, G. C.: Low-molecular weight heparin inhibition in classicial complement activation pathway during pregnanacy. *Thromb Res* Epub Preprint (2009)

408. Murray-Rust, T. A., Kerr, F. K., Thromas, A. R., Wu, T., Yongqoing, T. and etal: Modulation of the proteolytic activity of complement protease C1s by polyanions: implications for polyanion-mediated acceleration of interaction between C1s and SERPING1. *Biochem J* 422 (2), 295-303 (2009)

409. Beinrohr, L., Harmat, V., Dobo, J., Lorincz, Z., Gal, P. and Zavodsky, R.: C1 inhibitor serpin domain structure reveals the likely mechanism of heparin potentiation and conformational disease. *J Bio Chem* 282 (29), 21100-21109 (2007)

410. Vorup-Jensen, T., Chi, L., Gjelstrup, L. C. and etal: Binding between the integrin alphaXbeta2 (CD11c/CD18) and heparin. *J Biol Chem* 282 (42), 30869-30877 (2007)

411. Ferreira, V. P., Herbert, A. P., Cortes, C., McKee, K. A. and eta;: The binding of factor H to a complex of physiological polyanions and C3b on cells is impaired in atypical hemolytic uremic syndrome. *J Immunol* 182 (11), 7009-7011 (2009)

412. Black, S. C., Gralinski, M. R., Friedrichs, G. S., Kilgore, K. S., Driscoll, E. M. and Luchesi, B. R.: Cardioprotective effects of heparin or N-acetylheparin in an *in vivo* model of myocardial ischaemic and reperfusion injury. *Cardiovasc Res* 29, 629-636 (1995)

413. Hua, Y., Xi, G., Keep, R. F. and Hoff, J. T.: Complement activation in the brain after experimental intracerebral hemorrhage. *J Neurosurg* 92 (6), 1016-1022 (2000)

414. Calabrese, G. C., Alberto, M. F., Tubio, R., Marani, M. M., Frandandez, M. E. and etal: A small fraction of dermatan sulfate with significantly increased anticoagulant activity was selected by interaction with the first complement protein. *Thromb Res* 3-4 (243-250) (2004)

415. Thourani, V. H., Brar, S. S., Kennedy, T. P., Thornton, L. R., Watts, J. A., Ronson, R. S. and EtAl: Nonanticoagulant heparin inhibits NF-kappaB activation and attentuates myocardial reperfusion injury. *Am J Physiol Heart Circ Physiol* 278 (6), H2084-2093 (2000)

416. Groth, I., Grunewald, N. and Alban, S.: Pharmacological profiles of animal and nonanimal-derived sulfated polysaccharides - comparison of unfractionated heparin, the semisynthetic glucan sulfate PS3, and the sulfated polysaccharide fraction isolated from Delesseria sanguinea. *Glycobiology* 19 (4), 408-417 (2009)

417. Klegeris, A., Singh, E. A. and McGeer, P. L.: Effects of C-reactive protein and pentosan polysulfate on human complement activation. *Immunology* 106 (3), 381-388 (2002)

418. Fazekas, F., Lublin, F. D., Li, D., Freedman, M. S. and al, e.: Intravenous immunoglobulin in relapsing remitting multiple sclerosis (& see letters, v72:2134; v73:1077), . *Neurology* 71 (265-271) (2008)

419. Bayry, J., Lacroix-Desmazes, B. J. and Kaveri, S. V.: Novel therapeutic strategies for multiple sclerosis: potential of intravenous immunoglobulins. *Nat Rev Drug Discov* 8 (7), 594-595 (2009)

420. McDaneld, L. M., Fields, J. D., Bourdet, D. M. and Bhardwaj, A.: Immunomodulatory therapies in neurological critical care. *Neurocrit Care* 12 (1), 132-143 (2010)

421. Zandman-Goddard, G., Blank, M. and Shoenfeld, Y.: Intravenous immunoglobulins in systemic lupus erythematosus: from the bench to the bedside. *Lupus* 18 (10), 884-888 (2009)

422. Arnson, Y., Shoenfeld, Y. and Amital, H.: Intravenous immunoglobulin therapy for autoimmune diseases. *Autoimmunity* 42 (6), 653-660 (2009)

423. Durandy, A., Kaveri, S. V., Kuijpers, T. W., Basta, M., Miescher, S., Ravetch, J. B. and Rieben, R.: Intravenous immunoglobulins - understanding properties and mechanisms. *Clin Exp Immunol* 158 (Sup1), 2-13 (2009)

424. Crow, A. R., Brinc, D. and Lazarus, A. H.: New insight into the mechanism of action of IVIgG: the role of

dendritic cells. *J Thriomb Haemost* 7 (sup1), 245-248 (2009)
425. Hommes, O. R., Haas, J., Soelberg-Sorenson, R. and Friedrichs, M.: IVIG trials in MS: Is albumin a placebo? *J Neurology* 256 (2), 268-270 (2009)

426. Lopez-Diego, R. S. and Weiner, H.: Novel therapeutic strategies for multiple sclerosis - a muli-faceted adversary. *Nat Rev Drug Discov* 7 (Nov), 909-925 (2008)

427. Hurez, V., Kazatchkine, M. D., Vassilev, T., Ramanathan, S., Pashov, A., Basuyaux, B., deKozak, Y., Bellon, B. and Kaveri, S. V.: Pooled normal human polyspecific IgM contains neutralizing anti-idiotypes to IgG autoantibodies of autoimmune patients and protects from experimental autoimmune disease. *Blood* 90 (10), 4004-4013 (1997)

428. Hoffmann, J. N., Fertmann, J. M., Vollmar, B., Laschke, M. W., Jauch, K. W. and Menger, M. D.: Immunoglobulin M-enriched human intravenous immunoglobulins reduce leukocyte-endothelial cell interactions and attenuate microvascular perfusion failure in normotensive endotoxemia. *Shock* 29 (1), 133-139 (2008)

429. Rieben, R., Roos, A., Muizert, Y., Tinguel, C., Gerritsen, A. F. and Daha, M. R.: Immunoglobulin M-enriched human intravenous immunoglobulin prevents complement activation *in vitro* and *in vivo* in a rat model of acute inflammation. *Blood* 93 (3), 942-951 (1999)

430. Walpen, A. J., Laumonier, T., Aebi, C., Mohacsk\i, P. J. and Rieben, R.: Immunoglobulin M-enriched intravenous immunoglobulin inhibits classical pathway complement activation, but not bactericidal activity of human serum. *Xenotransplant* 11 (2), 141-148 (2004)

431. Adib, M., Ragimbeau, J., Avrameas, S. and Ternynck, T.: IgG autoantibody activity in normal mouse serum is controlled by IgM. *J Immunol* 145 (11), 3807-3813 (1990)

432. Jerne, N. K.: Towards a network theory of the immune system. *Ann Immunol (Inst, Pasteur)* 125C, 373 (1974)

433. Behn, U.: Idiotypic networks: Toward a renaissance. *Immunol Rev* 216, 142-152 (2007)

434. Gilles, J. G. G., Vanzieleghem, B. and Saint-Remy, J. M. R.: Natural autoantibodies and anti-idiotypes. *Sem Thromb Haemost* 26 (2), 151-155 (2000)

435. Menshikov, I. and Beduleva, L.: Evidence in favor of a role of idiotypic network in autoimmune hemolytic anemia induction: theoretical and experimental studies. *Int J Immunol* 20 (2), 193-198 (2007)

436. Cheng, H. M.: Antibodies to anionic phospholipids in normal human, rabbit, and mouse sera. *Thromb Res* 66, 461-462 (1992)

437. Kra-Oz, Z., Lorber, M., Shoenfeld, Y. and Scharff, Y.: Inhibitor (s) of natural anti-cardiolipin antibodies. *Clin Exp Immunol* 93, 265-268 (1993)
438. McIntyre, J. A., Wagenknecht, D. R. and Triplett, D. A.: Detection of antiphospholipid antibodies in heat inactivated and normal human sera. *Thromb Res* 69, 489-490 (1993)

439. Cabiedes, J., Cabral, A. R. and Alarcon-Segovia, D.: Detection of anticardiolipin antibodies in heat-inactivated normal human sera is not influenced by beta-2-glycoprotein-I. *Thromb Res* 72, 471-472 (1993)

440. Cabiedes, J., Cabral, A. R., Lopez-Mendoza, A. T., Cordero-Esperon, H. A., Huerta, M. T. and Alarcon-Segovia, D.: Characterization of anti-phosphatidylcholine polyreactive natural autoantibodies from normal human subjects. *J Autoimm* 18 (2), 181-190 (2002)

441. Matsuda, J., Tsukamoto, M., Saitoh, N., Gochi, K. and Kinoshita, K.: Absence of anticardiolipin antibody in non-treated and heat-inactivated normal human sera. *Thromb Res* 68, 441-442 (1992)

442. Pan, Z. J., Andersaon, C. J. and Stafford, H. A.: Anti-idiotypic antibodies prevent the serologic detection of antiribosmal P autoantibodies in healkthy adults. *J Clin Invest* 102, 215-222 (1998)

443. Stahl, D., Lacroix-Desmazes, S., Heudes, Mouthon, L., Kaveri, S. V. and Kazatchkine, M. D.: Altered control of self-reactive IgG by autologous IgM in patients with warm autoimmune hemolytic anemia. *Blood* 95 (1), 328-335 (2000)

444. Gyorgy, B., Tothfalusi, L., Nagy, G. and etal: Natural autoantibodies reactive with glycosaminoglycans in rheumatoid arthritis. *Arthritis Res Ther* 10 (5), R110 (2008)

445. Pozsony, E., Gyorgy, B., Berki, T. and etal: HLA-association of serum levels of natural antibodies. *Mol Immunol* 46 (7), 1416-1423 (2009)

446. Bieber, A. J., Warrington, A. and Pease, L. R.: Humoral immunity as a mediator of CNS repair. *Trends Neurosci* 11 (Supl 1), S 39-44 (2001)

447. Warrington, A. E., Bieber, A. J., Ciric, B., Pease, L. R., VanKeulen, V. and Rodriguez, M.: A recombinant human IgM promotes myelin repair after a single very low dose. *J Neurosci Res* 85 (5), 967-976 (2007)

448. Wright, B. R., Warrington, A. B., Edberg, D. E. and Rodriguez, M.: Cellular mechanisms of central nervous system repair by natural autoreactive monoclonal antibodies. *Arch Neurool* 66 (12), 1456-1459 (2009)

449. Liu, C. C., Walsh, C. M. and Young, J. D. E.: Perforin: structure and function. *Immunol Today* 16 (4), 194-201 (1995)

450. Baran, K., Dunstone, M., Chia, J., Ciccone, A., Browne, K. A. and etal: The molecular basis for perforin oligomerization and transmembrane pore assembly (with perspective by E Podack pg 668-70) *Immunity* 30 (5), 668-695 (2009)

451. Howe, C. L., Adelson, J. D. and Rodriguez, M.: Absence of perforin confers axonal protection despite demyelination. *Neurobiol Dis* 25 (2), 354-359 (2007)

452. Deb, C., Lafrance-Corey, R. G., Zoecklein, L., Papke, L., Rodriguez, M. and Howe, C. L.: Demyelinated axons and motor function are protected by genetic deletion of perforin in a mouse model of multiple sclerosis. *J Neuropathol Exp Neurol* 68 (9), 1037-1048 (2009)

453. Meri, S., Morgan, B. P., Wing, M., Jones, J., Davies, A., Podack, E. and Lachmann, P. J.: Human protectin (CD59), an 18-20-kD homologous complement restriction factor, does not restrict perforin-mediated lysis. *J Exp Med* 172 (Jul), 367-370 (1990)

454. Rodriguez, M.: Effectors of demyelination and remyelination in the CNS: implications for multiple sclerosis. *Brain Pathol* 17 (2), 219-229 (2007)

455. Warrington, A. E. and Rodriguez, M.: Remyelination-promoting human IgMs: developing a therapeutic reagent for demyelinating disease. *Curr Top Microbiol Immunol* 318, 213-239 (2008)

456. Rodriguez, M., Warrington, A. E. and Pease, L. R.: Invited article: Human natural autoantibodies in the treatment of neurological disease. *Neurology* 72 (14), 1269-1276 (2009)

457. Schwartz-Albiez, R., Monteiro, R. C., Rodriguez, M., Binder, C. J. and Shoenfeld, Y.: Natural antibodies, intravenous immunoglobulin and their role in autoimmunity, cancer and inflammation. *Clin Exp Immunol* 158 (S-1), 43-50 (2009)

458. Cid, C., Alvaerez-Cermeno, J. C., Salinas, M. and Alcazar, A.: Anti-heat shock protein 90beta antibodies decrease pre-oligodendrocyte population in perinatal and adult cell cultures: Implications for remyelination in multiple sclerosis. *J Neurochem* 95, 349-360 (2005)

459. Weerth, S. H., Rus, H., Shin, M. L. and Raine, C. S.: Complement C5 in experimental autoimmune encephalomyelitis (EAE) facilitates remyelination and prevents gliosis. *Am J Pathol* 163, 1069-1080 (2003)

460. Zhang, M., Alicot, E. M. and Carroll, M. C.: Human natural IgM can induce ischemia / reperfusion injury in a murine intestinal model. *Mol Immunol* 45 (15), 4036-4039 (2008)

461. Zhang, M. and Carroll, M. C.: Natural antibody mediated innate autoimmune response. *Mol Immunol* 44 (1-3), 103-110 (2007)

462. Zhang, M. and Carroll, M. C.: Natural IgM-mediated innate autoimmunity: A new target for early intervention of ischemia-reperfusion injury. *Expert Opin Biol Ther* 7 (10), 1576-1582 (2007)

463. Pinckard, R. N., Olson, M. S., Kelley, R. E., DeHeer, D. H., Palmer, J. D., O'Rourke, R. A. and Goldfein, S.: Antibody independent activation of human C1 after interaction with heart subcellular membranes. *J Immunol* 110 (5), 1376-1382 (1973)

464. Pinckard, R. N., Olson, M. S., Giclas, P. C., Terry, R., Boyer, J. T. and O'Rourke, R. A.: Consumption of classical complement components by heart subcellular membranes *in vitro* and in patients after acute myocardial infarction. *J Clin Invest* 56, 740-750 (1975)

465. Carroll, M. C.: The complement system in regulation of adaptive immunity. *Nat Immunol* 5 (10), 981-986 (2004)

466. Carroll, M. C.: Complement and humoral immunity. *Vaccine* 26 (sup8), I 28-33 (2008)

467. Tardif, M., Brouchon, L., Rablet, M. J. and Boulay, F.: Direct binding of a fragment of the Wiskott-Aldrich syndrome protein to the C-terminal end of the anaphylatoxin C5a receptor. *Biocehm J* 372 (Prt2), 453-463 (2003)

468. Ramesh, N. and Geha, R.: Recent advances in the biology of WASP and WIP. *Immunol Res* 44, 99-111 (2009)

469. Park, I. Y., Scherbina, A., Rosen, F. S., Proteus, A. B. and Reynold-O'Donnell, E.: Phenotypic perturbation of B cells in the Wiskott-Aldrich syndrome. *Clin Exp Immunol* 139, 297-305 (2005)

470. Pulccio, J., Tagliani, E., Scholer, A., Prete, F., Fetler, L., Burrone, O. R. and Benvenuti, F.: Expression of Wiskot-Aldrich syndrome protein in dendritic cells regulates synapse formation and activation of naive CD8+ T cells. *J Immunol* 181, 1135-1142 (2008)

471. Bosticardo, M., Marangoni, F., Aiuti, A., Villa, A. and Roncarolo, M. G.: Recent advances in understanding the pathophysiology of Wiscott-Aldrich syndrome. *Blood* 113 (25), 6288-6295 (2009)

472. Shoenfeld, Y. and Mozes, E.: Pathogenic idiotypes of autoantibodies in autoimmunity: lessons from new experimental models of SLE. *FASEB J* 4, 2646-2651 (1990)

473. McGuire, K. L. and Holmes, D. S.: Role of complementary proteins in autoimmunity: an old idea re-emerges with a new twist. *Trends Immunol* 26 (7), 367-372 (2005)

474. Johnson, P. M. and Smalley, H. B.: Idiotypic interactions between rheumatoid factors and other antibodies. *Scand J Rheumatol Suppl* 75 ( ), 93-96 (1988)

475. Su, J., Hua, X., Concha, H., Svenumgsson, E., Cederholm, A. and Frostegard, J.: Natural antibodies against phosphorylcholine as potential protective factors in SLE. *Rheumatology* 47 (8), 1144-1150 (2008)

476. Quan, C. P., Quan, C. P., Watanabe, S., Pamonsinlapatham, P. and Bouvet, J. P.: Different dysregulations of the natural antibody repertoire in treated and untreated HIV-1 patients. *J Autoimm* 17, 81-87 (2001)

477. Escher, R., Vogel, M., Escher, G., Miescher, S., Stadler, B. M. and Berchtold, P.: Recombinant anti-idiotypic antibodies inhibit human natural anti-glycoproten (GP) IIb/IIIa autoantibodies. *J Autoimm* 18, 71-81 (2002)

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