[Frontiers in Bioscience 13, 6472-6482, May 1, 2008]

Angiogenesis and inflammation in carotid atherosclerosis

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1. ABSTRACT

Carotid atherosclerosis is a leading cause of cerebrovascular events. The control of cardiovascular risk factors, i.e. tabacco smoking, alcohol abuse, hypertension, dyslipidemia, diabetes and obesity proved to reduce number of fatal and non-fatal strokes but failed to prevent important number of them. Screening of individuals at high risk of symptomatic vascular disease for biomarkers helped to identify some of them. However, as disease is by its nature multifocal, global testing for biomarkers may have limited practical application. New imaging techniques, including direct visualization of artery metabolism, by PET, has brought new tools for study of local progression and metabolic activity of individual atherosclerotic lesions. Advances in molecular biology helped to identify inflammatory genes and its strong link to angiogenesis. The later, is thought to play a key role in the transformation to unstable plaque. Studies of the complex role that plays angiogenesis in plaque development will help in future to design effective therapies addressed at the individual cell level. The purpose of the review is to bring new insights into complicated pathophysiology of carotid atherosclerosis.

2. EPIDEMIOLOGY OF STROKE

Ischemic stroke is the equivalent of a heart attack and is produced when blood flow is obstructed by a blood clot moving to the brain or by narrowing of an extracranial (carotid) or intracranial blood vessel. The brain loses its energy supply, tissue damage occurs and patients develop stroke. Annually, 15 million people worldwide suffer a stroke. Of these, 5 million die and another 5 million are left permanently disabled, placing a burden on family and community. The absolute number of strokes continues to increase because of the ageing population. Over 300 risk factors have been associated with coronary heart disease and stroke. A substantial number of strokes can be attributed to modifiable risk factors: tobacco smoking, high blood pressure, diabetes, high blood lipids, obesity and alcohol abuse. Unhealthy diets increase the risk of dying from coronary heart disease and cerebrovascular disease 2–3 fold. Physical inactivity is another main risk factor which increases an individual risk to have cardiovascular disease. Non-modifiable risk factors include sex and gender, excess homocysteine in blood, inflammation, abnormal blood coagulation and unknown genetic factors waiting to be identified (1-6).

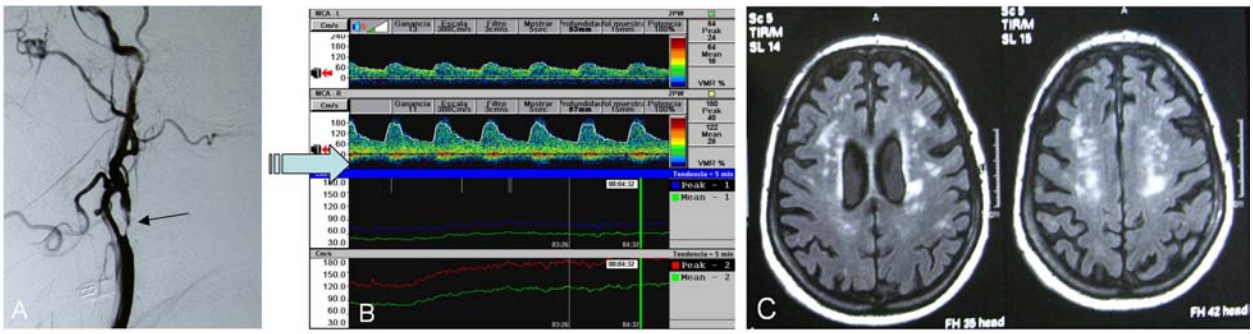

Figure 1. (A) Carotid angiography showing significant stenosis of left internal carotid artery (arrow). In 20-30% of patients suffering from cerebral infarction there is a significant carotid artery stenosis. (B) Impaired vasomotor reactivity in patients with carotid stenosis shown on transcranial ultrasonography. (C) MRI-FLAIR sequence showing small, silent brain infarcts which are frequent in patients with carotid stenosis.

3. CAROTID DISEASE AND STROKE

Atherosclerosis accounts for the majority of brain infarctions and it is a chronic process that is converted into an acute syndrome when a lesion ruptures and triggers thrombosis. Progressive stenosis of the carotid artery is a leading cause of cerebrovascular disease resulting in reduction in blood flow and subsequent reduction in oxygen and glucose delivery essential for proper brain function. In 20-30% of patients suffering from cerebral infarction exists a significant carotid artery stenosis as compared to 5-10% in general population. Carotid endarterectomy has been demonstrated to be beneficial in reduction of subsequent strokes as well as in the number of registered ipsilateral microemboli (Figure 1). The risk profile of advanced atherogenesis is signalled by markers of enhanced prothrombotic capacity, attenuated fibrinolysis and by clinical conditions associated with defective coagulation. Almost all patients with more than 3 procoagulant risk conditions have carotid stenosis or show progression of preexisting stenosis during a 5-year period. Furthermore, progressing atherosclerotic lesions become more heterogenous and complicated increasing the risk of thrombosis. Carotid plaque instability, rupture, intraplaque hemorrhage, and local thrombosis may lead to symptomatic cerebrovascular disease (7, 8).

4. BIOMARKERS OF DISEASE

Numerous bio-molecules have been studied as possible biomarkers of cerebrovascular disease. Fibrinogen, fibrin/fibrinogen degrading products and C-reactive protein are well established markers of vascular disease. Some new biomarkers have been identified in the recent years, like metalloproteases, Pregnancy Associated Plasma Protein-A, Lp-PLA2, Interleukin-6, Interleukin-12, lipoprotein- (a), plaque oxidative products and have been suggested to be likely predictors of the risk of a future stroke (9-11).

4.1. Fibrionogen and fibrin related antigens

Circulating molecules are associated with increased risk of symptomatic vascular disease in patients with moderate carotid stenosis and result in a worse outcome in subjects with ischemic stroke (12-14), The focal character of atherosclerosis is unquestionable, and there is some recent evidence that the plaque wall itself can secrete proteins that could be markers for atherosclerosis (8, 15). Fibrinogen was found to be a significant predictor of intima-media thickness (IMT) (16), and in younger patients with sub-clinical atherosclerosis, smoking status determined higher plasma fibrinogen (17). A link between plasma markers of fibrinogen/fibrin turnover and hyper-coagulation has been suggested in stroke patients (12, 18, 19). D-dimer appears to be a consistent marker of the risk of cardiovascular disease. The levels of D-dimer activity in lacunar and large atherothrombotic strokes were significantly higher than in healthy controls (20). Patients with a history of cardiovascular disease but a low risk of thromboembolism as assessed by IMT measurements had low plasma D-dimer levels (19). D-dimer was significantly associated with a risk of non-fatal myocardial infarction (21, 22). Whilst the relationship between plasma D-dimer and cerebrovascular disease is still a controversial issue, coronary instability and inflammation have been associated with multifocal plaque activation, simultaneously in various vascular systems, suggesting a systemic cause of clinical instability (23). We have shown that expression of intraplaque D-dimers was directly related to the presence of ulcerated-complicated plaques defined by anatomo-pathology and ultrasound analysis, whilst increased plasma D-dimer was associated with patients suffering from coronary artery disease (24). However, some studies in a healthy male population, reported that changes in expression of D-dimer did not correlate with any of the indicators of atherosclerosis, whilst indicators of coagulation and fibrinolysis were not linked to the incidence of brain infarction (25). In a recent, two year follow-up study, D-dimer level were higher within 24 hours after stroke, in patients who had a subsequent cardiovascular event and in patients who died of vascular causes compared with those who survived free of cardiovascular events (26). However, there was no significant difference in levels between survivors, and those who died of nonvascular causes, or patients who had a recurrent stroke or a cardiac event (26). This study failed to find any significant correlation between plasma fibrinogen, and advanced carotid disease measured 24 hours after stroke, which is in agreement with our findings carried out using a detailed atherosclerotic plaque analysis.

4.2. C-reactive protein

Increased concentrations of plasma C-reactive protein in subjects with symptomatic or asymptomatic carotid stenosis, whether surgically treated or not, are associated with increased IMT; development, progression, and rupture of atherosclerotic plaques; and subsequent cerebrovascular events (27, 28). In a recent 5-year follow-up study in patients with asymptomatic carotid disease, high C-reactive protein levels were predictive of clinical events (29). Furthermore, C-reactive protein predicted progression and recurrence of symptomatic intracranial large-artery atherosclerosis (30). This finding was also corroborated by experimental data showing that C-reactive protein was involved in the patophysiology of atherosclerosis (31, 32). Higher concentrations of C-reactive protein were associated with larger brain infarcts, stroke severity, or neurologic disability (33). In a recent case-control study involving patients with ischemic stroke before the age of 70 years, Ladenvall (34) found independent associations to elevated C-reactive protein serum levels in the acute phase and at the 3-month follow-up. C-reactive protein concentrations in patients with ischemic stroke can predict outcome or new vascular event independently of age, stroke severity, and other prognostic factors (35). However, plasma C-reactive protein levels may not always reflect state of the atherosclerotic lesion. Indeed, in our hospital-based population with advanced carotid athersclerosis C-reactive protein plaque and plasma levels were not correlated (31).

The contradictory findings of significance of different biomarkers in patients with cerebrovascular disease may be explained by the coexistance of a multiple vascular pathology in most of the patients studied. The later may contribute to the circulating pool of analysed biomarkers. The circulating levels may be demonstrative of the general proinflammatory and procoagulant state in our patients and thus be of limited practical importance (24). In summary, the value of the above biomarkers for routine screening in patients with cerebrovascular disease should be taken with a caution. The importance of each biomarker has to be evaluated individually in each patient with full consideration of clinical settings. Global measurement of multiple biomarkers is not warranted by currenty available clincal studies.

5. CLINICAL IMAGING OF INFLAMMATION

In recent years, advances in Magnetic Resonance Imaging (MRI) have improved our ability to identify carotid plaque cellular components (36, 37). Vulnerable atherosclerotic plaques have been characterized by high cellularity, especially inflammatory cells (8, 24, 31, 38, 39) and *in vivo* imaging of the current metabolic, dynamic state of the plaque would help to identify those patients at highest risk of ischaemic stroke (40, 41). A recent study established that Fluorine-18 fluorodeoxyglucose-Positron Emission Tomography (18-FDG-PET) imaging could be used to assess the severity of inflammation in human carotid plaques (42). 18-FDG accumulates in inflamed tissues and several groups have established that inflamed blood vessels and atherosclerotic lesions have increased uptake of 18-FDG (43-45). More recently, 18-FDG uptake was shown to be greater in carotid plaques obtained from patients with clinical evidence of carotid plaque instability (46, 47) and macrophage infiltration (42). The authors found a significant correlation between the PET signal from carotid plaques and macrophage staining from the corresponding histology sections. This correlation was even stronger when they compared mean FDG uptake with mean percentage CD68 staining. In animal models, macrophage density, assessed by anatomo-pathology, correlated with non-invasive PET measurements of FDG uptake in rabbit atherosclerotic aortas. FDG uptake did not correlate with either aortic wall thickness or smooth muscle cell staining of the specimens (48, 49). These findings are of interest as it has recently been shown that risk of plaque rupture, and, therefore, risk of a downstream embolic event, is determined more by plaque composition than plaque size or degree of stenosis (50). Furthermore, changes in vascular FDG activity can be identified by repeat PET/CT imaging (51). As FDG uptake is transient and present only at the time of active inflammation, it may offer a powerful tool to provide early detection of inflammatory foci within the carotid artery. We found FDG-uptake in contralateral arteries with moderate stenosis, less than 50% which may represent patients being at higher risk of contralateral stenosis progression, clinical neurological symptoms or silent brain infarction (Figure 2). Imaging findings support the idea of systemic inflammation in patients with carotid disease and being at risk of cerebrovascular events. Carotid FDG-uptake studies present promising results in detection of inflammatory foci, although the method is currently expensive (41, 47). A different technique of high-resolution ultrasmall superparamagnetic Iron-oxide (USPIO) enhanced MRI showed similar results in 20 patients with symptomatic carotid stenosis scheduled for CEA (52). USPIO is taken up by activated macrophages and allows the direct visualization of macrophage infiltration into the carotid atheroma *in vivo (*53). Despite a mean carotid stenosis of 46%, 95% of asymptomatic plaques demonstrated USPIO uptake, suggesting a bilateral, inflammatory burden within their carotid atheromas, although symptomatic carotid plaques showed significantly more inflammatory activity than did the contralateral side (52).

6. ANGIOGENESIS IN ATHEROSCLEROSIS

6.1. A historical background

Anatomic pathologists in the 18th and 19th centuries noted early changes during disease progression and altered morphology of those small vessels-*the vasa vasorum*-that feed the arterial wall. It is thought, that infiltration of microvessels into the media, intima and plaque, originates predominantly from proliferating vasa vasorum (54). The angiogenic response by adventitial *vasa vasorum* is stimulated by ischeamia and hypoxia (55). The media layer is also involved in the plaque growth and remodeling (56, 57). At the molecular level, pro-inflammatory intracellular signalling pathways are recruited which lead to transcriptional upregulation of cytokines, adhesion molecules, chemoattractant proteins (58, 59). There is promotion of wound healing through

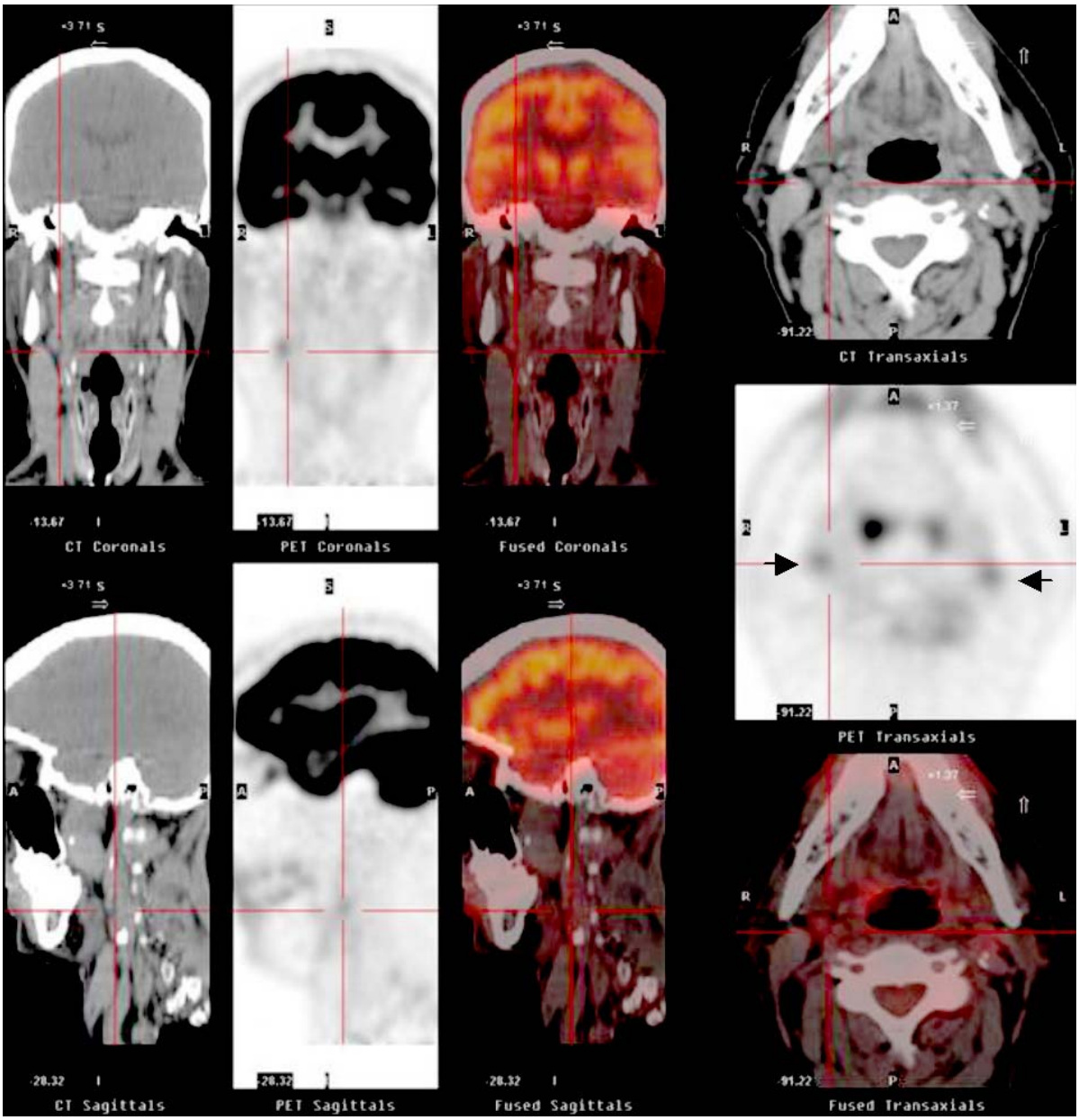

Figure 2. Fluorine-18 fluorodeoxyglucose PET (18-FDG-PET) in a patient with a preocclusive left internal carotid stenosis and 50% right internal carotid stenosis. Arrows demonstrate inflammatory infiltrates and high carotid plaque metabolic activity *in vivo* corresponding to increased 18-FDG plaque uptake.

enhanced expression of a variety of growth factors (60). With time, the subendothelial world becomes extremely heterogenous in composition. Components of the plaque itself become very thrombogenic i.e. lipidic core with high content of tissue factor, deposits of fibrinogen/fibrin related antigens and thrombin. The later, beyond its activity in generating a fibrin clot and activating platelets, stimulates endothelial cell migration and angiogenesis (61, 62).

Angiogenesis plays a complex role in atherothrombosis and is thought to be responsible for the majority of coronary and carotid artery symptomatic events (63-65). Newly formed blood vessels are very heteregenous (64). This can be observed at the intial steps of the plaque fromation as well later on when endothelial dysfunction occurs during atherosclerosis progression as a response to chronic minimal injury. Very often, the intima and media of coronary and carotid atherosclerotic vessels are infiltrated with a tumor-like mass of microvessels (31, 64, 66). These microvessels are prone to break and leak. Indeed, the hemorrhagic transformation of advanced coronary and carotid plaque is a frequent finding and is probably responsible for atherothrombotic complications (Figure 3).

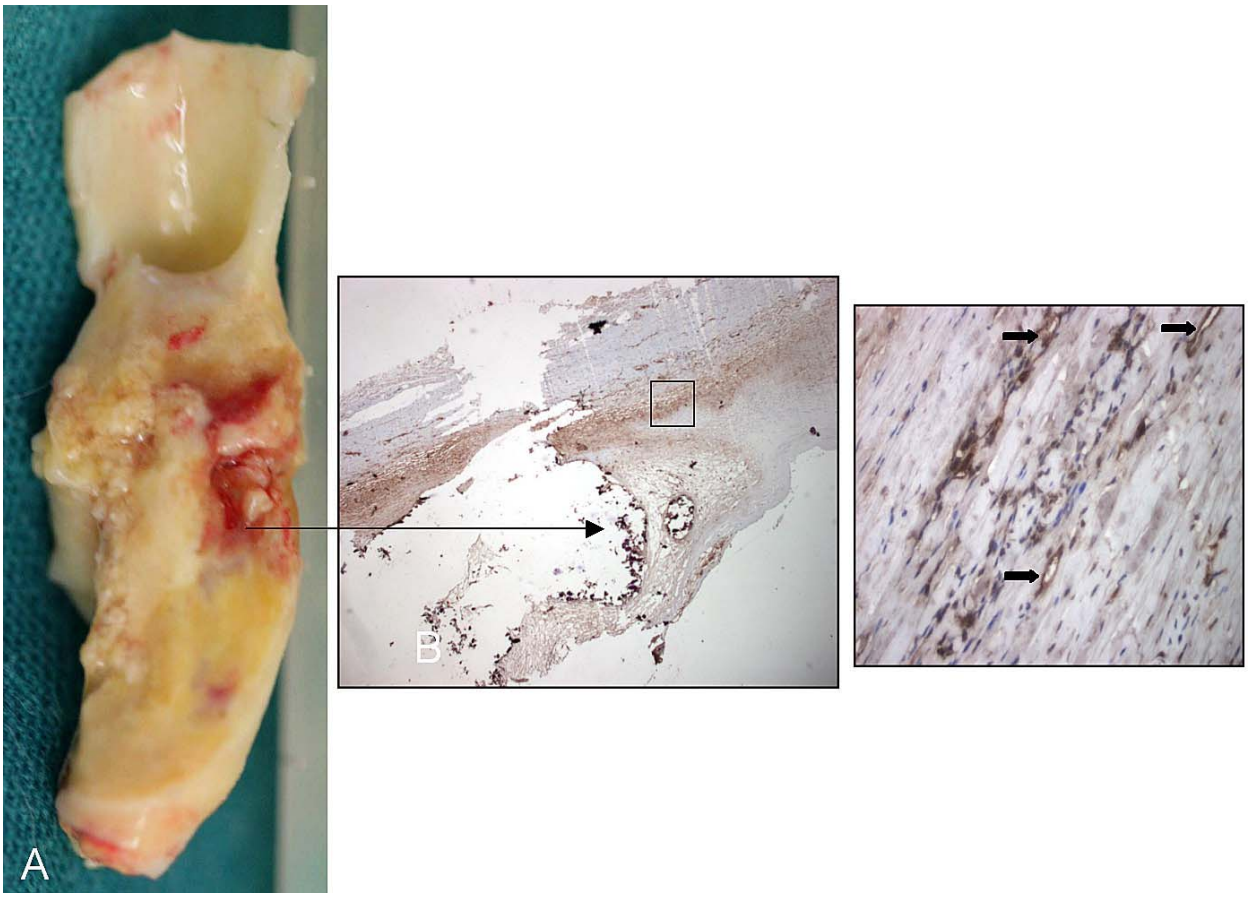

Figure 3. (A) Carotid plaque removed during endarterectomy shows heterogenous lesion. (B) Complicated, ulcerated area of the plaque with evidence of surface thrombosis, calcifications and inflammation. (C) Insert corresponding to the area with angiogenesis (arrows).

6.2. The link between Inflammation, procoagulant state and angiogenesis

6.2.1. C-reactive protein in angiogenesis

There is increasing clinical data suggesting that inflammation significantly contributes towards atherosclerotic plaque rupture. Identification of genes associated with vascular inflammatory biomarkers may provide new insights into local genetic determinants of vascular inflammation and risk of symptomatic vascular disease. C-reactive protein identified as an important biomarker provides information about the risk of developing vascular disease and may identify new criteria for treatment. It has multiple functions, including attraction of monocytes, mediation of LDL uptake by macrophages, reduction in NO release of human EC, up-regulation of adhesion molecules, stimulation of vascular smooth muscle cell proliferation and migration, increasing matrix metalloproteinase (MMP) expression in EC and macrophages, activating the complement system and inducing Plasminogen Activator Inhibitor-1 (PAI-1) expression and activity in human aortic EC (67-74). C-reactive protein has been shown to promote production of pro-angiogenic molecules ET-1 and IL-6 in human saphenous vein EC and activate intracellular signalling of NF-kB through the CD32 receptor (71, 75). Local synthesis of C-reactive protein could be involved in plaque neovascularization and increased risk of hemorrhagic transformation. Indeed, in our human advanced carotid artery plaques C-reactive protein gene expression was associated with increased expression of other proinflammatory genes like IL-6, MCSF-1, MCP-1, COX-2, further supporting the hypothesis that inflammation and angiogenesis are linked (31).

Our *in vitro* studies demonstrated that C-reactive protein stimulated an increase in gene expression of several angiogenic markers in human coronary artery endothelial cells (our unpublished data). This data suggests an important role for C-reactive protein in direct stimulation of angiogenesis and therefore it may be an important mediator of neovessel formation in the intima of vulnerable plaques (Figure 4).

6.2.2. Tissue Factor in angiogenesis

Tissue factor (TF), a key molecule in the coagulation cascade, is activated by inflammation increasing the risk of thrombogenecity. In our preliminary studies, asymptomatic patients with hypercholesterolemia and significant carotid stenosis had greater risk of TF-dependent coagulation pathway activation and plaque progression. Furthermore, blood-borne TF-activity predicts major cerebrovascular events in patients undergoing carotid endarterectomy: results from 1-year follow-up study (76).

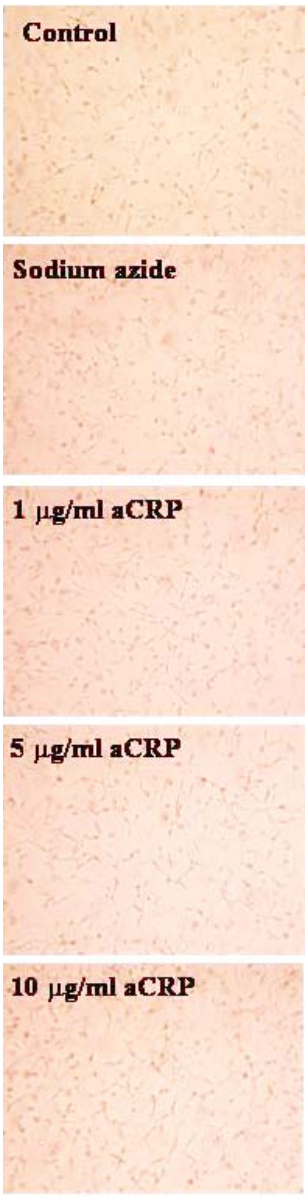

Figure 4. Effect of endotoxin-free ascites aCRP at different concentrations on bovine aortic endothelial cell (BAEC) tube formation (24h). Increased tube formation is observed at all concentrations as compared to control. CRP purity was tested and residual endotoxin was removed with detoxi-gel columns. Sodium azide was used as a control.

TF activation also depends on platelets activation which play a major role in atherothrombus formation. Platelets support thrombin formation, which in turn promotes vascular endothelial growth factor (VEGF) production. Platelets are a source of circulating VEGF and other cytokines like platelet-derived growth factor (PDGF) and transforming growth factor (TGF-beta). Therefore, platelet microparticles and its lipid content are angiogenic. VEGF upregulates TF *via* activation of transcription factors, which in turn will upregulate VEGF. VEGF and TF highly correlates in patients with peripheral vascular disease (PVD), both are increased in patients at risk for atherosclerosis or evidence of coronary artery disease suggesting link between the thrombotic diathesis and angiogenesis. Further, complex TF-VIIa promotes angiogenesis through protease activated receptors (PAR2) signaling (77).

6.3. Mechanisms of neovessel formation in the intima- a stepwise process?

6.3.1. Regulation of angiogenesis by hypoxia and ischemia

As the thickness of the intima/media increases, the diffusion capacity of oxygen and nutrients from the lumen is exceeded. An angiogenic response is stimulated by both hypoxia and ischemia: Hypoxia indicible factor (HIF-1) – VEGF interactions (55). HIF-1 is a key transcription factor for the hypoxic induction of angiogenic factors and hypoxia has been shown to be a major inducer of VEGF gene transcription (78). Oxidative stress induces high levels of VEGF and MMPs. Degradation of ECM by MMPs facilitates migration of *vasa vasorum* (8, 79). MMPs (MMP-9) further release angiogenic factors otherwise embedded in the ECM (80). Many growth factors and regulatory systems are involved in the vascular remodelling during atherogenesis. Many angiogenic factors can be found in the plaque: VEGF, PLGF, b-FGF, TGF-beta, MMPs, NO, PDGF, IL-8, PAF, thrombin (60). Endothelium of new microvessels is dysfunctional, promoting a further inflammatory process, attracting more macrophages *via* the *vasa vasorum*. Increased number of circulating cells cause that some of the blood vessels thrombose, enhancing local ischemia and stimulating angiogenesis. Others will proliferate and bleed.

6.3.2. Endothelial progenitor cells (EPCs)

Patients with vascular disease have associated damage of the endothelium on luminar surface causing its dysfunction. Circulating endothelial progenitor cells (EPCs), may play an important role in endothelial cell regeneration (81). EPCs have a significant role in virtually all stages of the atherosclerotic process and in the clinical manifestations of the disease: starting from the impact of risk factors on EPCs, through the mechanisms that link EPC reduction/dysfunction to plaque formation, and finally to the clinical syndromes (82). EPC may substantially contribute to the pathogenesis of vascular disease, mobilized from the bone marrow by angiogenic factors to the adventitial space (83). Bone marrow cells may have the potential to give rise to vascular progenitor cells that home in the damaged vessels and differentiate into smooth muscle cells or endothelial cells, at a very early stages of atherosclerosis, thereby contributing to lesion formation, but also to vascular repair and remodeling (84). Opposing to local resident endothelial cells poor proliferation rate, progenitor endothelial cells regenerative capacity, homing and integration into blood vessels have been interpreted as a protective role that play these cells in vascular homeostasis. Indeed, the number and function of EPCs corelate with the progression of atherosclerosis; the accumulation of cardiovascular risk factors or an increased overall risk is inversly associated with endothelial progenitor cells number and function. Recent studies have

shown a role of progenitor cells numbers to predict cardiovascular events, raising endothelial progenitor cells to the podium of novel prognostic biomarker.

6.3.3. Molecular mechanisms of angiogenesis in atherosclerosis

The molecular mechanisms involved in new blood vessel formation in patients with carotid disease are poorly understood and only few studies have addressed the question. Angiogenic immediate early genes like CYR61 are expressed in arteriosclerotic tissue (85). Symptomatic patients showed higher new vessel density in the fibrous cap and increased gene expression of 31 transcripts known to promote angiogenesis (86). Numerous pro-angiogenic genes are activated during atherosclerosis progression (87). Differential gene exppresion may depend on the type of the lesion studied and also the area of the lesion (our unpublished data). In terms of clinical events mechanisms leading to proper vessel maintanace and vessel regression leading to intraplaque hemorrhage and wound healing are of a particular importance. Few candidate genes are of interest, for example, VEGF, which is elevated both in atheroma and in the plasma of patients with coronary artery disease and acute coronary syndrome (88). VEGF is known to enhance TF gene expression in EC, and mobilize hematopoietic and EC precursors from the bone marrow (89).

The selection of EC which grow to form normal or abnormal new vessels depends on complex mechanisms. Heparin-binding VEGF-A is required for the directed extension of filopodia from branching microvessel networks. Furthermore, differential VEGF-A isoform localization in the extracellular space provides a control point for regulating vascular branching pattern (90, 91). Two players in vascular guidance are VEGF and Notch signalling. The Notch pathway is an intercellular signalling system in which both the signalling (ligand) and receiving (receptor) molecules are anchored to the cell surface, thereby restricting signal transmission to cells that are physically adjacent. Notch pathway components are expressed and have critical but poorly defined roles during vascular development. Recent studies identified Notch ligand Delta-like 4 (Dll4)/Notch signalling during vascular development, and clarified the mechanisms responsible for the vascular defects that result from reduced Notch signalling (92, 93). In atherosclerotic, highly angiogenic plaques, Notch signalling, participating in the selection of cells involved in branch fusion and terminal ramification maybe responsible for different patterns of plaque vasculature observed (64).

6.3.4. Cell specific responses in angiogenesis

Genes involved in angiogenesis may have different effects on new vessel formation and remodelling depending on the environment where they are expressed. In tumours, this has been shown recently for genes being downstream effectors of VEGF in endothelial cells. These genes when expressed by tumour cells confered vascular remodelling functions that are relevant to metastatic progression. These genes include the epidermal growth factor receptor (EGFR)/pan-HER ligand epiregulin (EREG), the prostaglandin-synthesizing enzyme cyclooxygenase 2 (COX2; also called PTGS2), and the matrix-remodelling metalloproteinases MMP1 and MMP2 (94). Silencing or overexpression of these genes in different combinations may have very different effects on vascular maturation and remodelling. It is probable that in human atheromas similar mechanisms occur. Indeed, during plaque development many pro-angiogenic pathways are re-actived and lead to formation of immature blood vessels prone to rupture. Overexpression of growth factors produced as a consequence of the inflammatory process induce signal transduction pathways, which impact on the critical stages of angiogenesis. Cell specific responses in angiogenesis may be key mechanisms leading to plaque instability. Identification of them may bring new targets for future treatments.

7. CONCLUSIONS

Angiogenesis plays a complex and a very interesting role in atherosclerosis, an inflammatory disease. The later seems to be important at all stages during plaque formation. An increase in local and systemic inflammatory response is thought to be responsible for most of the acute cardiovascular events. Numerous pro-inflamamtory cytokines are also involved in angiogenic responses. One of them, C-reactive protein is involved in direct stimulation of angiogenesis supporting the link between important inflammatory response and angiogenesis. Hypoxia and ischemia both stimulate angiogenesis and few important genes and transduction signal pathways have been identified recently. Current advances in molecular biology will prompt to further identify cell specific reponses in a complex environment of the atheroma.

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Key Words: Angiogenesis, Inflammation, Carotid Atherosclerosis, Review

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