Chemokines and B cells in renal inflammation and allograft rejection

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1. ABSTRACT

Recently the presence of intrarenal B cells in various inflammatory kidney diseases has been described and was in some cases linked to an unfavourable clinical course. Mechanisms leading to B cell influx into the kidney have therefore gained interest. Available data from the literature will be reviewed here with special focus on the contribution of chemokines. By far the most data from animal studies and human biopsies exist for BCA-1/CXCL13 pointing to a central role for this chemokine in B cell trafficking via interaction with its corresponding receptor CXCR5 on the B cell surface. Future studies will help to improve the knowledge on functional importance of B cell attracting chemokines as well as clinical significance of intrarenal B cell infiltrates.

2. INTRODUCTION

In contrast to the recruitment of T cells and monocytes not much attention has been paid so far to the renal infiltration of B cells as modulators of inflammatory kidney disease. B cells have classically been considered to exert long range effects mostly via activation in secondary lymphoid organs with subsequent antibody production. However, a number of groups including our own could describe the previously unrecognized high prevalence of intrarenal B cells in immunologically mediated disease including renal transplant rejection and glomerulonephritis. In many cases B cells appeared in dense cluster forming units with separated B and T cell zones, reminiscent of secondary lymphoid tissues. This striking presence in a growing number of renal pathologies has lead to many speculations on their functional importance. The current

Table 1. B cell attracting chemokines and their receptors

Chemokine(s)	Chemokine expression pattern	Chemokine receptor
LARC/CCL20	Small intestine, Liver	CCR6
ELC/CCL19, SLC/CCL21	Lymphoid tissue, lymphatic endothelium	CCR7
IP10/CXCL10	inflammed tissues	CXCR3
SDF-1/CXCL11	Bone marrow, lymphoid tissue	CXCR4
BCA-1/CXCL13	Lymphoid tissue, chronic inflammation	CXCR5

concepts regarding the function of intrarenal B cells as well as putative mechanisms leading to their tissue infiltration with a special focus on the contribution of chemokines will be reviewed here.

3.1. Chemokines and chemokine receptors

Chemokines are small chemotactic cytokines who are generally thought to be the main mediators in leukocyte trafficking under basal and inflammatory conditions (1, 2).

Chemokines compromise a group of small peptide molecules, which have a molecular weight ranging from 8 to 10 kDa and a 20% to 70% amino acid homology (3). To date nearly 50 human chemokines are characterized for which two nomenclatures exist: the historical names and a systematical nomenclature referring to their structure (4). In this review, for reasons of convenience, we will use both names. Chemokines are divided into families based on structural and functional characteristics. The classification based on structural characteristics is made according to the position of their cystein residues in the amino acid sequences of the molecules in C, CC, CXC and CX3C chemokines. Functionally two groups are differentiated, inflammatory and lymphoid chemokines. While the first group is only expressed upon proinflammatory stimuli in a time dependent manner, the latter group is constitutively secreted in secondary lymphoid organs (5). More recently it has become clear, however, that lymphoid chemokines can also be upregulated in extralymphatic tissues, including the kidney, in a number of immunologically mediated diseases as will be discussed in detail below.

The diverse biological effects of chemokines are mediated through binding to their corresponding chemokine receptors expressed on the surface of leukocytes. Chemokine receptors are single-chain, 7-helix membrane-spanning molecules that are coupled to G-proteins. Chemokine receptors are named and classified according to their chemokine ligands in C, CC, CXC and CX3C receptors (6). Chemokines act in concert with a large number of other cytokines in recruiting inflammatory cells. The specific composition of the different subsets of leukocytes appearing at the site of tissue inflammation, however, largely depends on the organ-specific pattern of chemokine expression. Several groups of chemokines exist that act predominantly on a defined leukocyte species, as for example B cells, which carry a set of chemokine receptors characteristic for this particular leukocyte subgroup.

### 3.2. Chemokines and B cell trafficking

Invasion of inflamed tissues by leukocytes is a complex multistep process (7). Therefore it is not surprising that multiple chemokines and chemokine receptors have been shown to be involved in B cell trafficking. Here we will summarize the available data from the literature regarding this topic.

A number of chemokine receptors have been described to be expressed on the surface of B cells (Table 1). Their presence is influenced by developmental stages and pathologic inflammatory conditions. The chemokine receptor CXCR4 is abundantly expressed on virtually all stages and subsets of human B cells. Essential roles for bone marrow and secondary lymphoid tissue homing have been described via interaction of CXCR4 with its ligand SDF1α/CXCL12 (8). The CXCR4 is, however, by no means specific for B cells, as it is widely expressed on many subsets of leukocytes. Another non B cell specific homing receptor found on almost all peripheral B cells is CCR7. The CCR7 ligands ELC/CCL19 and SLC/CCL21 are expressed constitutively in high endothelial venules. Studies in mice have shown that they are essential for the diapedesis of lymphocytes, including B cells, into secondary lymphatic organs (9, 10). Once a B cell has been stimulated with antigen, CCR7 is further upregulated and directs the B cells towards the T cell zones inside the lymph follicle (11). Therefore, the CCR7 is an important player in effective B cell crosstalk with T cells. Furthermore, expression of the CCR7 ligand SLC/CCL21 has recently been found in newly formed lymphatic endothelial cells in various human inflammatory settings including renal transplant rejection (12-14) and glomerulonephritis (own unpublished observation). Here it might be involved in B cell trafficking in and out of the kidney via attraction of CCR7 positive cells to lymphatic endothelium. Functional data to support this concept derive from animal studies by Debes et al who could show that the CCR7 was essential for lymphocyte exit from inflamed skin (15).

A far more B cell specific chemokine receptor than CXCR4 and CCR7 is CXCR5 which emerges on the B cell surface at the pro-B cell stage (16). CXCR5 has a dual role in B cell trafficking. Under basal conditions, B cells are recruited to secondary lymphoid tissues by interaction with the specific CXCR5 ligand BCA-1/CXCL13 which is constitutively expressed in lymphatic organs (17). Here this chemokine/ chemokine receptor pair regulates the microanatomical organization and establishes distinct B cell rich compartments. Under inflammatory conditions, however, it has become clear that BCA-1/CXCL13 can also be expressed in extralymphatic peripheral tissues. In many organs B cell recruitment via interaction of CXCR5 with locally secreted BCA-1/CXCL13 seems to be the main mechanism of B cell influx. Local secretion of BCA-1/CXCL13 and the presence of CXCR5 bearing B cells have been observed in a growing number of inflammatory diseases as e.g. MALT lymphoma, rheumatoid arthritis, Sjögren´s syndrome, autoimmune thyroiditis and CNS lymphoma (18-22). Recently we and others could also identify abundant BCA-1/CXCL13 expression in different renal pathologies which was in all cases associated with the presence of CXCR5 positive B cells (13, 23). The possible role of CXCR5 and BCA-1/CXCL13 in B cell recruitment in inflammatory kidney disease will be reviewed in detail below.
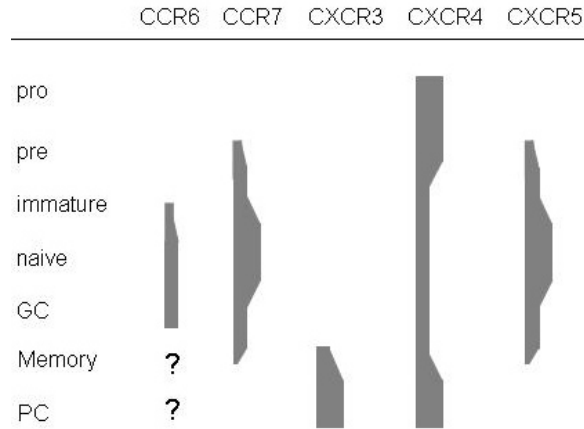
Figure 1. Chemokine receptor expression on B cells. pro: pro-B cell, immature: immature B cell, naive: naive B cell, GC: germinal centre, memory: memory B cell, PC: plasma cell

Another chemokine receptor for B cell targeting in inflammation is CCR6 which is upregulated upon B cell maturation and responds to its specific ligand LARC/CCL20. Activation of B cells as in autoimmune disease leads to an enhanced chemotactic response via CCR6 (24). A role for B cell adhesion to activated endothelial cells for this chemokine/chemokine receptor pair has been demonstrated (25). This argues for a general role for CCR6 and LARC/CCL20 in B cell invasion of inflamed tissues. Furthermore trafficking of CCR6 bearing B cells has been shown to play an important role in the gastrointestinal immune system. Studies in knockout mice have shown the severe defects in development of intestinal lymphoid structures as peyers patches and isolated lymphoid follicles due to impaired B cell trafficking (26). Another study could demonstrate intrahepatic expression of LARC/CCL20 in acute liver transplant rejection which was associated with the presence of CCR6 positive B cells (27). Expression of LARC/CCL20 has also been found in rheumatoid arthritis but correlation with infiltrating B cells was not determined (28). Similarly secretion of LARC/CCL20 by tubular endothelial cells in renal allograft rejection has been observed in a single study (29) where it was linked to dendritic cell recruitment. The possible role for CCR6 and LARC/CCL20 in attraction of B cells into the kidney has not been investigated so far.

The last chemokine receptor to be discussed here is the CXCR3 with its ligands Mig/CXCL9, IP10/CXCL10 and ITAC/CXCL11. Even though the CXCR3 has been characterized as classical receptor of Th1 differentiated T cells, it has been described to be expressed on a substantial percentage of peripheral human B cells (30). Functional significance has not been studied so far but as the receptor density is relatively low, CXCR3 induced migration of B cells is probably not of major importance. In contrast, upon differentiation into plasma cells, CXCR3 expression is significantly upregulated (31, 32) and seems to be one of the key molecules for plasma cell targeting. While in human rheumatoid arthritis the presence of CXCR3 positive plasma cells has been described and correlated with expression of the chemokine ligand Mig/CXCL9 in the synovial fluid (33), no data on CXCR3 positive plasma cells exist so far for diseases of the kidney. The changes in expression of chemokine receptors during B cell differentiation are summarized in Figure 1.

3.3. Possible roles of intrarenal B cells

B cells posses a number of immunological weapons to exert their functions. Classically they can differentiate into plasma cells and start production of antibodies which function as long range effectors. Apart from this well characterized function, B cells also posses mid and close range effectors. They produce a large number of immunmodulatory mediators which can be secreted into the surrounding interstitial space upon inflammatory stimuli. Furthermore they can take up foreign or self antigen which is then internally processed and subsequently presented on their surface to activate T cells. Last but not least, B cells play a central role in formation and organization of lymphoid tissue (34, 35).

Which of these functions might be fulfilled by intrarenal B cells ? To date no convincing functional data exist for human renal disease to answer this intriguing question. However a substantial number of studies has focussed on descriptive characterization of intrarenal B cells which has lead to the development of some putative concepts which will be discussed here. One possibility would be terminal differentiation of B cells into plasma cells which could start intrarenal antibody production. Small numbers of plasma cells seem to be regularly present in acute rejection processes. Some investigators have also described plasma cell rich rejections as a distinct pathological subgroup (36, 37). If these plasma cells differentiate locally inside the kidney from intrarenal B cells or if they immigrate from the circulation is still an open question. Likewise, their functional importance remains to be investigated as antibodies produced in the peripheral lymph organs can easily enter the kidney to exert their effects. Therefore intrarenal antibody production might not be of such great immunological significance, leaving room for speculations on alternative plasma cell functions.

Convincing functional data for antibody independent roles of B cells so far only derive from animal models. Shlomchik and co-workers have shown that depletion of B cells completely abrogated development of glomerulonephritis in a mouse model of systemic lupus erythematosus. In the same model, reconstitution of antibodies without B cells lead to development of only a mild nephritis. In contrast, restoring B cells incapable of antibody secretion that were otherwise intact, lead to a severe nephritis (38-40). In the human system only indirect data are available. Looney *et al* reported no change in quantity of pathologic antibodies after Rituximab induced B cell depletion in patients with lupus erythematosus (41). However, despite persistence of antibodies, the clinical disease activity score significantly improved in all patients. These data support the importance of B cell functions independent of antibody production. One of these functions might possibly be the production and secretion of pro-and

anti-inflammatory mediators such as cytokines and chemokines.

In human renal disease, a role as antigen presenters is likely. The close proximity to T cells and Monocytes/Macrophages (M/M) makes this a probable function. Furthermore the expression of the characteristic MHCII complex on their surface has been described (M. Sarwal, Abstract WTC #1012, 2006).

Apart from this putative role as antigen presenting cells, B cells might contribute to renal inflammation by producing cytokines and chemokines. Local secretion of these proinflammatory mediators by intrarenal B cells could recruit further immune cells from the circulation and co-activate surrounding leukocytes. Functional data from studies in mice with MHCII deficient B cells which lead to prolonged survival of cardiac allografts support this concept (42)

Finally, some recent studies have speculated on another possible role of intrarenal B cells. De novo formation of lymphoid tissue inside the inflamed kidney has been observed (12, 13) and linked to the presence of B cells (43). These ectopic lymphatic aggregates might serve as immunological shortcuts which ensure optimal immune cell activation by close cell/cell contacts in the right proinflammatory environment (44). Interestingly, it has been shown that ectopic overexpression of the B cell attracting chemokine BCA-1/CXCL13 in the pancreas of mice was sufficient for the development of intrapancreatic lymphoid tissue (45). A substantial role for B cells in ectopic lymphoid neogenesis at least in rodents is therefore quite likely. In conclusion, intrarenal B cells might exert a number of specific and important functions which however still remain speculative.

3.4. Chemokines and intrarenal B cells in renal transplantation

The first notion of intrarenal B cells in acute interstitial rejection came from Platt *et al.* in 1982 (46). However, in the next two decades, most attention was paid to infiltrating Monocytes and T cells. It took roughly 20 years after the observation by Platt until the interest of both, pathologists and clinicians started to focus on intrarenal B cells. Sarwal and colleagues published a report in 2001 which described large intrarenal B cell aggregates in 18 of 51 rejecting allografts from a pediatric kidney transplant collective. The presence of these B cell clusters was associated with a poor transplant prognosis. 15 of 18 the patients in which B cell clusters were present had steroid refractory rejections and 12 of these 18 patients later on lost their graft (47). A similar observation was published by our own group in 2005. Four of 13 patients with acute interstitial rejection displayed intrarenal B cell clusters. Three of these four patients could not sufficiently be treated with steroids (13). The third study on intrarenal B cells came from Hippen at el. who found clusters in six of 27 patients with interstitial rejection. The group with B cell aggregates was significantly more likely to have a steroid resistant rejection (4/6) than the group without (2/11). Furthermore four of the B cell positive grafts were

lost within four years after transplantation in contrast to only three of the 21 B cell negative transplants (48). In 2006 Tsai *et al* examined biopsies of 31 pediatric patients for the presence of intrarenal B cells. While the earlier studies focussed merely on B cell aggregates, Tsai *et al* classified biopsies in a group without B cells (n=16), another group with few B cells per high power field (2-10/hpf, n=14) and a third group with B cell clusters (11-100 cell/hpf, n=15). Interestingly not only the third group but also the group with only few scattered intrarenal B cells had a statistically worse outcome showing a 5.3 fold (11-100 B cells) and 4.6 fold (2-10 B cells) higher risk of graft failure two years after transplantation in comparison to the group without intrarenal B cells (49). These observations that uniformly found associations of intrarenal B cells with a worse transplant outcome could not be reproduced in a study by Doria *et al*. The authors could not find any effect of the presence of intragraft B cell nodules on creatinine levels before and up to 1 year after treatment of interstitial rejection (50). Furthermore, a large retrospective study of more than 1000 allograft biopsies by Mengel *et al* also failed to find a specific prognostic role for B cell infiltrates in acute transplant rejection. The only predictor of worse allograft outcome that could be identified was persistent inflammation in follow up biopsies irrespective of the presence of B cells in these infiltrates (51). In a third study, Kayler *et al.* reported a similar rate of steroid resistant rejections and similar transplant function in a small subgroup of 11 patients with intrarenal B cell clusters compared with roughly 100 patients without (52). One reason for these contradicting results could be the fact that the observed clusters which have so far been regarded as one single entity are not a uniform population. This is made especially clear as it does not even exist a definitive consensus of what is a B cell cluster or a B cell rich rejection, so that the authors of the above articles all used their own, differing definitions.

In addition to these studies, a number of other authors have also described regular presence of B cells in rejecting allografts (12, 53, 54), however without analyzing their effect on graft function. Given the high prevalence of B cells in interstitial rejection processes, which might be associated with a worse outcome, the mechanisms leading to the B cell influx into the transplanted kidney are rewarding issues to study. So far, in interstitial rejection only one report from our own laboratory exists that investigated B cell specific intragraft chemokine transcription and secretion (13). We found a striking upregulation of the B cell attracting chemokine BCA-1/CXCL13 in allografts undergoing acute rejection with intrarenal B cell clusters as compared to those without (27-fold). Regions of BCA-1/CXCL13 production co localized strictly to areas of infiltrating B cells. Furthermore these B cells were positive for the specific BCA-1/CXCL13 receptor CXCR5. It is therefore tempting to speculate that B cells are recruited into the kidney via interaction of locally transcribed and secreted BCA-1/CXCL13 with the corresponding receptor CXCR5 on their surface. Data from a recent study by Wengner *et al.* underlined the functional importance of this chemokine/ chemokine receptor axis in attraction of B cells. The authors could show a significantly

reduced number of synovial B cells and impairment of tertiary lymphoid tissue developement in an experimental model of arthritis in CXCR5 knockout mice (55). Another chemokine that might be involved in B cell influx into the kidney is SLC/CCL21. This chemokine has been described to be expressed by intragraft lymphatic endothelium which is newly formed in the vicinity of inflammatory infiltrates (12, 13). Here CCR7 bearing B cells could enter and leave the inflamed allograft via interaction with SLC/CCL21. This theory, which is supported by findings in a model of skin inflammation (15), however remains to be proven in the kidney by functional data e.g. from animal transplantation studies.

Intrarenal expression of other potential B cell attracting chemokines as LARC/CCL20 (29), Mig/CXCL9, IP10/CXCL10, ITAC/CXCL11 (56) as well as the receptors CXCR3 (56, 57) and CXCR4 (58, 59) has been detected in acute interstitial rejection episodes. In comparison to BCA-1/CXCL13, however, these chemokines and chemokine receptors are far less B cell specific and have been implicated in infiltration of other leukocyte subpopulations. An association of their presence with intrarenal B cells has not been investigated so far but a contribution to B cell recruitment cannot be ruled out. Data regarding vascular rejection are similarly sparse. B cells seem to be present with the same frequency and number as in interstitial rejection (60, 61) but clinical significance has so far not been studied. In analogy to the situation in interstitial rejection, our group could show expression of BCA-1/CXCL13 exclusively in regions of B cell infiltrates (61). A possible role for other less specific B cell attracting chemokines has so far not convincingly been described even though presence of CXCR4 and its ligand SDF-1α/CXCL12 has been demonstrated (58, 62) as well as SLC/CCL21 (61) and CXCR3 with its ligands Mig/CXCL9, IP10/CXCL10, ITAC/CXCL11 (62).

B cells have also been described in chronic rejection processes and might be important effectors (43, 54). Therefore it would be rewarding to investigate the mechanisms leading to their infiltration and persistence in chronic allograft nephropathy. SDF-1α/CXCL12 expression has been detected but possible contribution to B cell infiltration was not studied (62). So far, no systematical study regarding B cell attracting chemokines has been conducted.

In conclusion, a role for chemokines, especially BCA-1/CXCL13 and its receptor CXCR5 in infiltration of B cells into the kidney in acute interstitial and vascular rejection is likely but still not definitely proven by experimental animal studies. B cell attracting chemokines in chronic rejection processes remain to be characterized.

3.5. Chemokines and intrarenal B cells in autoimmune nephritis

As in renal transplantation, data on presence, possible function and mechanisms of influx of B cells are sparsely characterized in glomerulonephritis. A report by Cohen *et al.* has described B cells in membranous nephropathy in the form of clusters as well as in a scattered

pattern (63). No convincing clinical correlation with outcome parameters could be shown and the possible contribution of chemokines to B cell influx was not investigated. Heller *et al.* could demonstrate a significant contribution of B cells to the interstitial infiltrate in acute and chronic primary interstitial nephritis as well as in IgA nephropathy (64). Numbers of interstitial B cells correlated with intrarenal expression levels of the B-cell attracting chemokine BCA-1/CXCL13 in all three disease entities. Furthermore by immunohistochemistry, strong BCA-1/CXCL13 expression was found specifically at sites of CXCR5 bearing B cell infiltrates. As in transplant rejection, an important implication of the BCA-1/CXCL13 - CXCR5 axis in B cell influx is therefore quite likely. The clinical importance of these B cell infiltrates remains to be elucidated, however, as neither the amount of renal CD20 mRNA nor the area of CD20 positive cells correlated with serum creatinine at biopsy.

Some functional studies regarding chemokine mediated B cell trafficking have been conducted in a mouse model of lupus nephritis. Ishikawa and colleagues have reported ectopic expression of BCA-1/CXCL13 in the renal interstitium of NZB/NZW mice (65). The same group could show in a subsequent study that injected B1 lymphocytes which carry the corresponding receptor CXCR5 homed in significant numbers to the inflamed kidneys (66) Neither BCA-1/CXCL13 nor CXCR5 neutralization studies have been performed but nonetheless these data suggest that this chemokine/chemokine receptor pair is quite likely to play a significant role in B cell infiltration into the diseased kidneys in this model. This enhanced intrarenal expression of BCA-1/CXCL13 could also be observed by our own group in MRL/lpr mice, another animal model of lupus nephritis. Furthermore, by *in situ* hybridisation, CXCR5 mRNA expression could be localized to areas of infiltrating B cells. This situation is mirrored in human lupus nephritis. Here we found B cells either in a scattered pattern or in the form of dense clusters in a considerable number of biopsies. As in the other renal pathologies described above, BCA-1/CXCL13 expression was strongly upregulated in specimen with intrarenal B cells as compared to those without. Furthermore, CXCR5 positive B cells were found specifically in areas of BCA-1/CXCL13 expression. The same similarities between transplantation and lupus nephritis were found in the case of the chemokine SLC/CCL21. Lymphatic endothelial cells surrounding inflammatory infiltrates strongly express this chemokine which in theory might be implicated in CCR7 bearing B cell influx and efflux. (own unpublished data). No data exist to suggest possible roles in B cell trafficking into the kidney for CCR6, CXCR3 and CXCR4 and their chemokine ligands.

Summarizing the above findings regarding autoimmune nephritis, the most probable chemokine candidate responsible for B cell infiltration is BCA-1/CXCL13, exerting its effects via interaction with CXCR5. Unlike in renal transplantation some functional data exist from an animal model of lupus nephritis to support this concept. Neutralization experiments which could reveal the clinical importance are however still lacking.
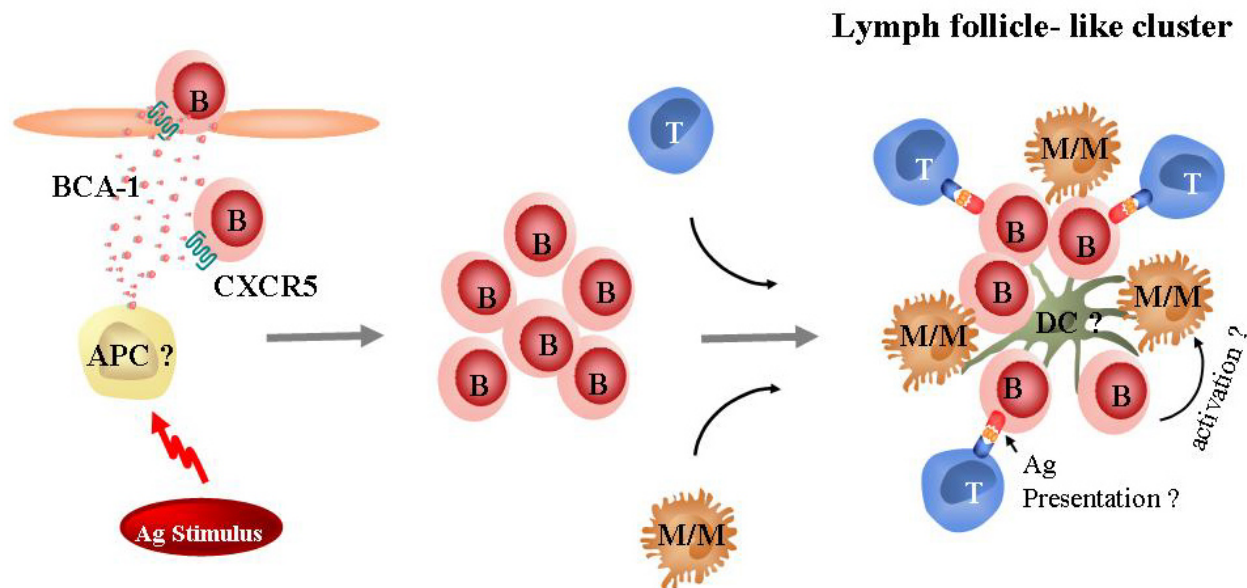
Figure 2. Proposed role of BCA-1/CXCL13 and CXCR5 in B cell trafficking into the kidney. Different immunological and non immunological stimuli lead to intrarenal expression of chemokines. BCA-1/CXCL13 is probably expressed by antigen-presenting cells (APC) of either monocytic or dendritic type which leads to infiltration of CXCR5-positive B cells from the circulation. Together with other leukocyte subtypes that enter the kidney via chemokine mediated mechanisms, lymph follicle like clusters are formed. These contain B cells, T cells, and Monocytes/ Macrophages (M/M). It still remains to be investigated wether follicular dendritic cells (fDCs) are also present as is the case in secondary lymphoid tissues. B cells probably act as antigen-presenting cells and activate T cells and M/M locally in the kidney. The activated T cells in turn mediate tissue damage via direct toxic effects, secretion of cytokines, and activation of M/M.

4. PERSPECTIVE

B cells have been found to be frequently present in all renal pathologies investigated so far including renal transplant rejection, different types of glomerulonephritis and primary interstitial nephritis. In some cases they are distributed in a scattered pattern while they can also form characteristic lymph follicle like clusters with compartmentalized T and B cell zones. Their presence has been linked to an unfavourable clinical course of renal transplant rejection by a number of small studies while a number of larger, more recent studies could not reproduce these findings. No impact on outcome in glomerulonephritis has been described so far. However, the definition of B cell clusters differed considerably between the studies and the clusters have so far simplistically been regarded as one single entitiy regardless of their organizational status and the contributing B cell subtypes. A more differentiated and uniformly used classification of B cell clusters therefore needs to be established. At present the clinical significance of intrarenal B cells is still unclear. The contribution of chemokines to their tissue invasion has been studied by various groups. The only chemokine / chemokine receptor pair for which functional data exist in a mouse model of lupus nephritis and in a model of arthritis is BCA-1/CXCL13 and its specific receptor CXCR5. Intrarenal expression of this chemokine has been found in different human renal pathologies and strictly co-localized in all cases with areas of CXCR5 bearing B lymphocytes. These observations make a significant role for BCA-1/CXCL13 and its receptor CXCR5 in B cell infiltration likely. A simplified model of the possible role of BCA-1/CXCL13 in the formation of renal B cell clusters is shown in Figure 2. While expression of other B cell attracting chemokines has been detected, their possible contribution to B cell influx in renal disease has not been investigated so far. As often the case with newly discovered phenomena, the observation of intrarenal B cells leaves more questions than answers. It is, for example, important to characterize the cascade of events triggering BCA-1/CXCL13 expression in the kidney and initiating B-cell infiltration and follicle formation. Furthermore, the cellular origin of BCA-1/CXCL13 production and the mechanisms that lead to the persistence of B-cell clusters need to be identified. In secondary lymphatic organs, follicular dendritic cells (fDCs), a specific subgroup of dendritic cells, are the main producers of BCA-1/CXCL13. In response to stimulation with BCA-1/CXCL13 via the CXCR5 receptor, B cells in secondary lymphatic organs secrete lymphotoxin alpha, which in turn stimulates fDCs to produce even more BCA-1/CXCL13. Thus, a positive feedback loop is created (17). The mechanisms in the kidney, however, could be different. So far, only in the MRL/lpr mouse model of lupus nephritis, intrarenal mRNA expression of lymphotoxin alpha has been detected (67). In addition, in B-cell follicles in non-renal tissues, BCA-1/CXCL13 production is localized to monocytic cells rather than fDCs (68). The presence of fDCs within B-cell clusters in the kidney remains to be investigated. While little is known regarding B cell influx, even less is known

about the regulation of B cell emigration from the inflamed kidney back into the circulation. SLC/CCL21 and its receptor CCR7 are potential candidates but so far, their functional role has not been studied and therefore remains elusive. In this regard it would also be interesting to investigate possible interactions of sphingosine-1-phosphate receptor 1 (S1P1) signalling with chemokine receptor mediated signalling in B lymphocyte emigration. Especially as S1P1 is one of the major players in lymphocyte egress from secondary lymphoid organs and has in a recent study emerged as regulator of T cell emigration from the intrinsic renal lymphatic system in mice (69). Last but not least large long term follow up studies for various renal pathologies are needed to address the key question regarding the clinical significance of intrarenal B cells.

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