

Chemokines in vasculitis

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1. ABSTRACT

The systemic vasculitides are a group of diseases where the primary pathological process is inflammatory injury to blood vessel walls. Their clinical manifestations are highly variable and range from organ specific disease to a systemic illness that can lead, if untreated, to multi-organ failure and death. The kidneys are often involved in systemic vasculitis, particularly in small vessel vasculitis, where the glomerular capillary bed is a target for injury. This leads to a vasculitic glomerulonephritis, with focal segmental inflammation and perivascular leukocyte accumulation evolving to extracapillary accumulation of mononuclear cells (including crescents). The kinetics of leukocyte infiltration and involvement in this setting are in part dependent on the combinatorial expression of chemokines and their receptors. We discuss the evidence base for the role of the chemokine network in the renal disease of small vessel vasculitis and extend this to non-renal aspects of small vessel vasculitis other systemic vasculitides.

2. CLASSIFICATION OF VASCULITIS

The classification of vasculitis is difficult due to considerable heterogeneity in disease entities; however the system proposed by the Chapel Hill consensus conference is widely accepted (1). Here the criteria are dependent on the smallest size of vessel affected. Table 1 is based on the Chapel Hill classification. There are also a broad group of causes of secondary vasculitides that can occur as a consequence of diverse primary disorders including autoimmune disease (Rheumatoid disease; systemic lupus erythematosus), drugs, infections and malignancies (2).

Primary small vessel systemic vasculitis is commonly associated with circulating antibodies against neutrophil cytoplasmic antigens (ANCA). These antibodies influence the development of disease (3). This review will focus predominantly on ANCA-associated vasculitis, however, the role of chemokines in Giant Cell Arteritis (GCA) and Takayasu's disease will also be considered and the influence of chemokine receptor polymorphisms on the

Table 1. Classification of primary systemic vasculitis

Size of dominant vessel affected	Granulomatous	Non-granulomatous
Large (Aorta and largest branches)	Giant Cell (Temporal) arteritis, Takayasu arteritis	
Medium (main visceral arteries)		Classic polyarteritis nodosa Kawasaki disease
Small (venules, capillaries, arterioles)	Wegener's granulomatosis ^{1,2} , Churg-Strauss syndrome ²	Microscopic polyangiitis ^{1,2} Henoch-Schonlein purpura ¹ Cutaneous leucocytoclastic vasculitis Essential cryoglobulinaemic vasculitis ¹

¹ Glomerular involvement common. ² Associated with ANCA

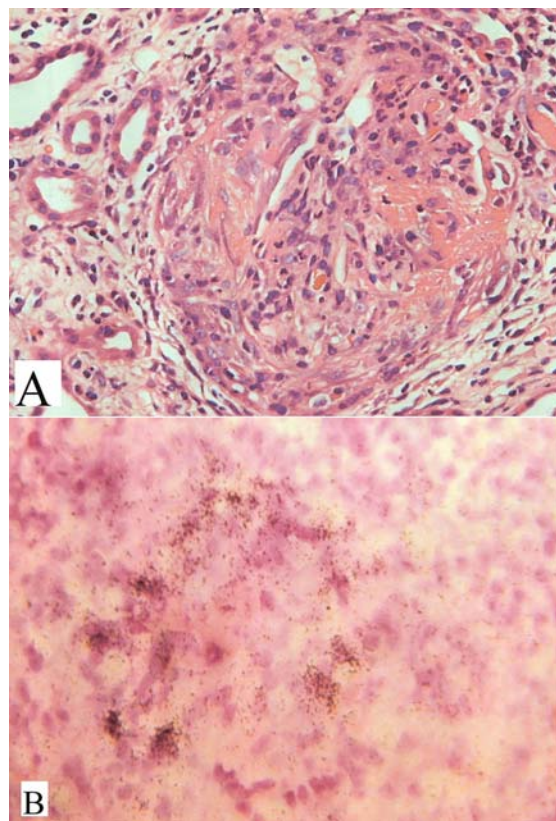


Figure 1. A. Renal biopsy specimen from a patient with WG and acute renal failure demonstrating focal, segment necrotising glomerulonephritis with crescent formation. Proliferating cells form a crescent and loss of Bowman's space. The glomerular tuft is very abnormal with segmental fibrinoid necrosis and extracapillary fibrin and necrosis. Inflammatory cell infiltrate at glomerular, periglomerular and interstitial sites. (H&E stain; original magnification x400; courtesy of Dr D Neil). B. Heavy IL-8/CXCL8 mRNA expression demonstrated by *in situ* hybridisation in a severely inflamed glomerulonephritis in a patient with ANCA associated vasculitis.

pathogenesis of Kawasaki disease and Henoch-Schonlein purpura will be discussed.

2.1. Anti-neutrophil cytoplasmic antibodies (ANCA)

ANCA-associated vasculitis includes Wegener's granulomatosis (WG), which is often preceded or accompanied by granulomatous inflammation, predominantly of the respiratory tract, and microscopic polyangiitis (MPA), where granulomatous inflammation is

not a feature. These diseases are commonly grouped together due to their strong association with ANCA.

There are two main patterns of staining for ANCA by indirect immunofluorescence: (i) granular cytoplasmic staining (c-ANCA) where the target antigen is the primary neutrophil granule protein proteinase 3 (PR3); (ii) a perinuclear pattern of staining (p-ANCA). Most p-ANCA are directed against myeloperoxidase (MPO), although some are directed against PR3 and other primary granule proteins such as elastase and lactoferrin. ANCA isolated from the serum of a single patient may be directed against more than one target antigen. Around 90% of patients with pauci-immune necrotizing glomerulonephritis (renal limited vasculitis), WG, or MPA have detectable circulating ANCA. PR3-ANCA are more common in patients with WG; MPO-ANCA are more common in patients with MPA (4).

A number of studies have shown that ANCA IgG isolated from patients with vasculitis activate neutrophils and monocytes *in vitro* (5). There are a number of other pathogenic effects of ANCA *in vitro*, these are reviewed in detail elsewhere (6). A role for pathogenesis is further supported by an animal model where anti-MPO antibodies or splenocytes are transferred from immunised MPO knock-out mice to normal or immune-deficient mice (7). Whilst this is not a model of autoimmunity, it represents the closest model yet to human disease. The animals develop a pauci-immune systemic vasculitis, including a vasculitic glomerulonephritis.

3. THE PATHOLOGY OF ANCA ASSOCIATED VASCULITIS

The nomenclature for ANCA-associated glomerulonephritis can be confusing. The lesion is the commonest of a number of causes of rapidly progressive glomerulonephritis (Figure 1A). The light microscopy appearance is conventionally described as a focal segmental necrotising (and thrombotic) glomerulonephritis (FSNGN) with crescents. Some clinicians will use the term crescentic glomerulonephritis. The most useful shorthand for the glomerular lesion is vasculitic glomerulonephritis (8). Whilst there are other causes of this lesion for the remainder of this review this term will be used, as many of the reports that are summarised below do not distinguish between different disease states.

A number of ultrastructural and histological studies have contributed to our understanding of ANCA-associated glomerulonephritis (9). In renal biopsies vasculitic lesions may be present at any stage from intracapillary thrombosis to glomerular scarring. The first changes are localised within the glomerular capillaries,

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with the focal presence of intracapillary thrombi, consequent to endothelial activation, deadherence, necrosis and platelet deposition. Interestingly, ultrastructural studies on pulmonary capillaries indicated the presence of lysed intracapillary leukocytes in very early lesions, supporting the paradigm that ANCA may activate neutrophils and monocytes within the intravascular compartment.

These early lesions may progress to areas of segmental inflammation, with accumulation of cells outside the glomerular capillary tuft and in Bowman's space. There are often breaks in the GBM at these sites, indicating that some cells are not trafficking across an intact endothelial cell monolayer. Further, the glomerular capillary bed is on the arterial side of the circulation, so some of the usual paradigms associated with trafficking at inflammatory sites may not apply. Features specific to the glomerulus in respect of trafficking have been difficult to analyse, although the development of new microvascular techniques may provide insights in this area (10).

On immunostaining or electron microscopy there may be sparse immune complex deposition (11). This is usually found on the epithelial side of the basement membrane, and differentiates this lesion from the heavy immunoglobulin deposition of immune complex mediated and anti-glomerular basement membrane (GBM) disease.

The kinetics of leukocyte infiltration in vasculitic glomerulonephritis is, in part, assumptive. However pathologists often identify predominantly neutrophils (and intravascular monocytes) in early lesions. These areas may progress to advanced disease with a dominant mononuclear cells infiltrate: around 50% of these cells are monocyte/macrophages, the remainder are T cells, predominantly CD4+ and often of an activated and memory phenotype (12).

4. NEUTROPHIL-DIRECTED CXC CHEMOKINES AND THEIR RECEPTORS

Neutrophils are present in all types of glomerulonephritis, however in ANCA-associated vasculitic glomerulonephritis a significant number of cells are retained within the glomerular capillaries (4). Further, many intraglomerular neutrophils in this setting are activated (13). Aberrantly activated neutrophils may promote bystander damage of endothelial cells and GBM and disrupt the barrier function of the glomerular capillary wall.

IL-8/CXCL8: The retention of neutrophils within the glomerular capillaries occurs despite the local upregulation of chemokines associated with neutrophil trafficking. Notably, there is heavy expression of IL-8/CXCL8 in the glomerulus, at vascular and extravascular sites (14) (Figure 1B). Classical promoters of chemokine production are present, with local expression of TNF-alpha and IL-1 beta (13). Endothelial cell production of IL-

8/CXCL8 may also be promoted by PR3, released by degranulating neutrophils and monocytes (15).

The pathways for frustrated trafficking of neutrophils may relate to autocrine or paracrine effects of neutrophil produced IL-8/CXCL8 within the microvasculature. There are elevated circulating levels of IL-8/CXCL8 in acute disease (16), and in vitro ANCA strongly stimulates the expression of the chemokine by neutrophils to inhibit the transendothelial migration of neutrophils toward an IL-8/CXCL8 gradient (14). These effects may be potentiated by decreased neutrophil deformability as a consequence of ANCA promotion of cell membrane F-actin polymerisation (17). Others have shown an increased integrin expression state on circulating neutrophils in patients with WG (18). The ability of ANCA to promote CXCL8 production is not restricted to neutrophils; cANCA purified from patients with WG stimulated monocyte IL-8/CXCL8 production via Fcγ crosslinking (19).

CXCR1 and CXCR2: Segerer and colleagues analysed the expression of CXCR1 in renal biopsies from patients with a range of human diseases, including crescentic glomerulonephritis, some of which were ANCA-associated (20). They demonstrated expression of the receptor on infiltrating leukocytes, predominantly neutrophils, and resident renal cells (arterial smooth muscle cells, endothelial cells of peritubular capillaries). In a study utilising a flow-based adhesion assay ANCA had no effect on expression of CXCR1 or CXCR2 but did enable an active conformational change of cell surface beta 2 integrin (CD11b/CD18) to stabilise endothelial cell adhesion (21), this supported other work by the same group that demonstrated that immobilization of ANCA-activated neutrophils was mediated by the activated beta 2 integrin (22).

Animal models: A study on chemokines in an animal model of ANCA-associated vasculitis was performed by Little and colleagues, who produced a model of systemic vasculitis by immunizing WKY rats with human MPO to produce anti-MPO antibodies (23). They then utilised intravital microscopy to study the mesenteric vasculature: they demonstrated that focal haemorrhage developed in the mesenteric vasculature in response to extravascular application of GROα/CXCL1, with adhesion and transmigration of neutrophils at these sites, compared with control rats.

5. MONONUCLEAR CELLS

Macrophages and T cells infiltrate Bowman's space by migrating from the glomerular tuft, in part through gaps in endothelial cells caused by capillary rupture. However intraglomerular leukocytes in vasculitic glomerulonephritis are not present in the same proportion as circulating leukocytes, indicating that pathways are in place to direct preferential recruitment. The interstitial accumulation of infiltrates is often a prominent feature of vasculitic glomerulonephritis and can occur in the absence of glomerular lesions, indicating that the tubulointerstitial vasculature itself may be a target for injury (24).

Table 2. Studies of chemokine and chemokine receptor expression in human vasculitic glomerulonephritis

Chemokine Group; chemokine	Site of chemokine expression (reference)	Chemokine Receptor	Site of receptor expression (reference)
CX3C			
Fractalkine/CX3CL1	Differential glomerular and tubulointerstitial expression (36) (37)	CX3CR1	Infiltrating mononuclear cells of glomerular and interstitial compartments (40)
CXC			
IL-8/CXCL8	Heavy glomerular & tubulointerstitial expression (14)	CXCR1	Infiltrating neutrophils in glomerulus and vascular endothelial and smooth muscle cells (20)
IP-10/CXCL10; Mig/CXCL9	Glomerular and tubulointerstitial expression (44)	CXCR3	Infiltrating and resident (mesangial) glomerular cells (42, 43)
CC			
MCP-1/CCL2	Variable Glomerular and tubulointerstitial expression (25-29)	CCR2	Infiltrating mononuclear cells of glomerular and interstitial compartments (29)
MIP-1 α /CCL3	Glomerular and tubulointerstitial expression (27, 28)	CCR1, CCR5	Infiltrating mononuclear cells of glomerular and interstitial compartments (65-67)
MIP-1 β /CCL4	Glomerular and tubulointerstitial expression (27)		
RANTES/CCL5	Glomerular and tubulointerstitial expression (27)		
MCP-4/CCL13	Periglomerular, peritubular, and perivascular expression (66)	CCR2, CCR3	Infiltrating mononuclear cells of interstitial compartments; predominantly macrophages (29, 66)

Most represent reports on subgroups derived from heterogeneous disease using immunohistochemical and/or *in-situ* hybridisation techniques

5.1. Mononuclear cell-directed chemokines and their receptors

5.1.1. MCP-1/CCL2, CCR2 and CCR5

In studies that predominantly focused on MCP-1/CCL2 expression in rodent anti-GBM glomerulonephritis, Rovin and colleagues performed a limited immunohistochemical analysis of human inflammatory glomerulonephritis. They reported the

presence of MCP-1/CCL2 in a focal, granular mesangial distribution in inflammatory and infiltrative glomerulonephritides, including vasculitic glomerulonephritis associated with WG, in association with mononuclear cell infiltration (25). In a subsequent immunohistochemical analysis, Prodjosadji and colleagues found expression of the chemokine at glomerular and tubulointerstitial sites in membranous nephropathy, conversely they found no glomerular MCP-1/CCL2 staining in vasculitic glomerulonephritis (26).

Subsequent studies confirmed glomerular MCP-1/CCL2 expression in ANCA-associated glomerulonephritis at glomerular and interstitial sites (27). The majority of infiltrating macrophages expressed MCP-1/CCL2 transcripts. *In situ* hybridisation also localised expression to endothelial cells. A separate study confirmed heavy expression of the chemokine, but suggested that expression was limited to interstitial sites (28). Subsequently Segerer and colleagues correlated glomerular MCP-1/CCL2 expression with leukocyte infiltration and CCR2 expression (29). They demonstrated that expression of the targeted receptor was primarily by infiltrating mononuclear cells, confirming a pathway for their recruitment.

MCP-1/CCL2 has been demonstrated to play a role *in vivo* in both lupus and cryoglobulinemic vasculitis. Hasegawa *et al* investigated if chemokine antagonists inhibited the initiation and progression of lupus nephritis in MRL/lpr mice (30). They injected mice with an MCP-1/CCL2 antagonist and subsequently showed diminished leukocyte infiltration and reduced renal damage in treated mice compared to controls. In humans with cryoglobulinemic vasculitis Gesualdo *et al* performed *in situ* hybridisation and immunohistochemistry to localise MCP-1/CCL2 in renal biopsies (31). They correlated these results with macrophage infiltration (CD68 positive cells). In diseased kidneys they demonstrated a significant up-regulation of MCP-1/CCL2 gene and protein expression. Interestingly, macrophages were observed to cluster around cells expressing MCP-1/CCL2 mRNA.

CCR5 has been implicated in mononuclear cell trafficking in WG. It has been suggested that genetic variations in CCR5 and its ligands may influence susceptibility to the disease. Zhou *et al* analysed lung biopsies from patients with active disease using immunohistochemistry and polymerase chain reaction (PCR); CCR5+ cells were enriched in lung lesions from patients with WG compared to controls (32). They reported enhanced protein concentrations for the ligands of CCR5 in patients with WG indicating redundancy in affected tissue. Twenty percent of patients in this cohort with WG possessed a deletion for CCR5.

5.1.2. Fractalkine/CX3CL1 and CX3CR1

Fractalkine/CX3CL1 is the prototype member of a novel family of mononuclear-directed cell-surface anchored chemokines with a CX3C motif (33). An extracellular chemokine module continues into a mucin chain, which acts as a transmembrane link to a 37 amino-

acid intracellular tail. Fractalkine/CX3CL1 is a potent adhesion mediator for T cells and monocytes to endothelial cells and may promote direct adhesion via ligation of its mononuclear-cell expressed receptor CX3CR1 in the absence of any other adhesive interactions (34). Fractalkine/CX3CL1 expression has been shown to be increased in patients with WG. Bjerkeli *et al* compared expression of chemokine and receptor in peripheral blood mononuclear cells from 18 patients with WG and 15 controls (35). WG patients had markedly elevated levels of fractalkine/CX3CL1 and CX3CR1 compared to controls and this was associated with increased fractalkine/CX3CL1-induced chemoadhesion. The authors concluded that given the ability of fractalkine/CX3CL1 to promote leucocyte infiltration, increased levels of chemokine and receptor could be involved in the pathogenesis of WG.

In a comparative human model of glomerular (ANCA-associated vasculitic glomerulonephritis) and tubulointerstitial (acute cellular renal allograft rejection) inflammation we used *in situ* hybridisation and immunohistochemistry and demonstrated differential expression of fractalkine/CX3CL1 to the dominant inflammatory compartment (36). These results were not consistent with a report from Furuichi and colleagues who by immunohistochemistry only demonstrated the chemokine in the tubulointerstitium in human crescentic glomerulonephritis (37). However two animal models of crescentic glomerulonephritis (34, 38), developed shortly after the original description of the chemokine, showed that inhibiting cellular recruitment mediated through fractalkine/CX3CL1 significantly attenuated the development of glomerulonephritis in these settings.

Fractalkine/CX3CL1 has also been implicated in the pathogenesis of lupus nephritis. Inoue A *et al* performed a functional study by antagonising fractalkine/CX3CL1 function in MRL/lpr mice (39). MRL/lpr mice are genetically predisposed to the development of a systemic lupus erythematosus-like syndrome, which has been found to be clinically similar to the human disease. Baseline expression of the chemokine was significantly increased in the MRL/lpr mice glomeruli. Injection of truncated fractalkine/CX3CL1 analogs before the onset of lupus nephritis significantly reduced glomerular hypercellularity and crescent formation compared to controls. The authors report that this seemed due to a reduction in macrophage accumulation.

Segerer and colleagues studied a heterogeneous group of biopsies including seven patients with crescentic glomerulonephritis. They showed that most infiltrating inflammatory leukocytes at both interstitial and glomerular sites expressed CX3CR1. The distribution pattern was consistent with expression by both T cells and monocytes/macrophages (40).

5.1.3. CXCR3 and ligands

CXCR3 is primarily expressed on Th1 cells and NK cells (41) and has three targeting chemokines; Mig/CXCL9, IP-10/CXCL10 and I-Tac/CXCL11. There

have been several studies which have analysed expression in heterogeneous groups of human native renal disease, including patients with vasculitic glomerulonephritis. Romagnì and colleagues reported an immunohistochemical analysis of CXCR3 expression in a group of patients, including two with rapidly progressive glomerulonephritis, which suggested expression of the receptor by mesangial cells (42). Subsequently Segerer and colleagues assessed mRNA production in the glomerular compartment in human disease and by mesangial cells in culture and showed no evidence for classical CXCR3 expression by mesangial cells (43), indicating that the antibody used in the study of Romagnì recognised an epitope that does not belong to the classical CXCR3 receptor. Segerer did however confirm that mesangial cells do respond to CXCR3 ligands, putatively by non-classical receptors.

Indeed, the dominant compartment expression of CXCR3 in human glomerulonephritis is in the tubulointerstitium and localised to infiltrating T cells, despite the production of IP-10/CXCL10 and Mig/CXCL9 in the glomeruli of biopsies from patients with glomerulonephritis (44). Animal models support this pattern of expression: in a rat model of renal endothelial microvascular injury that produced lesions with the features of vasculitis (45), Panzer *et al* demonstrated an upregulation of IP-10/CXCL10 mRNA that was predominately localised to endothelial cells in the tubulointerstitial area, co-localising with infiltrating T cells. Despite extensive glomerular injury there was no expression by glomerular endothelial cells. Treatment with neutralising anti-IP-10/CXCL10 antibody significantly reduced the number of infiltrating tubulointerstitial T cells. A subsequent study by the same group in a nephrotoxic nephritis model, characterised by a crescentic glomerulonephritis and severe tubulointerstitial inflammation, showed less T-cell infiltration and injury in CXCR3 knock-out mice than wild-type mice (46). Interestingly, there was no difference in baseline renal phenotype between knock-out and wild-type mice suggesting no homeostatic role for CXCR3 in the normal kidney.

5.1.4. Redundancy

At inflammatory sites there is usually expression of multiple inflammatory chemokines and most animal models confirm redundancy: targeting single chemokines may reduce disease load but the inflammatory process is not completely blocked. This principle is likely in vasculitic glomerulonephritis, in addition to the chemokines discussed above, transcripts for other mononuclear directed chemokines including MIP-1 α /CCL3, MIP-1 β /CCL4 and RANTES/CCL5 are also present in the glomerulus (27). Wada and colleagues analysed MIP-1 α /CCL3 in more detail, showing expression of the chemokine protein in cellular crescents, together with the targeted receptor CCR5. Urinary levels of the chemokine correlated with *in situ* expression of CCR5 and CD68 (28). Segerer and colleagues also assessed the relationship between infiltration of CCR5+ leukocytes and Duffy Antigen/Receptor for Chemokine (DARC). They

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demonstrated an increase in the mean number of DARC-positive venules and related this to interstitial and glomerular CCR5+ cells (47).

6. SERUM AND URINE CHEMOKINE LEVELS.

As vasculitis represents an inflammatory disease process that affects the vascular bed, elevated circulating levels of chemokines are often present. A recent study examined levels of RANTES/CCL5, MCP-1/CCL2 and IL-8/CXCL8 in WG and found elevated serum levels of all three chemokines in patients with active disease compared to controls (48). Of relevance to the treatment of vasculitis is that although methylprednisolone down regulated chemokine release from peripheral blood mononuclear cells *in vitro*, this effect was less pronounced in cells derived from patients with vasculitis. A strong indication of the target for disease in vasculitis is the presence of circulating inflammatory endothelial cells in patients with active disease (in WG). Their levels correlated with systemic inflammatory status and extent of organ involvements. These circulating cells expressed high levels of several neutrophil-directed chemokines and induced increased neutrophil migration *in vitro* (49).

Persistent inflammation in many diseases is associated with worse outcome. Ohlsson and colleagues studied this in respect to three cytokines, including IL-8/CXCL8, and showed higher serum levels in stable (remission) patients who subsequently developed adverse events (16). In contrast, Tesar *et al* have reported elevated IL-8/CXCL8 levels in the urine of patients with active ANCA-positive renal vasculitis but not in patients in remission, they concluded that increased renal production may be mediated by infiltrating macrophages and tubular cells (50). In a separate study on the medium vessel vasculitis polyarteritis nodosa (PAN), whilst the serum level of IL-8/CXCL8 was higher in active disease than in normal controls, there was no difference between patients with inactive disease and normal controls (51). In Takayasu's arteritis, a large vessel vasculitis primarily affecting the aorta and its branches, increased levels of IL-8/CXCL8 were present in patients with the disease compared to normal controls, with fourfold increased levels in active compared to inactive disease (52). In patients who went into disease remission, chemokine levels normalised.

In a recent study in patients with rheumatoid arthritis, serum fractalkine/CX3CL1 levels were significantly higher in those with active rheumatoid vasculitis, correlating with disease activity. Further, CX3CR1 messenger RNA levels were significantly greater in peripheral blood mononuclear cells from patients with active rheumatoid vasculitis than in patients with rheumatoid arthritis without vasculitis (53).

A number of authors have sought to utilise plasma and urinary chemokine levels to monitor disease progression and remission. Dhawan *et al* have documented elevated plasma MCP-1/CCL2 in patients with Takayasu's

arteritis and were able to utilise these measurements to identify patients in remission (54). Tam and colleagues have investigated the utility of urinary MCP-1/CCL2 and fractalkine/CX3CL1 for non-invasive assessment of renal vasculitis (55). They found increased urinary levels of MCP-1/CCL2 in patients with active or persistent renal vasculitis, compared to groups who included patients with inactive disease. Interestingly, on treatment, a fall in urinary MCP-1/CCL2 levels preceded an improvement in renal function. This study found no association between fractalkine/CX3CL1 levels and disease activity.

7. LESSONS FROM GIANT CELL ARTERITIS

One of the challenges in studying vasculitis in humans is moving beyond observational studies, to analyses that provide more detailed insights into pathogenetic processes. Whilst there are related animal models (see above), they do not truly represent human disease and have not been interrogated for the kinetics of leukocyte trafficking. Only one study has assessed a role for chemokines and this was a secondary aim of the analysis (see above) (23).

Giant Cell (Temporal) Arteritis (GCA) is a chronic vasculitis of large and medium size vessels that normally occurs in patients over the age of 50. Although it may be generalized, vessel inflammation most prominently involves the cranial branches of the arteries originating from the aortic arch. A number of insights have been derived from the study of GCA. In addition to studies showing increased expression of MCP/CCL2 *in situ* and in the serum of patients with active disease (56, 57) a putative association with differences between MCP-1/CCL2 haplotype frequency in patients and controls has been shown (58).

An important study in GCA linked chemokine receptor and chemokine expression *in situ* to the maturation and continuation of the immune response. In short, Krupa and colleagues showed that in temporal arteries from patients with GCA, at areas of active disease, dendritic cells express CCR7 as one of a number of markers indicating that these cells are present in a mature differentiated phenotype analogous to that seen in secondary lymphoid tissue (59). The cells produced the chemokines CCL18, CCL19, and CCL21, indicating paracrine and autocrine pathways for their aberrant retention. Further studies utilising adoptive T-cell transfer into temporal artery-SCID mouse chimeras showed dendritic cells in arteries gained T-cell stimulatory capacity after injection of lipopolysaccharide (60). Co-implantation of temporal arteries from patients with polymyalgia rheumatica, a subclinical variant of GCA, showed that dendritic cells from these sites could recruit and activate T cells derived from GCA lesions. The implications are that all the mechanisms may be present for local processing and presentation of auto-antigen to activate the afferent limb of the acquired cellular response. These intriguing observations may direct studies at tissues sites in small vessel vasculitis.

9. KAWASAKI DISEASE, HENOC SCHONLEIN PURPURA AND CHEMOKINE RECEPTOR POLYMORPHISMS

Kawasaki disease is an acute systemic vasculitis occurring in young children. The diagnosis is based on clinical symptoms, including fever for at least 5 days, cervical lymphadenopathy, bilateral conjunctivitis, rash, inflammation of the mucous membranes and peripheral oedema. The disease is normally self limiting; however, approximately 25% of patients will develop coronary artery lesions and subsequently develop heart disease (61). An infectious agent is suspected in the pathogenesis. Breunis *et al* have identified polymorphisms in chemokine receptor genes that render certain individuals more susceptible to developing Kawasaki disease (61). These polymorphisms occurred in the CCR3-CCR2-CCR5 gene cluster suggesting that chemokines play a role in mediating the vascular inflammation seen in Kawasaki disease through the association of linked polymorphisms and the clinical phenotype of disease development in response to an infectious agent.

These observations highlight a potential genetic contribution to the development of vasculitis. Animal models of spontaneous disease, such as the Kinjoh mouse, have previously raised this possibility (62). Further, chemokine polymorphisms are known to confer resistance/susceptibility in other human diseases; a 32-base pair deletion in the CCR5 gene has been shown to afford protection against human immunodeficiency virus (HIV) infection (63). In Henoch Schonlein purpura, a form of cutaneous vasculitis that is normally limited to the skin but may involve joints, gut and the kidney, Amoli *et al* have previously demonstrated that patients with HSP who carried the IL-8/CXCL1 allele A were more likely to develop renal involvement (64).

9. CONCLUSION

The data available in human vasculitis, particularly ANCA-associated small vessel vasculitis, suggest a central role for chemokines and their receptors in the pathogenesis of renal and extra-renal disease. This indicates that these molecules may be credible targets for treating the acute inflammatory component of the disease. Further work is required to substantiate the role of the chemokine network in the development of an acquired inflammatory response *in situ*, the persistence of this response in some patients, and the therapeutic targeting of these processes.

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Abbreviations: ANCA: anti-neutrophil cytoplasmic antibodies, GCA: giant cell arteritis, WG: Wegener's granulomatosis, MPA: microscopic polyangiitis, FSNGN: focal segmental necrotising glomerulonephritis, GBM: glomerular basement membrane, PCR: polymerase chain reaction

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