

# Clinical Relevance of Cytokines, Chemokines and Adhesion Molecules in Systemic Vasculitis

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## 1. Introduction

Although the causes of most vasculitis syndromes remain unclear, advances in molecular and cellular immunology have enabled the definition of many effector mechanisms that mediate inflammatory vascular damage. Vascular endothelial dysfunction is observed in a variety of immune-mediated inflammatory diseases. Therefore, endothelial cells (ECs) play a pivotal role in the pathogenesis of systemic vasculitis (Buckley et al. 2005; Kaneider et al. 2006), in large part by amplifying and perpetuating the inflammatory process through the expression and secretion of various cytokines, chemokines, cell adhesion molecules, and other inflammatory molecules. In addition, specific cell-cell interactions, especially between ECs and invading mononuclear cells, including macrophages and lymphocytes, also contribute to the progression of systemic vasculitis and other autoimmune diseases, including rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). In addition, recent studies of the pathogenesis of atherosclerosis have shown that a key feature of atherosclerotic disease is the alternating interaction and amplification of thrombosis and inflammation, which is considered an unusual form of chronic inflammation of the artery wall that is triggered by chemical (e.g., smoking and hyperlipidemia), biological (e.g., *Chlamydia pneumoniae*) and/or mechanical (e.g., shear stress in hypertension) insults to ECs (Libby 2002).

Among the various mediators secreted by activated inflammatory cells are cytokines and chemokines, which appear to be involved in both systemic vasculitis and atherosclerosis. The purpose of this review is to provide an overview of the expression and function of the cytokines and chemokines during the pathogenesis of vasculitic diseases, including systemic vasculitis and related conditions.

## 2. Endothelial cells are an important cellular component of vascular inflammation

The endothelium is the first obstacle to leukocyte transmigration, and both the properties of the chemokines expressed and the functionality of the cells support the idea that ECs serve as a gateway, controlling leukocyte extravasation at sites of inflammation. In this role, the ECs engage in significant proinflammatory activities, including amplifying and

perpetuating inflammatory processes. Among these processes is the proinflammatory facilitation of the expression and secretion of various cytokines, chemokines, cell adhesion molecules and other inflammatory mediators (Mantovani & Dejana 1989) that are critically involved in the pathogenesis of systemic vasculitis (Sneller & Fauci 1997; Cid et al. 2004; Bacon 2005; Buckley, Rainger et al. 2005; Kaneider, Leger et al. 2006). For example, the dysregulation of cytokine/chemokine expression and secretion is crucially involved in the pathogenesis of vasculitis (Cid & Vilardell 2001; Charo & Taubman 2004). Specific cell-cell interactions, especially between ECs and invading mononuclear cells, are also key contributors to the evolution of vascular inflammation and the progression of vasculitis and autoimmune diseases such as RA and SLE, as summarized briefly in Figure 1.

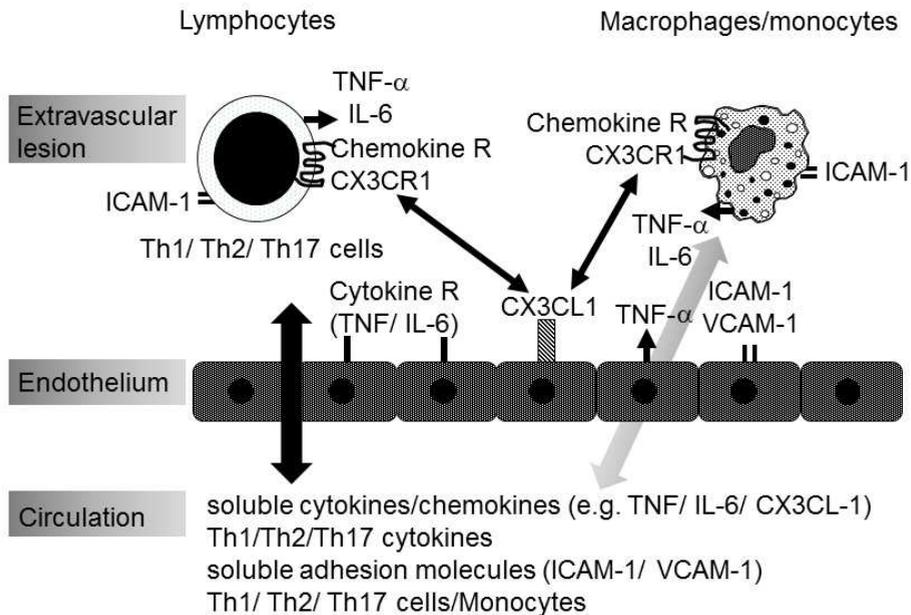


Fig. 1. Cytokines/chemokines and cell adhesion molecules involved in the interaction between endothelial cells and inflammatory/immune cells

The dysregulation of cytokine/chemokine expression, corresponding receptors (R) and adhesion molecules on inflammatory cells/endothelial cells is crucially involved in the pathogenesis of inflammatory vascular diseases.

### 3. Cytokines involved in systemic vasculitis and anti-neutrophil cytoplasmic antibody-associated vasculitis

Although little data are available regarding the participation of proinflammatory cytokines in the pathogenesis of systemic vasculitis, many cytokines are known to play a role in the pathogenesis of vasculitis syndrome (Sundy & Haynes 2000; Cid, Segarra et al. 2004; Muller-Ladner et al. 2005). The cross-talk between ECs, leucocytes, and cytokines fulfills a

homeostatic function and acts as a rapid response in situations of the vascular injury seen in systemic vasculitis.

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is the most common cause of rapidly progressive glomerulonephritis and immune-mediated pulmonary renal syndrome. Small-vessel vasculitis (SVV) is associated with the development of ANCA, which is directed against neutrophil intracellular enzymes, myeloperoxidase (MPO-ANCA), and proteinase-3 (PR3-ANCA). Now that the acute manifestations of the disease can generally be controlled using immunosuppressive drugs, ANCA-associated vasculitis has become a chronic and relapsing inflammatory disorder.

A number of cytokines are capable of cooperating with ANCA to mediate inflammatory events. A recent report by Nolan et al. indicates that circulating anti-MPO IgG acts synergistically with inflammatory stimuli to potentiate cytokine-induced leukocyte firm adhesion and transmigration within murine cremasteric venules and also promotes changes within leukocytes that drive injury at susceptible distant sites (Nolan et al. 2008). Taken together, these findings suggest that neutrophils primed by cytokines in the presence of anti-MPO IgG may exert systemic effects and target specific vascular beds.

Cytokines play a key role in the pathogenesis of systemic inflammation, both in systemic inflammatory processes, such as the upregulation of acute-phase protein synthesis, and as a focal point for the interplay of cytokines in the vascular endothelium (Kunkel et al. 1996; Firestein 2003; Middleton et al. 2004; McInnes & Schett 2007). This endothelial layer is the primary target of circulating mediators and thus, this layer controls the trafficking of cells and molecules from the bloodstream into the underlying tissue.

### 3.1 TNF

TNF has a wide range of biological effects, such as the cellular activation of cells that play a role in host defense, including monocytes/macrophages, B and T lymphocytes and neutrophils, and is considered a primary cytokine in chronic inflammation.

Recently, increasing evidence has indicated that TNF- $\alpha$  plays important roles in vasculitis inflammation. Turesson et al. showed that higher levels of TNF are observed in patients with clinical signs of systemic vasculitis compared with those without any evidence of systemic involvement (Turesson et al. 2001). In addition, Lamprecht et al. showed that intracytoplasmic TNF- $\alpha$  and IL-12 expression is significantly increased in Wegener's granulomatosis (WG) compared with healthy controls. The elevated TNF- $\alpha$  and IL-12 expression in monocytes normalized after clinical remission through treatment with cyclophosphamide and corticosteroid (CYC + GC) (Lamprecht et al. 2002).

In another study, serum levels of TNF- $\alpha$  and soluble CD4 (sCD4), sCD8, IL-6, and sIL-6 receptor (sIL-6R) were examined in RA patients to evaluate the relationship between extra-articular manifestations (EAMs) and immunological alterations (Kuryliszyn-Moskal 1998). Serum concentrations of TNF- $\alpha$ , IL-6, sIL-6R, and sCD4 are significantly increased in RA patients compared with those in healthy individuals. Furthermore, RA patients with clinical signs of systemic vasculitis show significantly higher levels of TNF- $\alpha$  (Kuryliszyn-Moskal 1998).

Recent clinical findings support that TNF- $\alpha$  plays important pathological roles. Indeed, TNF-target therapy such as infliximab in ANCA-associated vasculitis was recently reported to be beneficial in several open-label studies (Booth et al. 2004; Huugen et al. 2006). Taken together, the results of these studies demonstrate that TNF- $\alpha$  exerts crucial effects on the

pathogenesis of vasculitis, and the results further suggest an important role for cellular immune activation in the pathogenesis of microvascular damage.

### 3.2 IL-6

Numerous investigations have demonstrated that IL-6 plays a central role in the regulation of inflammatory and immune responses and hematopoiesis, including B-cell maturation, immunoglobulin production, induction of acute-phase proteins in the liver, and T-cell maturation and activation (Akira et al. 1993). In response to diverse stimuli, IL-6 is expressed in a wide variety of cell types, including monocytes/macrophages, T cells, fibroblasts, and ECs (Akira, Taga et al. 1993; Naka et al. 2002). IL-6 potentially contributes to immune responses, especially B-cell maturation, stimulation and immunoglobulin production, and IL-6 may also play a role in the development of autoimmune disorders such as SLE, which is characterized by the dysregulated production of autoantibodies and polyclonal B-cell activation (Cross & Benton 1999).

Both anti-PR3 and anti-MPO positive IgG fractions from patients with AAV activate ECs in vitro. Interestingly, IL-6 is secreted by human umbilical vein endothelial cells (HUVEC) that are activated by the ANCA-positive IgG fraction isolated from patients with WG and/or microscopic polyangiitis (MPA) (Muller Kobold et al. 1999).

Increased serum levels of IL-6 can be detected in patients with giant cell arteritis (GCA) and polymyalgia rheumatica (PMR), and IL-6 concentrations are significantly correlated with the parameters of disease activity, such as C-reactive protein (CRP) levels and the erythrocyte sedimentation rate (ESR) (Roche et al. 1993; Emilie et al. 1994; Weyand et al. 2000). In addition, Emilie et al. showed that both IL-6 protein and mRNA are detectable in the biopsied temporal artery, and most of the IL-6-producing cells were macrophages and, to a lesser extent, fibroblasts in the intima (Emilie, Liozon et al. 1994).

As mentioned previously, Kuryliszyn-Moskal also observed increased IL-6 levels in RA patients with vasculitis (rheumatoid vasculitis; RV) (Kuryliszyn-Moskal 1998). Statistical analyses encompassing all RA patients, with and without vasculitis, demonstrated a significant correlation among the levels of IL-6, sCD4 and sCD8 and ESR. In turn, although IL-6 and sIL-6R levels were significantly higher in RA patients than in healthy controls, there were no significant differences between the RA groups with and without vasculitis. Furthermore, there was no association between the severity of microvascular damages and the levels of IL-6 and sIL-6R (Kuryliszyn-Moskal 1998). The lack of correlation between IL-6 or sIL-6R and vasculitis complications in RA patients suggests that the IL-6/IL-6R systems might be regulated during the development of vasculitis by different mechanisms or RV disease stage.

### 3.3 Th1 and Th2 cytokines

Churg-Strauss syndrome (CSS) is a type of AAV and is further characterized by severe eosinophilia and, often, granulomatous inflammation. Activated T cells from CSS patients are predominantly T-helper type 2 (Th2) cells, which exhibit an increased production of IL-4 and IL-13. In addition, the PBMCs isolated from patients with CSS and cultured with T-cell-specific stimuli secrete significantly increased amounts of IL-5 compared with PBMCs from healthy controls (Hellmich et al. 2005). The Th2-mediated immune response in CSS may result from an abnormal eosinophil response causing T cell activation and Th2 cytokine production. Similarly, in a majority of patients with CSS, there is a marked increase in Th1

cytokines, including IL-2 and interferon (IFN)- $\alpha$ , in the serum (Grau et al. 1989). IL-25, which is produced by epithelial cells and other innate cells such as eosinophils, basophils, and mast cells, links innate and adaptive immunity by enhancing Th2 cytokine production (Angkasekwinai et al. 2007). Increased levels of IL-25, which are correlated with disease activity and eosinophil levels, have been observed in the serum of active patients with CSS (Terrier et al. 2010). Furthermore, IL-25 has been found within the vasculitic lesions of patients with CSS. This suggests that eosinophils, through the production of IL-25, may play a critical role in promoting Th2 responses in the peripheral blood and target tissues in CSS.

WG is characterized by a predominance of the Th1 response. As described above, Lamprecht et al. showed that intracytoplasmic IL-12 and TNF- $\alpha$  expression is significantly increased in WG patients compared with healthy controls. Monocytic cytokines, especially IL-12, may play a role in the early determination and skewing of the immunoregulatory response toward a Th1 profile. The normalization of the skewed cytokine pattern by CYC + GC treatment may be a prerequisite and an indicator of inducing remission of WG (Lamprecht, Kumanovics et al. 2002). Furthermore, Lamprecht et al. clearly indicated the important role of the Th1-dominant axis in the pathogenesis of WG (Lamprecht et al. 2003). Based on recent evidence, the Th1 phenotype expresses certain chemokine receptors, including CCR5 ligands for CCL3 and CCL5 (Sallusto et al. 1998; Rossi & Zlotnik 2000), while the Th2 phenotype expresses CCR4, ligands for CCL17 (TARC) and CCL22 (MDC). It now appears that chemokines not only have the ability to recruit specific subsets of lymphocytes but also aid in determining the type of immune response that is elicited. These and other aspects of chemokine function may have a significant effect on the development of autoimmune disorders.

Higher expression levels of CCR5, the functional receptor of CCL3-5 (MIP-1), in CD4<sup>+</sup>CD28<sup>-</sup> T cells in localized WG may favor stronger CCR5-mediated recruitment of this T-cell subset into the granulomatous lesions in localized WG, and Th1 cells that lack CD28 expand independent of age and immunosuppressive therapy. The expansion of Th1-type CD4<sup>+</sup>CD28<sup>-</sup>CCR5<sup>+</sup> effector memory T cells might contribute to disease progression and autoreactivity, either directly by maintaining the inflammatory response or as a result of bystander activation (Lamprecht, Bruhl et al. 2003).

### 3.4 Th17 cytokines

The recently characterized IL-17-producing T helper cell lineage (Th17), rather than the Th1 lineage, is involved in several autoimmune diseases (Lyakh et al. 2008; Takatori et al. 2008). In addition, IL-23 is associated with the generation of the Th17 response and IL-17 production (Lyakh, Trinchieri et al. 2008). However, little is known about the role of IL-23 in AAV (Hruskova et al. 2008). Recently, Nogueira et al. showed that serum levels of IL-17A and IL-23 are significantly elevated in acute AAV patients compared with those in healthy controls. In contrast, no significant differences in IFN- $\gamma$  levels were detected between the patient group and the control group. The patients with elevated levels of IL-23 compared with those with low levels of IL-23 had more active disease as measured by the Birmingham Vasculitis Activity Score (BVAS) and had higher ANCA titers. Critically, immunosuppressive therapy did not always effectively suppress the IL-23 or IL-17 production. Additionally, autoantigen-specific IL-17-producing, but not IFN-g-producing, cells were significantly elevated in patients during disease convalescence compared with healthy controls. Taken together, these findings indicate that the Th17 axis and specifically IL-23 may serve as important mediators in the severity of AAV (Nogueira et al. 2010).

The possible role of Th17 cells in WG has not yet been elucidated. Patients with WG who are in remission have a significantly decreased percentage of CD69<sup>+</sup>CD4<sup>+</sup> T cells in response to PR3. These patients also tend to have a lower percentage of CD69<sup>+</sup>CD4<sup>+</sup> T cells in response to other stimuli compared with healthy controls. WG patients who are in remission have significantly increased percentages of Th17 cells (IL-4<sup>-</sup>, IL-17<sup>+</sup>, IFN- $\gamma$ ) and Th2 cells (IL-4<sup>+</sup>, IL-17<sup>-</sup>, IFN- $\gamma$ ) within the activated CD69<sup>+</sup>CD4<sup>+</sup> T cell population. Consistent with the results from Lamprecht, WG patients in remission and healthy controls have similar percentages of Th1 cells (IL-4<sup>-</sup>, IL-17<sup>-</sup>, IFN- $\gamma$ <sup>+</sup>). Furthermore, in Kawasaki disease (KD), Th17 proportions and the expression levels of relevant cytokines (IL-17, IL-6 and IL-23) are upregulated (Sohn et al. 2003; Jia et al. 2010). The skewed Th17 response found in ANCA-positive WG patients following stimulation with the autoantigen PR3 and also in KD patients suggests that IL-17 is involved in disease pathogenesis and may constitute a new therapeutic target (Abdulahad et al. 2008).

### 3.5 MIF

Macrophage migration inhibitory factor (MIF) was originally identified as a soluble factor in the culture medium of activated T lymphocytes that inhibited the migration of macrophages (Bloom & Bennett 1966; Bloom & Shevach 1975) and is recognized as a multipotential cytokine in the regulation of immune and inflammatory responses (Calandra & Roger 2003). Several cell populations, including T cells (Bacher et al. 1996), macrophages/monocytes (Calandra et al. 1994), synovial fibroblasts (Leech et al. 1999) and endothelial cells (Nishihira et al. 1998) express and secrete MIF. Furthermore, MIF is implicated in various inflammatory and immune-mediated diseases, including RA (Leech, Metz et al. 1999; Ayoub et al. 2008), SLE (Hoi et al. 2003; Foote et al. 2004), scleroderma (Selvi et al. 2003) and inflammatory bowel diseases (de Jong et al. 2001). Serum MIF levels are also increased in systemic vasculitis, including WG and AAV (Ohwatari et al. 2001; Becker et al. 2006).

We recently showed that patients with systemic vasculitis have increased serum MIF levels compared with normal controls. Interestingly, patients with MPA have significantly increased levels of serum MIF compared with patients with medium-vessel vasculitis (MVV) and large-vessel vasculitis (LVV). The elevated MIF levels seen in MPA patients are positively correlated with BVAS, CRP levels, ESR, and serum MPO-ANCA titers. Notably, MPA patients in clinical remission after treatment have significantly diminished levels of MIF. Similarly, Becker et al. showed that AAV patients have elevated serum MIF levels (Becker, Maaser et al. 2006). Patients with vasculitis have increased serum levels of endothelial-related molecules, such as adhesion molecules and EC-derived cytokines (Bradley et al. 1994; Johnson et al. 1997; Sundry & Haynes 2000). Indeed, vasculitis-affected small vessels, such as those found in MPA, may have dysregulated EC function (Filer et al. 2003). In patients with MPA, the increased serum MIF may originate from endothelial cells and/or inflammatory cells, including monocytes and neutrophils because these cells are capable of secreting MIF (Calandra, Bernhagen et al. 1994; Nishihira, Koyama et al. 1998; Riedemann et al. 2004) and secreted MIF participates in regulating the proliferation of ECs (Yang et al. 2000). However, there have been no data demonstrating the stimulating capacity of MPO-ANCA to secrete any cytokines including MIF. The lack of evidence may be related to the disease activity and MIF levels because there is a positive relationship between the MPO-ANCA titers and the disease activity of vasculitis (Sinico et al. 2005). Furthermore, MIF upregulates the expression of intercellular adhesion molecule-1 (ICAM-1) on

endothelial cells (Lin et al. 2000). In addition, MIF stimulates the expression and secretion of other inflammatory cytokines, including TNF- $\alpha$  and IL-8 (Leech, Metz et al. 1999; Onodera et al. 2004). The recruitment of leukocytes to the sites of inflammation involves adhesion molecule-dependent interactions with ECs. Collectively, the dysregulated orchestration of MIF from ECs and/or leukocytes and adhesion molecules and the cytokines induced by MIF may play crucial roles in the development of SVV, including MPA.

Taken together, these results suggest that increased MIF appears to be involved in the pathogenesis of systemic vasculitis, especially the small vessel vasculopathy seen in MPA, and may serve as a useful serologic marker of disease activity in vasculitis.

### 3.6 IL-18

IL-18, originally called an IFN- $\gamma$ -inducing factor, has recently been identified as a cytokine synthesized by Kupffer cells and activated macrophages. In combination with IL-12, IL-18 induces IFN- $\gamma$  production by Th1 and NK cells in Th1 cells, B cells, and natural killer cells, promoting Th1-type immune responses (Okamura et al. 1998).

AAV patients have an increased deposition of IL-18 in their renal biopsies, as assessed by immunoperoxidase staining (Hewins et al. 2006). Immunofluorescence microscopy demonstrated that podocytes are the predominant glomerular IL-18-positive cell type, whereas in the interstitium, the myofibroblasts, distal tubular epithelium, and infiltrating macrophages stained positive for IL-18. In vitro, IL-18 primed the superoxide production by ANCA-activated neutrophils at similar levels as TNF- $\alpha$ . Hewins et al. concluded that IL-18 is likely to be important for neutrophil recruitment and priming in AAV (Hewins, Morgan et al. 2006).

The inflammatory activity of vascular lesions in GCA is mediated by adaptive immune responses, with CD4<sup>+</sup> T cells undergoing clonal expansion in the vessel wall and releasing IFN- $\gamma$  (Weyand et al. 2005). Additionally, several polymorphisms within the IL-18 promoter gene are associated with different inflammatory and autoimmune diseases (Sivalingam et al. 2003). Therefore, IL-18 may be implicated in the pathogenesis of GCA. Indeed, a recent study showed that the IL18 -607 allele A is significantly increased in GCA patients compared with controls. In addition, an additive effect between the associated IL-18 and Toll-like receptor 4 genetic variants was observed (Palomino-Morales et al. 2010). In addition, serum IL-18 as well as IL-6 levels were elevated in patients with TA, especially in those with active disease (Park et al. 2006). Serum IL-18 levels correlated well with disease activity of TA. These results suggest that IL-6 and IL-18 might contribute to the pathogenesis of TA and that IL-18 could be a useful marker for monitoring the disease activity of TA.

### 3.7 AIF

The allograft inflammatory factor-1 (AIF-1) is an IFN- $\gamma$ -inducible Ca<sup>2+</sup>-binding cytokine originally cloned from activated macrophages in human and rat atherosclerotic allogeneic heart grafts undergoing chronic transplant rejection (Utans et al. 1995). AIF-1 appears to play a role in the survival and proinflammatory activity of macrophages (Yang et al. 2005). Broglio et al. showed that the biopsied arterial walls of vasculitic neuropathies have increased AIF-1 compared with the nerves of chronic inflammatory demyelinating polyneuropathies and that vascular smooth muscle cells (VSMCs) in vasculitic nerves have increased expression of AIF-1 protein (Broglio et al. 2008). AIF-1 is involved in the proliferation and migration of VSMCs and is rapidly expressed in response to injury and

inflammatory cytokines, but AIF-1 is not expressed in unstimulated VSMCs (Autieri et al. 2000). These studies suggest that AIF-1 plays an important role in inflammatory nerve disease, with either autocrine- or paracrine-induced vasculitis and VSMC proliferation in the damaged vascular tissues.

#### **4. Chemokines involved in systemic vasculitis**

Chemokines are a family of over 40 small secreted proteins that induce chemotaxis and other functional changes in subsets of leukocytes *in vitro*, and they are known to belong to two major superfamilies that share substantial homology via four conserved cysteine residues (Kunkel, Lukacs et al. 1996; Baggiolini 1998; Moser et al. 2004; Szekanecz et al. 2006). They are produced by a wide variety of cell types of both hematopoietic and nonhematopoietic origin (Kasama et al. 2005), and they play a key role in the migration and activation of leukocytes *in vivo* as well as in several autoimmune diseases (Arimilli et al. 2000; Haringman et al. 2004). The CXC chemokine family [e.g., CXCL1 (growth-related oncogene alpha; GRO- $\alpha$ ), CXCL5 (expression of neutrophil-activating protein-78; ENA-78), CXCL8 (IL-8), CXCL9 (monokine induced by interferon-gamma; MIG), CXCL10 (interferon-inducible protein 10; IP-10), CXCL11 (interferon-inducible T cell A chemoattractant; I-TAC) and CXCL16 (CXC chemokine ligand 16)] induces chemotaxis mainly in neutrophils and T lymphocytes. The CC chemokine family [e.g., CCL2 (macrophage chemoattractant protein 1; MCP-1), CCL3 (macrophage inflammatory protein 1 alpha; MIP-1 $\alpha$ ), CCL4 (MIP-1 $\beta$ ) and CCL5 (regulated on activation normal T cells expressed and secreted; RANTES)] induces chemotaxis in monocytes and subpopulations of T lymphocytes. There are two other minor groups, the C and CX3C chemokines, which include CX3CL1 (fractalkine). The members of these families show considerable structural homology and often possess overlapping chemoattractant specificities. In addition to their roles in chemoattraction, the chemokines have been implicated in rheumatic disorders, including RA and SLE (Kunkel, Lukacs et al. 1996; Gerard & Rollins 2001; Bodolay et al. 2002). Few studies have documented the localization of various chemokines in pathological conditions such as systemic vasculitis (Cid & Vilardell 2001; Charo & Taubman 2004; Eardley et al. 2009).

##### **4.1 CC chemokines**

###### **4.1.1 CCL2**

In contrast with CXCL8, CCL2 (MCP-1) plays an important role in chronic inflammation, particularly in activating the migration of macrophages and specific T cells (Daly & Rollins 2003). CCL2 is expressed in mesangial glomerulonephritis, including the vasculitic lesions of the WG kidney, in association with mononuclear cell infiltration (Rovin et al. 1994). Both the protein and the mRNA of CCL2 are detectable in the kidney with cryoglobulinemic vasculitis, which correlates with the infiltration of macrophages (Gesualdo et al. 1997). Furthermore, CCR5, a functional receptor for CCL2, also plays an important role in the tissue inflammation seen in WG. A recent report by Ohlsson et al. showed that elevated CCL2 levels are found in the urine of patients with AAV, even those in remission, and the CCL2 levels are associated with poor prognosis and possibly also with risk of relapse, suggesting that urinary CCL2 is a promising potential prognostic marker in SVV (Ohlsson et al. 2009).

CCL2 and CCL5 appear to be involved in LVV in similar ways as in SSV, including WG, cryoglobulinemic vasculitis, and Takayasu's arteritis (TA). TA is a chronic obliterative inflammatory disease involving the aorta and its main branches. Patients with TA have increased serum concentrations of both CCL2 and CCL5 compared with normal healthy controls; these concentrations closely correlate with disease activity (Noris et al. 1999; Dhawan et al. 2006). These findings suggest that CCL2 and CCL5 can be used as reliable markers in determining the activity of TA. In addition, patients with KD or MVV disease have elevated serum levels of CCL2 and CXCL10 (Shikishima et al. 2003).

#### 4.1.2 CCL26 and CCL17

Recently, a chemokine family that specifically mediates the trafficking of eosinophils to inflammatory and allergic sites has been characterized. CCL11, CCL24 and CCL26 are grouped together as eotaxins (Bisset & Schmid-Grendelmeier 2005). Although these chemokines share only ~40% homology and their genes are located on different chromosomes, they all bind to a common receptor: CCR3. Interestingly, CCL26 (eotaxin-3), rather than the other eotaxins, has also been implicated in the pathogenesis of eosinophilic esophagitis (Blanchard et al. 2006). Eosinophilic infiltration into inflamed tissues is the histologic hallmark of CSS (Zwerina et al. 2009). Recently, studies showed that patients with CSS have increased CCL26, but not CCL11 or CCL24, in serum, and the elevated levels of CCL26 significantly diminished following successful treatment and clinical improvement. The serum CCL26 levels in CSS patients are significantly correlated with the levels of CRP and serum IgE (Polzer et al. 2008).

Recently, studies showed that CSS patients with active disease have significantly elevated serum CCL17 levels compared with controls and patients with inactive disease, and the serum CCL17 levels are correlated with the clinical disease course of CSS and with the absolute eosinophil counts as well as IgE levels (Dallos et al. 2010). CCL17 is a chemokine that is secreted from monocyte-derived dendritic cells (DCs) and ECs and is responsible for the selective recruitment and migration of activated Th2 lymphocytes to affected tissues. Regarding the polarization of Th responses, CSS is a Th2-mediated systemic vasculitis characterized by eosinophilic infiltration, blood eosinophilia, and high IgE levels (Zwerina, Axmann et al. 2009). CCL17 may serve as a biomarker for eosinophilic tissue damage. Taken together, CCL26 and CCL17 seem to be crucial pathogenic mediators that facilitate the development of a targeted pharmacotherapy for CSS.

#### 4.1.3 Other CC and XC chemokines

CCL3, CCL4 and CCL5 may contribute to the pathophysiology of immune disorders including RA and SLE. Zhou et al. demonstrated that the lung tissues from patients with WG are infiltrated by CCR5-positive mononuclear cells and have increased protein concentrations for the ligands of CCR5, including CCL3, CCL4 and CCL5 (Zhou et al. 2003). Moreover, CCR5 and CXCR3 are highly expressed by infiltrating leucocytes that are in the tissue sections from patients with GCA, and the adventitia has a predominant clustering of CCR5- and CXCR3-positive leucocytes, which are co-localized with the expression of CCL5/RANTES mRNA (Bruhl et al. 2005). In addition, XCL1, also known as lymphotactin, is the sole member of the C subgroup of chemokines, and its primary chemotactic activity is controlling the movement of CD4<sup>+</sup> and CD8<sup>+</sup> T cells. XCL1 is mainly expressed by CD4<sup>+</sup>CD28<sup>-</sup> T cells in WG patients (Blaschke et al. 2009). In renal biopsies, the presence of XCL1 is only detected within interstitial CD4<sup>+</sup> and CD8<sup>+</sup> T cells. Meanwhile, there are no

significant differences in XCL1 serum concentrations between WG patients and controls. In functional studies, PMN stimulated with XCL1 demonstrated a significant enhancement of CXCL8 production. Considering its function as a lymphocyte-specific chemoattractant, XCL1 might be a key modulator of T cell recruitment in WG and may support vascular inflammation by the induction of CXCL8 secretion by the PMN. These chemokines and related T cell populations may contribute to the granuloma formation and disease progression in WG.

## 4.2 CXC chemokines

### 4.2.1 CXCL8

The main function of CXCL8 (IL-8) is its role in acute inflammation stimulating the migration of polymorphonuclear neutrophils. However, CXCL8 may be involved in the immune response that induces the migration of specific T cell populations (Moser & Loetscher 2001; Rot & von Andrian 2004). Indeed, CXCL8 has been implicated in lupus nephritis (Holcombe et al. 1994; Rovin et al. 2002).

CXCL8 has been implicated in MVV, including Kawasaki disease (KD) (Asano & Ogawa 2000). In the acute phase of KD, the expression of CXCL8 mRNA in mononuclear cells and polymorphonuclear neutrophils, the level of CXCL8 protein, and the neutrophil chemoattractant activity within the plasma were all increased. Patients with TA, particularly those with LVV, have increased serum levels of CXCL8 (Tripathy et al. 2004).

### 4.2.2 CXCL10

CXCL10 (IP-10) is expressed and secreted by monocytes, fibroblasts, and ECs after stimulation with IFN- $\gamma$  (Neville et al. 1997; Luster 1998; Hanaoka et al. 2003) and plays important roles in the migration of some subsets of T cells into inflamed sites. In contrast to CXCL8, CXCL10 also promotes the regression of angiogenesis (Angiolillo et al. 1995; Strieter et al. 1995). Despite these findings, few studies have been conducted in the field of vasculitis. Mixed cryoglobulinemia (MC) + HCV patients have increased CXCL10 levels that are significantly associated with the presence of active vasculitis (Antonelli et al. 2008).

Recently, Panzer et al. showed that the damage of endothelial cells in different renal compartments induced in rats by selective renal artery perfusion with an anti-endothelial antibody leads to different chemokine expression patterns (Panzer et al. 2006). CXCL10 is expressed in the tubulointerstitium by peritubular capillaries, whereas glomerular endothelial cells do not express CXCL10. The CXCL10 expression pattern overlaps with the pattern of T cell influx. Massive tubulointerstitial T cell infiltration was observed, whereas no T cells were found inside the glomeruli. In this regard, we previously demonstrated that the interaction of monocytes with HUVECs resulted in synergistic increases in CXCL10 expression and secretion, which consequently inhibited endothelial tube formation *in vitro* (Kasama et al. 2002). This induction of CXCL10 was mediated via specific cell surface molecules such as CD40 molecules. This finding suggests the contribution of CXCL10 to the regulation of angiogenesis and the initiation of inflammatory vascular diseases. Taken together, the expression and regulation of CXCL10 play an important, but limited, functional role in microvascular damage.

### 4.2.3 CXCL13

CXCL13, also known as B cell-attracting chemokine 1 or B-lymphocyte chemoattractant, is a member of the CXC subtype of the chemokine superfamily. Similar to the increased levels of

CXCL10, significantly increased levels of CXCL13 were observed in HCV-related MC patients; these levels correlated with vasculitis disease activity (Sansonno et al. 2008). In this report, the mRNA expression of CXCL13 was detected in the portal tract of biopsied liver tissues and also in the skin tissues from MC patients with active cutaneous vasculitis. CXCL13 is mainly associated with extracellular fibrils and, to a much lower extent, with cells displaying a follicular dendritic cell phenotype. Extravasated monocytes, which are potent inducible producers of this chemokine, in inflammatory lesions such as cutaneous vasculitis of patients with cryoglobulinemia may give rise to cells capable of producing CXCL13. In these patients, CXCL13 production may be involved in the exacerbation of cryoglobulinemic vasculitis, particularly through the aberrant dissemination of antigen-priming information from the liver to extrahepatic sites.

### 4.3 CX3C chemokine

#### 4.3.1 CX3CL1

The chemokine CX3CL1, also known as fractalkine, is synthesized as a type I transmembrane protein by ECs (Bazan et al. 1997). The unique CX3C chemokine domain of CX3CL1 is attached to a 241-amino acid mucin stalk, a 19-amino acid transmembrane domain, and a 37-amino acid intracellular domain of unknown function (Bazan, Bacon et al. 1997; Pan et al. 1997). The soluble form of CX3CL1 reportedly exerts a chemotactic effect on monocytes, natural killer (NK) cells, and T lymphocytes. CX3CL1 acts via its receptor CX3CR1 as an adhesion molecule that promotes the firm adhesion of a subset of leukocytes to the ECs under conditions of physiologic flow (Imai et al. 1997; Umehara et al. 2001). Thus, CX3CL1 appears to possess immunoregulatory properties that affect inflammatory and immune cell-EC interactions and the inflammatory responses at inflamed sites. Indeed, numerous studies have implicated CX3CL1 in a variety of inflammatory disorders, including glomerulonephritis, RA, systemic sclerosis, and SLE (Chen et al. 1998; Ruth et al. 2001; Blaschke et al. 2003; Hasegawa et al. 2005; Yajima et al. 2005).

We recently found that serum CX3CL1 levels were significantly higher in all vasculitis patients than in healthy controls (Matsunawa et al. 2009; Kasama et al. 2010). Among the vasculitis patients, CX3CL1 levels were highest in the SVV group, whereas patients with MPA had the strongest expression overall. The elevated CX3CL1 levels observed in MPA patients, as well as in all systemic vasculitis patients, were positively correlated with BVAS, CRP levels and ESR. Similarly, an increased expression of cell-surface CX3CR1 was observed on the peripheral blood CD4<sup>+</sup> and CD8<sup>+</sup> T cells from patients with MPA. Notably, MPA patients in clinical remission after treatment had significantly diminished levels of both CX3CL1 and CX3CR1. Recently, Bjerkeli et al. showed that serum CX3CL1 levels were significantly higher in patients with WG than in healthy controls (Bjerkeli et al. 2007), although no data were presented for the other types of SVV (MPA or CSS). The disease activity in patients with either WG or MPA is closely correlated with the markers of EC damage (Hergesell et al. 1996). Moreover, we found that higher serum CX3CL1 levels are observed in patients with RV than in those with RA without vasculitis or in healthy controls (Matsunawa et al. 2006). The elevated CX3CL1 levels in the RV patients are positively correlated with BVAS, VAI and serum parameters, including rheumatoid factor titers, immune complex (IC-C1q) levels, and ICAM-1 levels. CX3CL1 levels are negatively correlated with complement C4 levels. CX3CL1 levels are diminished in RV patients successfully treated with glucocorticoids and other immunosuppressive drugs. The correlation between CX3CL1 levels and ICAM-1 expression in RV patients suggests

endothelial damage and/or vascular inflammation (Blann et al. 1995; Boehme et al. 1996; Kuryliszyn-Moskal et al. 1996). The higher CX3CL1 levels observed in RV patients compared with RA or extraarticular manifestation (EAM)-RA patients may be an indicator of undiagnosed vasculitis in RA patients. The difference in CX3CL1 levels may also support the hypothesis that vasculopathy underlies EAMs in RA. The accumulation of activated cells and the upregulated expression of inflammatory molecules, including ICAM-1 and CX3CL1, reflect the pathophysiological events leading to vasculitis, suggesting the magnitude of activation and inflammation of ECs. In this regard, increasing evidence suggests that by mediating vascular endothelial activation, TNF- $\alpha$ , which is known to be a potent inducer of CX3CL1 in ECs (Fong et al. 1998; Ahn et al. 2004), plays a key role in the pathophysiology of systemic vasculitis (Kuryliszyn-Moskal 1998; Bacon 2005; Feldmann & Pusey 2006). Thus, CX3CL1 and CX3CR1 appear to possess immunoregulatory properties that affect inflammatory and immune cell-EC interactions and inflammatory responses at inflamed sites. Moreover, their coordinated regulation appears to be involved in the pathogenesis of systemic vasculitis, especially the small vessel vasculopathy seen in MPA, WG and RV, and may serve as a useful serologic marker of vasculitis disease activity.

#### **4.4 Adhesion molecules involved in systemic vasculitis**

Intercellular adhesion is mediated through a variety of receptors that have unique physical and kinetic characteristics, regulatory patterns, and tissue and cell localization that is well suited to their diverse functions. Adhesion molecules, such as ICAM-1, vascular cell adhesion molecule-1 (VCAM-1), and other related molecules, are thought to mediate intercellular adhesion (Gearing et al. 1992). The adhesion molecules ICAM-1, VCAM-1, and E-selectin are regulated by proinflammatory cytokines and play an important role in the binding and activation of leukocytes in inflammatory diseases (Kaneider, Leger et al. 2006).

##### **4.4.1 ICAM-1**

ICAM-1, also known as CD54, is a cell surface glycoprotein that contributes to the interactions between leukocytes and several other cell types, including ECs, fibroblasts, and keratinocytes (Springer 1990; Mackay & Imhof 1993). Although ICAM-1 is constitutively expressed by numerous cell types, including monocytes/macrophages, lymphocytes, and ECs, the stimulation of cells with cytokines or microbial infections can induce a marked increase in ICAM-1 expression. ICAM-1 and endothelial selectin are expressed on the activated endothelium to facilitate the localization of leukocytes to the site of vascular injury.

The presence of adhesion molecules, such as ICAM-1, may reflect the presence of inflammation and damage to the vascular endothelium (Bradley, Lockwood et al. 1994) and suggests that ICAM-1 plays a crucial role in autoimmune rheumatic diseases, including vasculitis and RA (Sfikakis & Tsokos 1997).

Circulating ICAM-1 was detected in the serum of patients with systemic vasculitis and RA (Aoki et al. 1993; Blann, Herrick et al. 1995; Johnson, Alexander et al. 1997; Ara et al. 2001). Patients with active WG have significantly elevated serum levels of ICAM-1, which are correlated with disease activity. These findings suggest that ICAM-1 plays an important role in the pathogenesis of WG and may be used as an additional parameter of disease activity (Ohta et al. 2001). Di Lorenzo et al. showed that in MPO-ANCA-positive MPA patients, higher ICAM-1 and ELAM-1 levels during the active phase and their slower decline during

the treatment period could be a prognostic risk factor for chronic renal factor development (Di Lorenzo et al. 2004).

The ICAM-1 protein, TNF- $\alpha$ , and E-selectin are expressed in ECs and perivascular mononuclear cells in areas of microvascular damage in the salivary glands of RV patients (Flipo et al. 1997). Furthermore, RV patients have elevated levels of sICAM-1 (Voskuyl et al. 1995; Kuryliszyn-Moskal, Bernacka et al. 1996; Witkowska et al. 2003). In addition, Voskuyl et al. (Voskuyl, Martin et al. 1995) demonstrated the involvement of ICAM-3 and ICAM-1 in patients with RV. This involvement suggests that ICAM-1 and ICAM-3 in serum may be useful markers of vascular inflammation in patients with RV, and these proteins may play a crucial role in vasculitis development in RA.

#### 4.4.2 VCAM-1

The immunoglobulin superfamily member VCAM-1 recognizes alpha 4 beta 1 integrin and is expressed on all leukocytes, but not neutrophils (Gearing, Hemingway et al. 1992; Zimmerman et al. 1996). The blockade or inhibition of VCAM-1/alpha 4 beta 1 interaction is expected to have therapeutic potential in treating various inflammatory disorders and autoimmune diseases because the VCAM-1/alpha 4 beta adhesion pathway has a major influence on eosinophil, lymphocyte, and monocyte trafficking (van Dinther-Janssen et al. 1991; Dean et al. 1993; Foster 1996; Matsuyama & Kitani 1996). Several investigators have shown that, in addition to the involvement with adhesion molecules such as ICAM-1, VCAM-1 is clinically involved in RA and systemic vasculitis.

Recently, the significance of VCAM-1 was shown in AAV (Ara, Mirapeix et al. 2001; Schneeweis et al. 2010). The levels of VCAM-1 were higher in all patient groups with vasculitis compared with healthy controls. Enhanced levels of VCAM-1 may be a marker for endothelial cell activation in AAV. The observed correlation between VCAM-1 and creatinine levels might indicate the influence of the vasculitic process on renal function (Schneeweis, Rafalowicz et al. 2010). Noguchi et al. clearly showed that patients with TA have significantly higher levels of VCAM-1 compared with those in healthy controls in Japanese populations and hypothesized that the increased levels of VCAM-1 may be related to disease activity (Noguchi et al. 1998).

In contrast to the role of ICAM-1, the role of VCAM-1 in RV and RA is contradictory. Immunohistological analysis revealed significantly greater expression of VCAM-1 and ICAM-1 in the muscle biopsies from RA patients with RV compared with those RA patients without vasculitis (Verschuereen et al. 2000). In addition, Salih et al. (Salih et al. 1999) reported that RA patients with neuropathy had significantly higher serum levels of soluble VCAM-1 than patients without neuropathy and healthy controls. On the other hand, VCAM-1 was not immunohistochemically detected in the vasculitis lesions in the salivary glands of RV patients, despite the significant expression of ICAM-1 in ECs and perivascular cellular infiltrates (Flipo, Cardon et al. 1997). Taken together, these findings indicate that the role of VCAM-1 is limited in the pathogenesis of RV and RA compared with the role of ICAM-1.

#### 4.4.3 E-selectin

The selectin family of adhesion molecules has been implicated in the initial steps of the interaction between lymphocytes and the endothelium during lymphocyte homing. E-selectin, also known as endothelial-leukocyte adhesion molecule-1, mediates the early phase

of neutrophil binding, as well as the binding of eosinophils, basophils, monocytes, and certain subsets of T cells. E-selectin is also an inducible endothelial adhesion molecule, although its expression follows slower kinetics and reaches its maximum level after 4–6 hours of stimulation with inflammatory mediators. Antibodies against E-selectin strongly bind to the endothelium in the RA synovium, predominantly on the venules and capillaries. In osteoarthritic synovial sections, anti-E-selectin stained a substantially lower percentage of blood vessels and fewer endothelial cells.

Increased serum levels of E-selectin, ICAM-1 and VCAM-1 in active AAV and the normalization of E-selectin during the remission phase suggest that the concentration of soluble levels of these adhesion molecules reflects disease activity (Ara, Mirapeix et al. 2001). Importantly, Tripathy et al. showed the significant roles of these adhesion molecules in LVV, including TA. Patients with inactive TA have elevated levels of E-selectin, but not sVCAM-1 or sICAM-1, and the elevated levels of E-selectin may indicate persistent vasculopathy in clinically inactive disease (Tripathy et al. 2008). Because E-selectin is exclusively expressed on the activated endothelium, elevated levels of E-selectin in inactive TA indicate a persistence of subclinical vascular inflammation during remission of the disease.

Blann et al. (Blann, Herrick et al. 1995) observed a significant augmentation of soluble E-selectin in patients with RA, vasculitis, and scleroderma. Interestingly, the strongest correlations in RA patients were between ICAM-1 and VCAM-1, and a significant correlation between E-selectin and ICAM was observed in systemic vasculitis patients. Similar to other adhesion molecules and TNF- $\alpha$ , the E-selectin protein is expressed at significantly higher levels by ECs and perivascular cellular infiltrates according to immunohistochemistry in labial salivary glands of patients with RV compared with those of patients with inactive RV, RA, or Sjögren's syndrome (Flipo, Cardon et al. 1997). In contrast, Voskuyl et al. (Voskuyl, Martin et al. 1995.) reported no significant elevation of circulating E-selectin in patients with RV. Because the expression of E-selectin and other molecules in the salivary glands was especially high in active RV, the presence of microvascular damage in the salivary gland tissues of patients with RV may reflect the limited and specific dissemination of the vascular inflammatory process.

#### 4.4.4 CD40 ligand

CD40 ligand (CD40L), a member of the tumor necrosis family of transmembrane glycoproteins, is expressed on the surface of recently activated CD4<sup>+</sup> T cells. The interactions between CD40L and CD40 help to activate B cells, induce immunoglobulin production and activate monocytes and dendritic cell differentiation (Grewal & Flavell 1998). Activated T lymphocytes that express CD40L engage CD40 on ECs to augment the expression of proinflammatory cytokines and adhesion molecules (Miller et al. 1998; Thienel et al. 1999). Kim et al. (Kim et al. 2005) described an eosinophilic vasculitis with an infiltration of CD40L-positive eosinophils and a marked increase in serum TNF- $\alpha$  levels. Furthermore, enhanced expression of CD40L on CD4<sup>+</sup> T cells and platelets and increased serum levels of sCD40L were observed in patients with Kawasaki disease, an acute febrile vasculitic syndrome in children (Wang et al. 2003). Although few studies have examined this, these findings suggest that sCD40L is a marker of pathogenic B-cell activation in RA, which often occurs in cases with vasculitis. CD40L and/or CD40 in B-cell-T-cell interactions or interactions of other cells may have important pathogenic roles in vasculitis.

#### 4.4.5 CD44

CD44 is a broadly distributed transmembrane glycoprotein that plays a critical role in a variety of cellular behaviors, including adhesion, migration, invasion, and survival. CD44 mediates cell-cell and cell-matrix interactions primarily through its affinity for hyaluronan (HA), a glycosaminoglycan constituent of extracellular matrices, and potentially through its affinity for ligands, such as osteopontin, collagens, and matrix metalloproteinases (Lesley et al. 1993). Most primary cells express CD44 in a low-affinity state that does not confer sufficient binding to HA. Cellular activation can induce a CD44 transition to a high-affinity state, which then mediates HA binding. The transition from the "inactive" low-affinity state to the "active" high-affinity state of CD44 on leukocytes can be induced by the ligation of antigen receptors to leukocytes, ECs, and other mesenchymal cells by soluble factors, including cytokines (Levesque & Haynes 1997; Cichy & Pure 2000; Brown et al. 2001). In addition to its localization with adhesion molecules, a soluble form of CD44 has been detected in circulation. CD44 has been detected in the serum, lymph nodes, and arthritic synovial tissues (Haynes et al. 1991; Takahashi et al. 1992; Johnson et al. 1993; Katoh et al. 1994). Malignant disease, immune activation and inflammation are often associated with increased plasma levels of sCD44. These findings indicate that the release of CD44 correlates with enhanced local proteolytic activity and matrix remodeling, and CD44 may be a potential biomarker for immune activation and inflammation.

Seiter et al. (Seiter et al. 1998) observed some isoforms of CD44 (e.g., CD44v10) in the vasculitis of patients with either skin-associated vasculitis or autoimmune disease. However, as was the case with VCAM-1, CD44 protein is only weakly expressed in the vasculitis of the salivary glands of RV patients (Flipo, Cardon et al. 1997). These findings indicate that CD44 has a limited role in the development of vasculitis.

#### 4.4.6 Fibronectin

Fibronectin (FN) is a large adhesive glycoprotein found in the extracellular matrix of many tissues. It is also present in body fluids such as synovial fluid (SF) and plasma. FN regulates cellular adhesion and spreading, cell motility, cell growth, differentiation and opsonization via heparin-binding domains (Ruoslahti 1988; Schwarzbauer 1991). Some splice variants of FN are expressed in the synovial endothelium in RA, and the expression of FN is upregulated by the proinflammatory cytokine IL-1 (Boyle et al. 2000). Circulating FN is increased in experimental vascular injury and in the serum of patients with active vasculitis syndromes (Peters et al. 1986; Peters et al. 1989). These observations indicate that the presence of FN reflects the inflammation and injury of the blood endothelium (Jennette et al. 1991).

FN and von Willebrand factor antigen (vWfAg) are produced by blood vessel endothelial cells in response to injury. Bleil et al. examined the sera of 61 patients with various types of systemic vasculitis, the sera of 13 patients with retinal vasculitis, and the sera of 199 patients with rheumatic diseases (Bleil et al. 1991) and found significantly elevated levels of FN and vWfAg in almost all patients with vasculitis syndromes. Therefore, we consider C-ANCA a marker specific for the diagnosis of WG or polyarteritis nodosa, whereas FN and vWfAg are nonspecific but sensitive markers of vascular damage.

Interestingly, FN may be indicative of vascular injury and/or inflammation in RV (Voskuyl et al. 1998). RA patients with RV and RA patients with EAMs have a five-fold and two-fold increase in the serum levels of FN, respectively, compared with patients with uncomplicated RA. These findings suggest that increased levels of FN are more frequently observed in RA patients with EAMs and, in particular, in patients with RV. The mechanisms by which FN is

increased in RV patients remain to be defined. The release of FN into the circulatory systems has been observed after experimental pulmonary injury, and inflammation is considered the result of local blood vessel injury. The high FN levels in RV patients compared with RA patients might be an indicator of undiagnosed vasculitis in RA patients or may support the hypothesis that vasculopathy underlies EAMs in RA. These studies reflect the various levels of tissue inflammation and stimulation of vascular ECs that could ultimately lead to an enhanced release of FN into circulation. Serum FN, in combination with other molecules, such as adhesion molecules and cytokines, may be of significant clinical value as serological markers for vasculitis, including RV.

## 5. Conclusions

Despite outstanding progress made in recent years, the pathophysiology of systemic vasculitis and vasculitic complications has not yet been fully elucidated. The orchestration of the cytokine network and cell-cell interactions may be critical for the development of vascular inflammation. Because subclinical EC damage and vasculitis are occasionally seen in inflammatory rheumatic diseases, it will be important to clinically evaluate and diagnose the complications of systemic and localized vasculitis. Table 1 summarizes the cytokines and inflammatory molecules based on systemic vasculitic diseases.

Diseases	Cytokines	Chemokines	Adhesion molecules
ANCA-associated vasculitis and/or Microscopic polyangiitis	IL-17, IL-23 MIF, IL-18	CX3CL1	ICAM-1, VCAM-1 ELAM-1
Wegener's granulomatosis	TNF, IL-12, IL-17	CCL2, CCL3 CCL4, CCL5 XCL1, CX3CL1	ICAM-1
Churg-Strauss syndrome	IL-4, IL-13, IL-5 IL-2, IFN- $\alpha$ IL-25	CCL26, CCL17	
Kawasaki disease	IL-6, IL-17, IL-23	CCL2, CXCL8 CXCL10	CD40L
Takayasu arteritis	IL-6, IL-18	CCL2, CCL5 CXCL8	E-selectin
Giant cell arteritis	IL-6, IL-18	CCL5	
Rheumatoid vasculitis	TNF, IL-6, sIL-6R	CX3CL1	ICAM-1, ICAM-3 VCAM-1, E-selectin CD40L, CD44, FN
Cryoglobulinemic vasculitis		CCL2, CXCL10 CXCL13	

Table 1. Detectable cytokines, chemokines and adhesion molecules involved in several vasculitis diseases

Taken together, the results of multiple studies indicate that the assessment of serum concentrations of cytokines and inflammatory molecules will provide useful clinical information and a method to monitor therapeutic interventions. Further elucidation of the complex molecular networks will be helpful in understanding the immunopathology of systemic vasculitis and related conditions.

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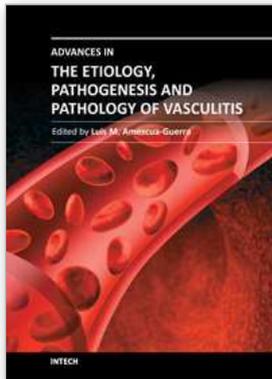
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## **Advances in the Etiology, Pathogenesis and Pathology of Vasculitis**

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This book represents the culmination of the efforts of a group of outstanding experts in vasculitis from all over the world, who have endeavored to devote their work to this book by keeping both the text and the accompanying figures and tables lucid and memorable. Here, you will find an amalgam between evidence-based medicine to one based on eminence, through an exciting combination of original contributions, structured reviews, overviews, state-of-the-art articles, and even the proposal of novel pathogenetic models of disease. The book contains contributions on the etiology and pathology of vasculitis, the potential role of endothelial cells and cytokines in vascular damage and repair as well as summaries of the latest information on several primary and secondary vasculitis syndromes. It also covers selected topics such as organ-specific vasculitic involvement and quality of life issues in vasculitis. The editor and each of the authors invite you to share this journey through one of the most exciting fields of the medicine, the world of Vasculitis.

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