Critical Involvement of Cytokines and Chemokines in the Pathogenesis of Rheumatoid Vasculitis

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Abstract: Vasculitis in rheumatoid arthritis (rheumatoid vasculitis) has a heterogeneous clinical presentation that includes skin disorders, neuropathy, eye symptoms and systemic inflammation. The molecular mechanisms underlying rheumatoid vasculitis are not fully understood; however, the importance of a chronic imbalance of the cytokines and chemokines involved in orchestrating inflammatory responses is well established in patients with rheumatoid arthritis, and similar dysregulation of these mediators has been suggested to occur in patients with rheumatoid vasculitis. In the present review, we discuss the involvement of cytokines and chemokines in the pathogenesis of rheumatoid vasculitis and evaluate their utility as laboratory parameters of active vasculitic disease. Also the involvement of adhesion molecules is discussed.

Introduction

Rheumatoid vasculitis (RV) is an uncommon but severe complication of rheumatoid arthritis (RA) that can cause skin disorders, neuropathy, eye symptoms and systemic inflammation (Vollertsen and Conn, 1990; Genta et al. 2006). Although it is well known that chronically imbalanced expression of cytokines and chemokines is important for orchestrating the inflammatory responses observed in RA patients (Kunkel et al. 1996a; Choy and Panayi, 2001; Firestein, 2003; McInnes and Schett, 2007), the pathogenesis of RV is still not fully understood. RV is defined histologically as vasculitis with an inflammatory infiltrate and destruction of the vessel wall (Vollertsen and Conn, 1990; Bacons and Kitas, 1994; Voskuyl et al. 2003) induced by circulating immune complexes containing rheumatoid factor (RF) and autoantibodies, which form deposits on vessel walls and trigger inflammatory reactions that lead to endothelial cell (EC) activation and injury (Scott et al. 1981; Breedveld et al. 1988). Although the precise mechanisms underlying the pathogenesis of RV have not yet been resolved, it has been suggested that dysregulation of cytokine and chemokine networks, like that which occurs in RA, also occurs in RV.

The purpose of this review is to provide an overview of the involvement of cytokines, chemokines and also adhesion molecules in the pathogenesis of RV and to evaluate their utility as laboratory parameters of active vasculitic disease.

ECs Act as Vasculitic Effectors

Although the causes of most vasculitic syndromes remain unclear, advances in molecular and cellular immunology have enabled many of the effector mechanisms that underlie inflammatory vascular damage to be defined. ECs play a pivotal role in the pathogenesis of systemic vasculitis, and vascular endothelial dysfunction is a well studied feature of a variety of immune-mediated inflammatory diseases, including vasculitis (Sneller and Fauci, 1997; Cid et al. 2004; Buckley et al. 2005; Kaneider et al. 2006; Bacon, 2005). ECs engage a number of proinflammatory activities, including expression and secretion of various cytokines, chemokines, cell adhesion molecules and other inflammatory mediators (Mantovani and Dejana, 1989). Specific cell-cell interactions, especially between ECs and invading mononuclear cells, are key contributors to the progression of vasculitis and autoimmune diseases such as RA and systemic lupus erythematosus (SLE).

Another important feature of inflammatory and immune responses is expression of adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1

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(VCAM-1) and other related molecules by ECs. This response is mediated via a variety of receptors with unique physical characteristics, kinetics, regulatory patterns, and tissue and cell distributions that are well suited to the diverse functions of these mediators (Springer, 1990; Gearing et al. 1992). Once expressed, the activities of adhesion molecules are regulated by proinflammatory cytokines and are crucial for the binding and activation of leukocytes in inflammatory diseases (Kaneider et al. 2006).

Involvement of Cytokines

Cytokines are essential to the pathogenesis of RA, acting both in systemic inflammatory processes, such as upregulation of acute phase protein synthesis, and as a focal point for interplay with the vascular endothelium (Kunkel et al. 1996a; Firestein, 2003; Middleton et al. 2004; McInnes and Schett, 2007). This interplay between circulating mediators and the endothelium controls the trafficking of cells and molecules from the bloodstream into the underlying tissue. Indeed, recently developed approaches to the treatment of RA focus on blocking the actions of one such mediator, tumor necrosis factor alpha (TNF-α), using an anti-TNF-α monoclonal antibody and a soluble TNF receptor-fusion protein complex (Feldmann et al. 1996; Taylor, 2003).

Cross-talk between ECs, leucocytes and cytokines fulfills a homeostatic function and acts as a rapid response facility in situations of vascular injury, like those seen in RV and systemic vasculitis.

TNF-α

There is increasing evidence of cytokine abnormalities in rheumatic disease, but few data dealing with their contribution to the pathogenesis of RV in RA are available. One of the many proinflammatory cytokines known to be involved in the pathogenesis of both RV and RA (Cid et al. 2004; Sundy and Haynes, 2000; Muller-Ladner et al. 2005) is TNF-α, a member of the TNF cytokine superfamily. TNF -α is expressed as a transmembrane protein that is cleaved by a specific metalloprotease and released as a soluble homotrimer, whereupon it binds to membrane receptors p55 (TNF-RI) and p75 (TNF-RII), via which it exerts a wide range of biological effects, including activation of cells involved in host defence (monocytes/macrophages, B and T lymphocytes, and neutrophils). Flipo et al. (Flipo et al. 1997) demonstrated that significant amounts of both immunoreactive TNF-α and ICAM-1 are expressed in ECs and in perivascular cellular infiltrate within labial salivary glands from patients with active RV. This expression occurred independently of, and perhaps in combination with, RA and Sjögren's syndrome. Importantly, there was a significant reduction in TNF-α expression in salivary glands after successful treatment of the vasculitic disease. In addition, when serum levels of TNF-α, soluble CD4 (sCD4), sCD8, IL-6 and sIL-6 receptor (sIL-6R) were assayed in 80 RA patients to evaluate the relationship between extra-articular manifestations (EAMs) and immunological alterations (Kuryliszyn-Moskal, 1998), it was found that levels of TNF-α, IL-6, sIL-6R and sCD4 were all significantly higher in RA patients than healthy individuals. Furthermore, RA patients with clinical signs of systemic vasculitis showed significantly higher levels of TNF-α and IL-6 than patients without vascular involvement (Kuryliszyn-Moskal, 1998). Consistent with those findings, Turesson et al. observed higher levels of TNF-α in patients with clinical signs of systemic vasculitis than in those without evidence of systemic involvement (Turesson et al. 2001).

Although anti-TNF therapy (e.g. infliximab) effectively reduces disease activity and inflammation in RA, the complication of cutaneous vasculitis can develop during anti-TNF-α therapy (McCain et al. 2002; Guillevin and Mouthon, 2004; Scott and Kingsley, 2006; Olsen and Stein, 2004). It is noteworthy in that regard that Srivastava et al. recently demonstrated that cytokine expression is dysregulated in patients with Crohn's disease complicated by cutaneous lymphocytic vasculitis, but not in those with RA (Srivastava et al. 2005). In that report, upregulated expression of RANTES, eotaxin, IL-15, IL-16 and IL-18 accompanied the exacerbation of vasculitis after infliximab administration, indicating polarization of a Th1-skewed inflammatory response. In addition, a permanent B-cell line (MD-B) established from the same patient with vasculitis exhibited markedly increased expression of IL-8, IP-10, MIP-1 and RANTES, as well as TNF-α and IL-6, during the highly active phase of the vasculitis.

In contrast to adverse effects of anti-TNF therapy, there are some evidences that anti-TNF therapy leads to marked clinical improvement in

patients with active RV (van der Bijl et al. 2005; Puéchal et al. 2007). Puéchal et al. demonstrated that clinical remission was achieve in two thirds (6 patients) of refractory RV patients with a significant decrease in prednisone dose. In addition, preliminary data suggest that several forms of vasculitis, Behçet's disease, Churg-Strauss vasculitis, polyarteritis nodosa, and giant cell arteritis, among others, appear responsive to TNF antagonists: as reviewed byAtzeni et al. (Atzeni et al. 2007).

Taken together, these results indicate that TNF-α occupies a central position in the cytokine network involved in the pathogenesis of RV and suggests that activation of cellular immune responses makes an important contribution to the observed microvascular damage.

IL-6

It is well established 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). IL-6 is expressed in a wide variety of cell types, including monocytes/macrophages, T cells, fibroblasts and ECs in response to diverse stimuli (Akira et al. 1993; Naka et al. 2002). Given the potential contribution of IL-6 to immune responses, especially stimulation and maturation of B cells and their production immunoglobulins, it has been suggested that IL-6 is involved in the development of autoimmune disorders like SLE, which are characterized by dysregulated production of autoantibodies and polyclonal B cell activation (Cross and Benton, 1999). In addition, IL-6 is crucially involved in inflammatory conditions and immune-mediated diseases and is an important mediator of RA (Hirano et al. 1988; Alonzi et al. 1998; Naka et al. 2002; Nishimoto and Kishimoto, 2006), though little information is available on IL-6 expression in vasculitis (Weyand, 2000; Ohlsson et al. 2004; Hernandez-Rodriguez et al. 2004). Kuryliszyn-Moskal demonstrated that IL-6 levels are elevated in RA patients with vasculitis (Kuryliszyn-Moskal, 1998). They reported that serum levels of IL-6 and its specific soluble receptor (sIL-6R), as well as TNF-α and sCD4, were significantly higher in RA patients than healthy individuals. Furthermore, 33 RV patients with clinical signs of systemic vasculitis showed significantly higher levels of IL-6 (37.9 ± 21.3 pg/mL) than 47 RA patients without vascular involvement (15.4 ± 13.0 pg/mL). Statistical analyses of all RA patients, with and without vasculitis, showed significant correlations between IL-6 levels and those of sCD4 and sCD8, as well as the erythrocyte sedimentation rate (ESR). Although IL-6 and sIL-6R levels were significantly higher in RA patients than healthy controls, there were no significant differences between RA patients with and without vasculitis. There was also no association between the severity of microvascular damage and the levels of IL-6 and sIL-6R (Kuryliszyn-Moskal, 1998). The apparent absence of a correlation between IL-6 or sIL-6R and vasculitic complications in RA patients suggests that the mechanisms regulating IL-6/sIL-6R systems during the development of vasculitis differ from those acting at later disease stages.

Involvement of Chemokines

Chemokines are a family of over 40 small, secreted proteins known to induce chemotaxis and other functional changes in subsets of leukocytes *in vitro*. They are produced by a wide variety of cell types of both hematopoietic and nonhematopoietic origin, and have been shown to play key roles in the activation and migration of leukocytes *in vivo*. Chemokines are known to belong to two major superfamilies that share substantial homology via four conserved cysteine residues (Kunkel et al. 1996b; Baggiolini, 1998; Moser et al. 2004). The CXC chemokine family [e.g. CXCL1 (growth related oncogene alpha; GRO-α), 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, whereas the CC chemokine family [e.g. CCL2 (macrophage chemoattractant protein 1; MCP-1), CCL3 (macrophage inflammatory protein 1 alpha; MIP-1α) and CCL5 (regulated on activation normal T cells expressed and secreted; RANTES)] induces chemotaxis in monocytes and subpopulations of T lymphocytes. Two other minor groups, the C and CX3C chemokines, which include CX3CL1 (fractalkine), also have been identified. Members of these families show

considerable structural homology and often possess overlapping chemoattractant specificities. In addition to their chemoattractant activity, chemokines have been implicated in rheumatic disorders, including RA and SLE (Kunkel et al. 1996b; Gerard and Rollins, 2001; Bodolay et al. 2002). Although a number of studies have documented localization of various chemokines in regions affected by pathological conditions such as systemic vasculitis (Charo and Taubman, 2004; Cid and Vilardell, 2001), thus far there is no published evidence of the involvement of chemokines other than CX3CL1 in RV.

CX3CL1

CX3CL1, also known as fractalkine or neurotactin, is synthesized as a type I transmembrane protein (Bazan et al. 1997). Its unique CX3C chemokine domain 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 et al. 1997; Pan et al. 1997). The soluble form of CX3CL1 (sCX3CL1) reportedly exerts a chemotactic effect on monocytes, NK cells and T lymphocytes. Acting via its receptor, CX3CR1, sCX3CL1 functions as an adhesion molecule able to promote firm adhesion of a subset of leukocytes to ECs under conditions of physiological flow (Imai et al. 1997; Umehara et al. 2001). Studies of vasculitis (Lucas et al. 2001; Cockwell et al. 2002) have shown ECs to be the major cellular source of CX3CL1, and EC-derived CX3CL1 likely plays a key role in such pathological conditions as vascular inflammation, glomerulonephritis and pulmonary arterial hypertension (Chen et al. 1998; Chapman et al. 2000; Furuichi et al. 2001; Balabanian et al. 2002; Umehara et al. 2004). Thus, CX3CL1 appears to possess immunoregulatory properties that affect inflammatory and immune cell-EC interactions and inflammatory responses at inflamed sites. Indeed, investigations by several groups, including our laboratory, 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 also recently demonstrated significant expression of CX3CL1 in RV (Matsunawa et al. 2006). In that report, 98 patients with RA were classified into three groups: 1) RA patients with no clinical signs of vasculitis (RA group); 2) RA patients with a recent onset of EAMs, including peripheral neuropathy, skin ulcers, necrotizing glomerulonephritis, fibrosing alveolitis, ischaemiccolitis, nailfold lesions, pericarditis, pleuritis, (epi-)scleritis and multiple rheumatoid nodules, but no histologically proven vasculitis (EAM-RA group); and 3) RA patients with a recent onset of histologically proven vasculitis (RV group). Significantly higher serum levels of sCX3CL1 were seen in the RV (4980.1 ± 719.3 pg/mL) and EAM-RA (3946.9 ± 575.3 pg/mL) groups than in the RA group (1846.7 ± 410.9 pg/mL). In the RV group, moreover, there were significant correlations between sCX3CL1 levels and disease activity scores for vasculitis. There were also significant positive correlations with serum immune complex levels (IC-C1q) and negative correlations with serum complement levels (C4). What's more, sCX3CL1 levels in the RV group correlated significantly with ICAM-1 levels, which suggests endothelial damage and/or vascular inflammation (Kuryliszyn-Moskal et al. 1996; Blann et al. 1995; Boehme et al. 1996). We suggest that the accumulation of activated cells and upregulated expression of inflammatory molecules, including ICAM-1 and CX3CL1, described here reflect the pathophysiological events leading to vasculitis. Consistent with that idea, our immunohistochemical analysis clearly shows that CX3CL1 protein is localized mainly in ECs within vasculitic arteries. Furthermore, expression of CX3CL1 mRNA was significantly greater in peripheral blood mononuclear cells from RA patients with active RV than from RA patients without RV or controls. The elevated sCX3CL1 levels sometimes seen in the RA or EAM-RA patients might be interpreted as an indicator of undiagnosed vasculitis in RA patients or as support for the hypothesis that vasculopathy underlies EAMs in RA. Notably, serum sCX3CL1 levels were significantly diminished following successful treatment and clinical improvement.

More recently, Bjerkeli et al. showed that serum CX3CL1 levels in patients with Wegener's granulomatosis (WG) were significantly higher than in healthy controls (Bjerkeli et al. 2007). Together with our results from RV patients (Matsunawa et al. 2006), these results suggest that the level of sCX3CL1 in serum is indicative of the degree of EC activation and inflammation in small vessel vasculitis, especially in RV and WG.

Finally, it has been demonstrated that stimulation of ECs by TNF-α is a significant and potent inducer of CX3CL1 expression (Fong et al. 1998; Imaizumi et al. 2004; Ahn et al. 2004). Moreover, it now appears that through its activation of ECs TNF-α contributes substantially to the pathophysiology of systemic vasculitis (Genta et al. 2006; Feldmann and Pusey, 2006). Thus pathogenesis of cytokine cascades involving CX3CL1 and inflammatory cytokines, especially TNF-α, are apparently central to the pathogenesis of RV.

Involvement of Adhesion Molecules

Adhesion molecules, such as ICAM-1 and VCAM-1 are thought to mediate intercellular adhesion (Gearing et al. 1992). The adhesion molecules ICAM-1 and VCAM-1 are regulated by proinflammatory cytokines and play an important role in the binding and activation of leukocytes in inflammatory diseases such as RV (Kaneider et al. 2006).

ICAM-1 is expressed on rheumatoid synovial tissues (Hale et al. 1989; Ziff, 1991; Johnson et al. 1993), and administration of ICAM-1antibodies in animal models of arthritis slows disease progress (Kakimoto et al. 1992). Circulating sICAM-1 was detected in the serum of patients with RA and systemic vasculitis (Aoki et al. 1993; Blann et al. 1995; Johnson et al. 1997; Ara et al. 2001), and *in situ* expression of ICAM-1 protein in patients with RV has been reported (Flipo et al. 1997). In that report, ICAM-1 protein, TNF-α, and E-selectin were expressed in ECs and perivascular mononuclear cells in areas of microvascular damage in salivary glands of RV patients (Flipo et al. 1997). Furthermore, RV patients had elevated levels of sICAM-1 (Voskuyl et al. 1995; Kuryliszyn-Moskal et al. 1996; Witkowska et al. 2003). RA patients with clinical signs of systemic vasculitis showed significantly higher levels of sICAM-1 than those without vascular involvement. That study assessed levels of circulating ICAM-1 (cICAM-1), ICAM-3 (cICAM-3), and E-selectin (cE-selectin) in 14 RA patients with vasculitis, 47 RA patients without vasculitis, and 100 healthy controls. RA patients with RV had significantly elevated levels of cICAM-1 (683 ± 241 ng/mL) and cICAM-3 (369 ± 150 ng/mL) but not cE-selectin compared to RA patients without RV (cICAM-1, 418 ± 76; cICAM-3, 167 ± 112 ng/mL) (Voskuyl et al. 1995).

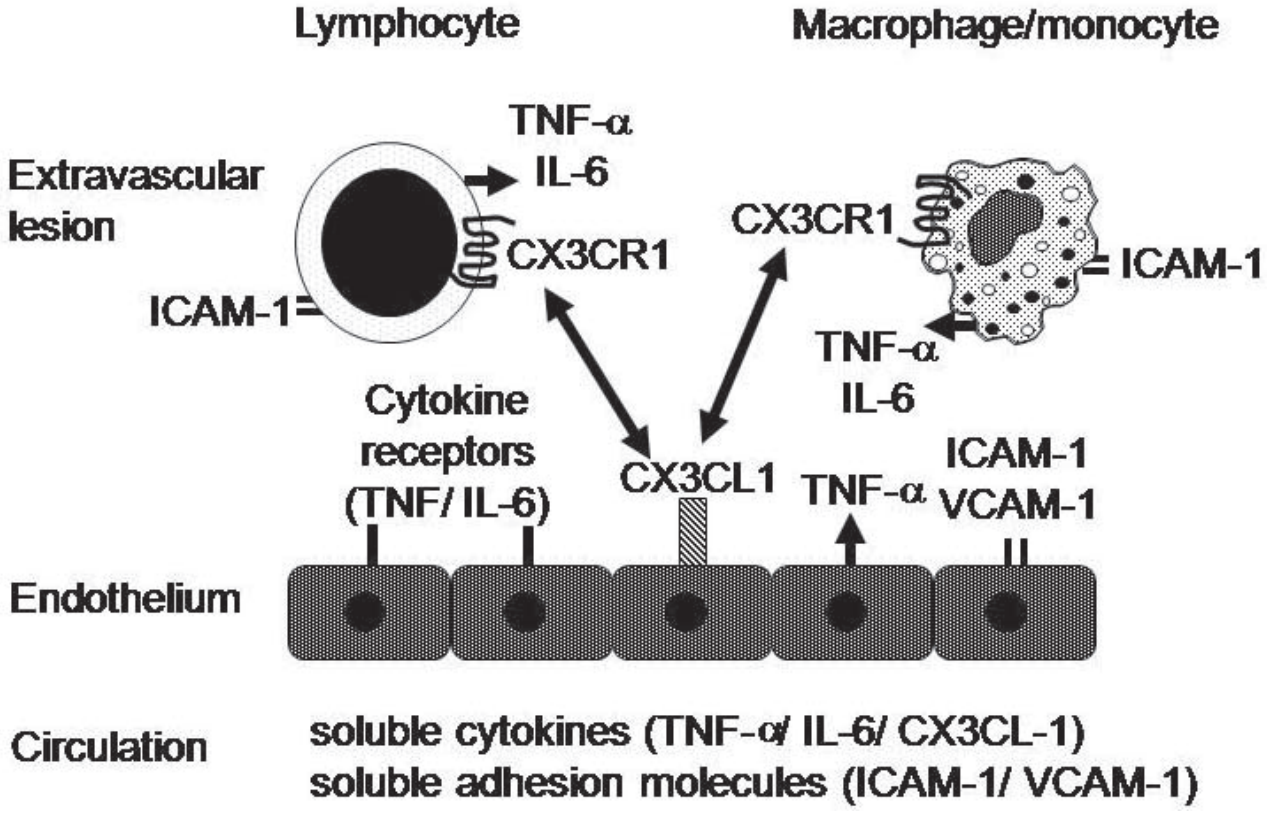

Figure 1. Cytokines/chemokines and cell adhesion molecules involved in RV.

Table 1. Serum levels of soluble cytokines in RA patients with or without vasculitis and correlations with other markers of inflammation.

Soluble molecules in serum	RV	RA	Correlated with	Reference
TNF-α (pg/ml)	55.4 ± 18.3	43.6 ± 10.5	N.D.	Kuryliszyn-Moskal
IL-6 (pg/ml)	37.9 ± 21.3	15.4 ± 13.0	CD4*, CD8*, ESR*	Kuryliszyn-Moskal
CX3CL1 (ng/ml)	4.98 ± 0.7	1.85 ± 0.4	immune complex, complements sICAM-1, disease activity	Matsunawa et al.

*The results of correlations are from all RA patients.
Abbreviations: N.D.: not done; RA: rheumatoid arthritis; RV: rheumatoid vasculitis; TNF-α: tumor necrosis factor-α.

This suggests that cICAM-1 and cICAM-3 may be useful markers of vascular inflammation in patients with RV, and have a crucial role in vasculitis development in RA.

In addition to adhesion molecules, such as ICAM-1, VCAM-1 has been reported to be clinically involved in RA and systemic vasculitis by several investigators (Koch et al. 1991). In contrast to ICAM-1, data concerning VCAM-1 in RV and RA are contradictory. Salih et al. (Salih et al. 1999) reported that RA patients with neuropathy had significantly higher serum levels of soluble VCAM-1 (sVCAM-1) than patients without neuropathy and healthy controls. On the other hand, circulating levels of sVCAM-1 were lower or unchanged in RA and systemic vasculitis (Blann et al. 1995). Taken together, these findings indicate that the role of VCAM-1 is limited in the pathogenesis of RV and RA compared to ICAM-1.

Conclusions

Despite outstanding progress made in recent years, the pathophysiology of RA and RV is not yet fully understood. Altered orchestration of the cytokine network and cell-cell interactions are likely essential for the development of RV. Listed in Figure 1 are the cytokines/chemokines and cell adhesion molecules seen in RV. Their correlations with other markers are outlined in Table 1. The fact that subclinical EC damage and vasculitis are occasionally seen in inflammatory rheumatic diseases (e.g. RA) highlights the importance of clinical evaluation and diagnosis of complications involving systemic and localized vasculitis. Collectively, the results of the investigations summarized in this article indicate that assay of the serum concentrations of cytokines and inflammatory molecules will provide useful clinical information and a way to monitor the efficacy of therapeutic interventions. Further elucidation of the complex molecular networks will certainly add to our understanding of the immunopathology of systemic vasculitis and the RV seen in RA.

Abbreviations

RA, rheumatoid arthritis; RV, rheumatoid vasculitis; TNF, tumor necrosis factor; IL-6, interleukin-6; EC, endothelial cell.

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