Vasculitis and Adhesion Molecules

2. Role of Adhesion Molecules in Vasculitis Syndrome

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Introduction

Vasculitis, which is defined as inflammation and necrosis of the vessel wall, is a primary process or it is associated with other underlying pathological conditions such as collagen-vascular, infectious, and malignant diseases (1, 2). It has been demonstrated that both primary vasculitis and vasculitis associated with collagen-vascular diseases are based on the immunopathological mechanisms (3). Although immune complex formation and subsequent complement activation is a main arm in the process, increasing evidence supports the notion that mechanisms other than immune complexes may be involved in the pathogenesis of vasculitis (1). Here, we review the clinicopathological features of vasculitis syndrome, and focus on the role of adhesion molecules in the mechanisms of vasculitis, particularly associated with systemic lupus erythematosus, a prototype autoimmune disease.

Caliber of affected vessels and the clinical conditions

A long list of individual diseases with vasculitis is now integrated into the "vasculitis syndrome", which is categorized into subgroups primarily according to the size of affected vessels (4) as shown in Fig. 1. Given the size of affected vessels, one can speculate the clinical manifestations (5) (Fig. 1). Vasculitis in the capillaries, arterioles, or venules in the dermis may result in erythema, palpable purpura or livedo reticularis and pathological features in these conditions are largely leukocytoclastic vasculitis and the prognosis is fairly good. In contrast, vasculitis in small and medium-sized muscular arteries sometimes leads to infarction of vital organs, a life-threatening condition. Necrotizing vasculitis is a typical pathological picture in this subgroup, particularly in polyarteritis nodosa (6). The vasculitis affecting the large vessels such as the aorta or its main branch exhibit unique clinical manifestations such as signs of lack of pulse or hypertension.

Since necrotizing vasculitis is the most important entity in clinical settings in terms of prognosis, we focus on the mechanism of the vasculitis affecting small – medium arteries with necroizing vasculitis. Since polyarteritis nodosa is rare in Japan, we attempt to investigate the mechanism of necrotizing vasculitis in patients with systemic lupus erythematosus (SLE), that is intractable and often fatal (7).

Role of surface structures on peripheral blood lymphocytes from SLE patients with vasculitis

In the affected vessels, leukocytes can be observed around vessels even without immune complex depositions. So, we hypothesize that surface structures important for the pathogenesis of vasculitis should be expressed on the peripheral blood leukocytes from patients with vasculitis. To determine these surface molecules, we attempted to develop monoclonal antibodies (mAbs) which react against these structures by immunizing the PBL from vasculitis patients (8). We successfully established a series of mAbs against PBL from a SLE patient complicated with necrotizing vasculitis of superior mesenteric artery and perforation of ileum. Then, those mAbs were screened in the criteria that the expression level of the surface molecules on PBL from vasculitis patients is higher than that from normal PBL. Among a series of candidate mAbs, we found that the expression of the surface molecules defined by the clone, SM-27 was significantly high in the SLE patients with vasculitis (8). Immunoprecipitation analysis has been shown that the surface molecule identified by SM-27 is VLA-4, one of β1 integrin, which mediates adhesion between lymphocytes and endothelial cells through interaction between VLA-4 and VCAM-1 (9) (Fig. 2). These results may imply that increased expression of VLA-4 is responsible for the pathogenesis of vasculitis by virtue of enhanced adhesion between peripheral blood lymphocytes and vascular endothelium.

VLA-4 and vasculitis

To this end, we analyzed the expression of various integrin adhesion molecules on PBL from normal subjects, and from SLE patients without and with vasculitis (10). We found that the expression of β2 integrins such as LFA-1 and Mac-1 are significantly elevated in active SLE with or without vasculitis, suggesting that these adhesion molecules may be related to the activity of the disease. In contrast, enhanced expression of VLA-4 is observed in SLE patients with vasculitis, whereas its expression in SLE without vasculitis is comparable to that in normal controls. Furthermore, the adhesive function of VLA-4 against CS-1 domain of fibronectin as well as VCAM-1 on cytokine-activated human umbilical vein endothelial cells (HUVEC) was also significantly increased in SLE patients with vasculitis (10).

Accumulating evidence now supports the above observa-
- erythema
- purpura
- glomerulonephritis
- livedo reticularis
- mononeuritis multiplex
- nodules
- skin ulcers
- infarction
- hypertension
- pulseless

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**Clinical manifestations**

<table>
<thead>
<tr>
<th>Disease entity</th>
<th>Caliber of affected vessels</th>
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<tbody>
<tr>
<td>Aorta</td>
<td>Small artery</td>
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<tr>
<td>Leukocytoclastic vasculitis</td>
<td>Arteriole</td>
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<tr>
<td>Henoch-Schönlein purpura</td>
<td>Capillary</td>
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<tr>
<td>Mixed cryoglobulinemia</td>
<td>Venule</td>
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<tr>
<td>Microscopic polyarteritis</td>
<td>Vein</td>
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<tr>
<td>Wegener’s granulomatosis, Churg-strauss syndrome</td>
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<tr>
<td>Polyarteritis nodosa</td>
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<tr>
<td>Temporal arteritis</td>
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<tr>
<td>Takayasu Aortitis</td>
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**Expression of integrin ligands in vasculitis**

Given the evidence that integrin adhesion molecules are upregulated in peripheral blood lymphocytes and leukocytes, one can speculate that the ligands for integrins are also upregulated. The adhesion molecules on vascular endothelial cells are independently regulated. P-selectins and E-selectins are rapidly induced upon activation, while ICAM-1 and VCAM-1 are induced after 24 to 48 hours by stimulation, such as lipopolysaccharides (LPS) or pro-inflammatory cytokines such
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**Figure 2. Adhesion between leukocytes and endothelial cells.**

**Figure 3. Mean fluorescence intensity of VLA-4 (SM-27) in a series of rheumatic diseases.**

**Figure 4. Expression of adhesion molecules in endothelial cells (16).**

as IL-1 or TNF-α (16, 17) (Fig. 4). It has been demonstrated that the level of VCAM-1, ICAM-1, and E-selectin on vascular endothelial cells is upregulated in skin biopsy specimens from SLE patients or in kidney biopsy samples from renal vasculitis patients (18, 19). These results further suggest that the pairs of integrins and integrin-ligands are simultaneously upregulated and participate in the pathogenesis of vasculitis. Soluble ICAM-1 and VCAM-1 has been shown to be increased during the active stage of the vasculitis (20–23), implying that the proinflammatory cytokines or LPS may stimulate vascular endothelial cells to upregulate these integrin ligands and selectins as a priming factor.

**Schwartzman reaction, an alternative mechanism for systemic vasculitis**

It has been pointed out that circulating or deposited immune complexes are not detected in many vasculitis patients. However, immune deposits may be demonstrated in vessel walls without accompanying vasculitic lesions, indicating that the mere presence of immune deposits does not necessarily result in tissue injury with inflammatory infiltrates and fibrinoid necrosis of the vessel wall. In this setting, an alternative mechanism such as the Schwartzman reaction has been postulated to participate in the pathogenesis of vasculitis (24). In this model, intravascular LFA-1/ICAM-1 (leukocyte-endothelium) adhesion was shown to be necessary for this type of cytokine-primed, leukocyte-dependent vasculitis to occur. In this regard, our results demonstrating the upregulated expression and function of VLA-4 in addition to that of LFA-1 are consistent with the Schwartzman reaction hypothesis. This notion is now widely accepted not only in vasculitis associated with collagen-vascular diseases, but also in primary vasculitis syndromes (14, 15, 25).
Introduction

Takayasu arteritis is defined as a nonspecific aortitis involving the aorta and its branches. It is also called pulseless disease (1–3). Even though the prognosis is markedly improved due to the progress in diagnosis and therapy, the etiology of this morbid condition is still obscure, and a major complication of Takayasu arteritis, aortic regurgitation, affects the prognosis among Japanese. Ethnic differences in the prevalence of this disease and findings from genetically identical twin cases strongly suggest that some genetic factors may play a role in the pathogenesis of Takayasu arteritis. To elucidate these genetic factors, we studied Human Leukocyte Antigen (HLA) in this disease and found that HLA-B52 and B39.2 are significantly associated with Takayasu arteritis in Japanese. In addition, linkage analysis using microsatellite marker showed that...