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Contribution of Myeloperoxidase in Vasculitis Development

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SUMMARY: Infiltrated neutrophils is believed to contribute to the progression of vasculitis. In particular, myeloperoxidase (MPO)-specific antibodies against neutrophils, anti-neutrophil cytoplasmic antibodies (MPO-ANCA) is involved in the development of vasculitis microscopic polyangiitis etc. In Japan a higher percentage of MPO-ANCA than that in Europe has been reported In addition, we showed a correlation of MPO-ANCA epitopes of Kawasaki disease patients by 47% with that of mothers'. On the other hand, mice having CADS/CAWS-induced vasculitis is a good model for the analysis of the production of MPO-ANCA. We have clarified that MPO is a major antigen for MPO-ANCA production using MPO KO mice. We also investigated the role of activated neutrophils in nephritis renal lesions using SCG/Kj mice. In the phase of nephritis with low grade of proteinuria, the spontaneous release of MPO from peripheral neutrophils increased, indicating that neutrophils are activated and contribute to the development of active crescentic lesion in SCG/Kj mice.

Activated neutrophils in patients with vasculitis suggest that they contribute to the progression of vasculitis has been investigated (1). Target molecules of the antibodies against neutrophils, anti-neutrophil cytoplasmic antibodies (ANCA) related to the develop-

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ment of vasculitis are myeloperoxidase (MPO) and proteinase-3 (PR3) contained in the granules of neutrophils. In particular, MPO-ANCA is associated with certain subtypes of primary vasculitis. Thus, MPO-ANCA has been demonstrated to be involved in the development of vasculitis microscopic polyangiitis etc. (2). Patients with MPO-ANCA related glomerulonepheritis (GN) also show an increase in the activated neutrophils in peripheral blood (1) in addition to Kawasaki disease. In Japan a higher percentage of MPO-ANCA than that in Europe has been reported (3). Recently, role of ANCA by the European Vasculitis Study Group trials have also been studied (4).

Furthermore, in addition to these diseases, elevation in the levels of MPO-ANCA in sera of patients with Kawasaki disease and systemic lupus erythematosus (SLE) has also been observed. Then, we analyzed a correlation of MPO-ANCA epitopes of Kawasaki disease patients with their mother to know the etiology related to MPO-ANCA. Most of healthy mothers showed MPO-ANCA positive in their sera with lower titer. Epitopes in sera of patients were coincident by 47% with that of mothers', but less father's (Table 1), suggesting that source of auto-antibody MPO-ANCA may be same to that of patient's mother (5).

Table 1. Correlation of epitopes of MPO-ANCA of KD patients with their parents

MPO-ANCA Positive 85.7 %		
Correlation	Epitopes	% Prevalence
with Father	Ha	5.9
	Hg	5.9
	No-relation	0
with Mother	Ha	17.6
	Hg	29.4
	No-relation	11.8
with parents		5.9

Eighteen families were examined in 42 patients in Hiroshima City Hospital from Mar. 1998 to Dec. 2000.
Ha: N-terminus of heavy chain, Hg: C-terminus.

On the other hand, ANCA may be important in the pathophysiology of necrotizing vasculitis due to neutrophils activated with inflammatory cytokines such as tumor necrosis factor- α (TNF-α), IL-6 and IL-8 in blood circulation. Interestingly, it has been demonstrated that ANCA activates neutrophils primed with TNF-α in vitro, resulting in the translocation of ANCA antigens to the cell surface.

As the basis for clinical studies, animal models are often used to understand the mechanisms of the development of vasculitis, and to establish therapeutic strategies. Both MRL lpr/lpr, and SCG/Kj strains are known to show high levels of MPO-ANCA in association with renal lesions including GN and vasculitis. On the other hand, CADS or CAWS-induced vasculitis have been used for the analysis of the development and progression of vasculitis (6). CADS/CAWS-induced vasculitis with coronary arteritis is a good model for the analysis of the production of MPO-ANCA. We have clarified that MPO is a major antigen for MPO-ANCA production using MPO KO mice (7). Moreover, the study using NZB/W F1 mice with the Fcγ receptor-deficiency has shown that Fcγ receptor on neutrophils and/or macrophages has been demonstrated to be necessary in the occurrence of GN. However, the more precise pathogenic roles of MPO-ANCA and neutrophils in the development of GN and vasculitis in these murine models are undetermined. We investigated the role of activated neutrophils in nephritis renal lesions using SCG/Kj mice. The mice having spontaneous CrGN and vasculitis showed higher levels of MPO-ANCA and TNF-α than those of normal mice C57BL/6. In the phase of nephritis with low grade of proteinuria, the spontaneous release of MPO from peripheral neutrophils increased, while superoxide generation increased before spontaneous MPO release occurred. In addition, the renal lesion in histological observations aggravated with aging and the glomerular neutrophil infiltration was positively correlated with MPO-ANCA levels as well as with histological indices of nephritis, active renal injury score, especially crescent formation was correlated with spontaneous MPO release. These findings indicate that neutrophils are activated and contribute to the development of active crescentic lesion in SCG/Kj mice (8).

The certain neutrophil infiltration into tissue showing vasculitis suggests that neutrophils may cause the development of vasculitis. MPO released from activated neutrophils occasionally causes self-damage to tissues due to the toxicity of its product OCl^- or other radicals such as O_2^-, H_2O_2, OCl^-, NO as well killing fungi improved with MPO-KO mice.

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