The meeting and expanded the format to include not only other cations and setting the stage for future meetings. The 3rd conference, the University of Iowa, USA, the meeting in 1998 was a great success on Fraueninsel in Lake Chiemsee, in Bavaria, Germany. Organized convening to meet this charge and was held in a Benedictine Abbey biology and role in health and disease. The second meeting was devoted to an effort of MPO could come together to discuss important aspects of its functions by K-H Krause will be presented. In addition, five sessions: MPO-ANCA-related diseases, action and molecular aspects of peroxidases, inflammation and peroxidase-related diseases, and disease. We hope that the insights and information provided at the meeting would serve to confirm the need for an international meeting where investigators, clinical and basic, who shared an interest in the biology 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.

**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.

**REFERENCES**


**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-
matory cytokines such as tumor necrosis factor-
alpha (TNF-alpha). Patients with MPO-ANCA related glomerulonephritis (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 (2). 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

<table>
<thead>
<tr>
<th>Correlation</th>
<th>Epitopes</th>
<th>% Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>with Father</td>
<td>Ha</td>
<td>5.9</td>
</tr>
<tr>
<td></td>
<td>Hg</td>
<td>5.9</td>
</tr>
<tr>
<td></td>
<td>No-relation</td>
<td>0</td>
</tr>
<tr>
<td>with Mother</td>
<td>Ha</td>
<td>17.6</td>
</tr>
<tr>
<td></td>
<td>Hg</td>
<td>29.4</td>
</tr>
<tr>
<td></td>
<td>No-relation</td>
<td>11.8</td>
</tr>
<tr>
<td>with parents</td>
<td></td>
<td>5.9</td>
</tr>
</tbody>
</table>

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-alpha (TNF-alpha), IL-6 and IL-8 in blood circulation. Interestingly, it has been demonstrated that ANCA activates neutrophils primed with TNF-alpha 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 Ipr/Ipr 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 arthritis 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 CγG and vasculitis showed higher levels of MPO-ANCA and TNF-alpha than those of normal mice (57BL/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 O2, H2O2, OCT, NO as well killing fungi improved with MPO-KO mice.

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