

Department of Internal Medicine

Division of Rheumatology

Daitaro Kurosaka, *Professor*
Ken Yoshida, *Assistant Professor*

Isamu Kingetsu, *Assistant Professor*

General Summary

An internist must aim to practice patient-oriented medicine that is well grounded in medical science. Therefore, our department encourages its staff members to do basic and clinical research. Major fields of research are clinical and experimental immunology.

Research Activities

We have performed clinical and experimental studies of rheumatic diseases.

1. Power Doppler ultrasonography for detecting abnormal fascial vascularity: a potential early diagnostic tool in fasciitis of dermatomyositis

We have previously demonstrated that fasciitis is a common lesion of dermatomyositis detectable early after disease onset with *en bloc* biopsy and magnetic resonance imaging. Therefore, the detection of fasciitis plays an important role in the diagnosis of dermatomyositis, especially in its early stage. Power Doppler ultrasonography is useful for detecting inflammation and vascularity in rheumatic diseases. We showed that fasciitis is detected with power Doppler ultrasonography in patients with dermatomyositis and that angiogenesis is observed in fasciitis associated with dermatomyositis. This year, we have examined with immunohistochemical staining whether angiogenesis-related factors and inflammatory cytokines are expressed in the fascia.

2. Analysis of psychological tendency in patients with rheumatoid arthritis and a dissociation between disease activity and arthritic pain

Psychological factors are known to contribute to pain in motor disorders, in addition to localized inflammation. Therefore, through the use of a self-rating scale we evaluated depression and anxiety in patients with rheumatoid arthritis (RA). With a visual analogue scale as an indicator of pain and with the synovial blood flow signals as an indicator of synovitis, subjects were divided into 4 groups. We analyzed the associations between psychological tendency and arthritic pain in patients with RA.

3. Citrullination of peptidylarginine deiminase in RA

Citrullination, catalysed by peptidylarginine deiminase (PAD), is a posttranslational modification of arginine to citrulline, which contributes to the pathogenesis of RA. We undertook a study to examine the presence and functions of citrullinated chemokines in RA. A newly developed enzyme-linked immunosorbent assay system showed that concentrations of citrullinated epithelial-derived neutrophil-activating peptide 78 (ENA-78)/chemokine (C-X-C motif) ligand 5 (CXCL5) were higher in synovial fluid from patients with RA than in synovial fluid from patients with other rheumatic diseases and correlated with the C-reactive protein level and the erythrocyte sedimentation rate. Although ENA-

78/CXCL5 is a neutrophil chemotactic factor, an *in-vitro* chemotaxis assay and *in-vivo* experiments showed that citrullinated ENA-78/CXCL5 has a monocyte-recruiting function and stimulates inflammation in an inflammatory arthritis model. Recently, autocitrullination of PAD has also been reported. In general, the enzyme activity of PAD is decreased after citrullination. However, the function of citrullinated PAD other than enzyme activity remains to be elucidated. This year, we investigated the functions of citrullinated PAD and noncitrullinated PAD.

4. *Bombina variegata* peptide 8/prokineticin 2 in RA

Prokineticin and its receptors are expressed in various tissues and are involved in diverse physiological functions, such as angiogenesis, neurogenesis, circadian rhythm, and the pain threshold. Of these functions, angiogenesis plays an important role in the pathogenesis of RA. We previously investigated prokineticin 2 expression in mice with collagen-induced arthritis, the animal model of RA, and reported that the expression of prokineticin 2 is significantly elevated in the joints of collagen-induced arthritis mice and correlates with the severity of arthritis. However, the mechanism of *Bombina variegata* peptide 8 regarding the onset of arthritis remained unknown. This year, we investigated the effect of an antagonist of prokineticin 2 on collagen-induced arthritis. Our data showed that administration of a prokineticin 2 antagonist suppressed the severity of arthritis. These results suggest that targeting prokineticin 2 provides a new therapeutic strategy for RA.