Department of Internal Medicine
Division of Rheumatology

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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. Fasciitis in 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 at an early stage. Power Doppler ultrasonography is useful for detecting inflammation and vascularity in rheumatic diseases. We have shown 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 examined with immunohistochemical staining whether angiogenesis-related factors and inflammatory cytokines are expressed in the fascia. We found that angiogenesis, the number of cells expressing vascular endothelial growth factor, and the number of cells expressing tumor necrosis factor α were higher in the fascia of dermatomyositis (DM) than polymyositis and were increased predominantly in the fascia rather than in the muscle of the early-phase DM. The degree of inflammation correlated with that of angiogenesis in the fascia of DM. We speculate that the fascia can, therefore, be a primary site of inflammation and angiogenesis in the pathogenesis of DM. We are conducting research with RNA sequencing analysis on gene expression in the fascia and muscle in patients with DM compared with polymyositis.

2. Neuropathic like pain in patients with rheumatoid arthritis

Pain in rheumatoid arthritis (RA) has been thought to be due to nociceptive pain, but it was recently reported to also include a mechanism associated with neuropathic pain. Therefore, we examined the frequency and clinical characteristics of patients who have RA and neuropathic-like pain. Neuropathic-like pain with RA was evaluated with the PainDETECT Questionnaire, a screening tool for neuropathic pain. We compared the clinical variables between patients with and without neuropathic-like pain. We showed that neuropathic-like pain in patients with RA was associated with subjective indicators, including tender joint count and the health-related quality of life, rather than with objective indicators of disease activity, including swollen joint count C-reactive protein, and the erythrocyte sedimentation rate. Proper treatment of neuropathic-like pain in patients

with RA might improve the health-related quality of life. This year, to examine central sensitization in patients with RA we have used the central sensitization inventory and analyzed the change of the central nervous system in a mouse model of RA.

3. Citrullination of peptidylarginine deiminase in RA

Citrullination, catalyzed by peptidylarginine deiminase (PAD), is a posttranslational modification of arginine to citrulline, which contributes to the pathogenesis of RA. We performed 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) in synovial fluid were higher from patients with RA than 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 a model of inflammatory arthritis. 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 unclear. Last year, we found that citrullinated recombinant human PAD had monocyte-chemotactic activity in vitro and arthritis-inducible activity in vivo, whereas noncitrullinated PAD did not. We are trying to develop a detection system for citrullinated PAD in patients with RA.

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 the expression of prokineticin 2 and its receptors (prokineitcin receptor 1 and prokineticin receptor 2) in mice with collagen-induced arthritis, the animal model of RA, and reported that the expression levels of prokineticin 2 and prokineticin receptor 2 are significantly elevated in the joints of collagen-induced arthritis mice and correlate with the severity of arthritis. Therefore, we investigated the effect of an antagonist of prokineticin 2 on collagen-induced arthritis. Our data showed that administration of a prokineticin 2 antagonist suppresses the severity of arthritis. However, whether the effect of this antagonist depends on prokinteicin receptor 1 or prokinteticin receptor 2 is unclear. This year, we attempted to establish a tissue-specific prokineticin receptor 2 knockout mouse and have established a prokineticin receptor 2 floxed mouse.

Publications

Yoshida K, Ito H, Ukichi T, Matsushita T, Furuya K, Noda K, Kurosaka D. Fasciitis as a disease manifestation in immune-mediated necrotizing myopathy with anti-signal recognition particle antibodies: a case report of two cases. *Rheumatol Adv Prac.* 2018; **2:** rky015.

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