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 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. We found that angiogenesis, the number of VEGF-expressing cells, and the number of TNF-α-expressing cells were higher in the fascia of DM than PM, 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 on gene expression in the fascia in patients with DM compared to PM using RNA-seq analysis.

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 reported recently to include a mechanism associated with neuropathic pain as well. We therefore examined the frequency and clinical characteristics of RA patients with neuropathic-like pain. Neuropathic-like pain with RA using the PainDETECT Questionnaire (PDQ), a screening tool for evaluating neuropathic pain. We compared the clinical parameters between the patients with and without neuropathic-like pain. We showed that neuropathic-like pain in RA patients was associated with subjective indicators, including TJC and the health-related quality of life, rather than objective indicators of the disease activity, including SJC, CRP, and ESR. Proper treatment of neuropathic-like pain in RA patients may improve the health-related quality of life. This year, we have examined central sensitization in RA patients using central sensitization inventory.

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 found that citrullinated PAD had monocyte-chemotactic activity in vitro and arthritis-inducible activity in vivo, while non-citrullinated PAD did not. We are trying to detect 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 prokineticin 2 and its receptors (prokineitcin receptor 1 and prokineticin receptor 2) expressions in mice with collagen-induced arthritis, the animal model of RA and we reported that the expressions of prokineticin 2 and prokineticin receptor 2 are significantly elevated in the joints of collagen-induced arthritis mice and correlates 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 suppressed the severity of arthritis. However, it is unclear whether the effect of this antagonist depends on prokinteicin receptor 1 or prokinteticin receptor 2. This year, we attempted to establish tissue-specific prokineticin receptor 2 knockout mouse.

Publications

Yoshida K, Ito H, Furuya K, Ukichi T, Noda K, Kurosaka D. Angiogenesis and VEGF-expressing cells are identified predominantly in the fascia rather than in the muscle during the early phase of dermatomyositis. *Arthritis Res Ther.* 2017; **19:** 272.

Noda K, Ukichi T, Furuya K, Yoshida K, Kingetsu I, Tanaka T, Kurosaka D. Tacrolimus-induced hypertrophic cardiomyopathy in a patient with dermatomyositis. *Rheumatology.* 2017; **56:** 2037-8.