

## 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.

##### 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. This year, we have examined the frequency and characteristics of neuropathic-like pain in rheumatoid arthritis(RA) patients.

##### 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 about chemotaxis activity in vitro and arthritis-inducible activity in vivo.

#### 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.

### Publications

**Yoshida K, Nishioka M, Matsushima S, Joh K, Oto Y, Yoshiga M et al.** Power Doppler ultrasonography for detection of increased vascularity in the fascia: A potential early diagnostic tool in fasciitis of dermatomyositis. *Arthritis Rheumatol.* 2016; **68**: 2986-91.

**Noda K, Yoshida K, Ukichi T, Furuya K, Hirai K, Kingetsu I, Kurosaka D.** Myalgia in patients with dermatomyositis and polymyositis is attributable to fasciitis rather than myositis: a retrospective study of 32 patients who underwent histopathological examinations. *J Rheumatol.* 2017 Apr; **44**: 482-7. Epub 2017 Feb 1.

**Ito H, Noda K, Yoshida K, Otani K, Yosiga M, Oto Y et al.** Prokineticin 2 antagonist, PKRA7 suppresses arthritis in mice with collagen-induced arthritis. *BMC Musculoskelet Disord.* 2016; **8**:

387.

**Chiba M, Yanaba K, Kohara A, Nakayama M, Nakagawa H, Fukuda T, Ishii N, Yoshida K.** Septic arthritis caused by *Mycobacterium marinum* infection. *J Dermatol.* 2016 Nov; **14**. doi: 10.1111/1346-8138.13673. [Epub ahead of print]

**Kohara A, Yanaba K, Muro Y, Ito H, Nakagawa H, Noda K, Kurosaka D.** Anti-PM/Scl antibody-positive dermatomyositis in a Japanese patient: a case report and review of the literature. *Int J Rheum Dis.* 2017 Oct; **44**: 1179-80. Epub 2016 Nov 14.

**Ito H, Noda K, Hirai K, Ukichi T, Furuya K, Kurosaka D.** A case of systemic lupus erythematoses (SLE) following Human papillomavirus (HPV) vaccination. *Nihon Rinsho Meneki Gakkai Kaishi (Jpn J Clin Immunol).* 2016; **39**: 145-9.