

## 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 autoimmune disease.

1. Evaluation and analysis of synovial blood flow signals of patients with rheumatoid arthritis on power Doppler ultrasonography

We have previously demonstrated that the serum level of vascular endothelial growth factor is significantly correlated with disease activity in patients with rheumatoid arthritis (RA). We evaluated RA disease activity before and after administration of abatacept or tocilizumab and examined whether this administration affects serum levels of angiogenesis-related factors and the synovial blood flow signals in patient's joints measured with power Doppler ultrasonography. Our data have demonstrated that both tocilizumab and abatacept decreased the disease activity but that tocilizumab decreased the vascular endothelial growth factor level and synovial blood flow signals more quickly than did abatacept.

2. 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. This year, we have examined whether fasciitis is detectable with power Doppler ultrasonography in patients with dermatomyositis.

3. Analysis of telomerase activity in peripheral blood mononuclear cells of patients with autoimmune disease

Telomerase activation is observed in healthy cells, including normal lymphocytes. An increase in telomerase activity is associated with the activation of lymphocytes. Much attention has been paid to the role of telomerase in immunocytes. This year we measured telomerase activity in peripheral blood mononuclear cells obtained from patients with autoimmune diseases, especially RA.

#### 4. Citrullination of chemokines in RA

Citrullination, catalysed by peptidylarginine deiminase, 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.

#### 5. Bombina variegata peptide 8/prokineticin 2: a novel arthritis-inducible chemokine

The chemokine Bombina variegata peptide 8 (Bv8)/prokineticin 2 is related to angiogenesis, circadian rhythm, and the lowering of the pain threshold. We have previously shown that Bv8 is highly expressed in synovial tissues in mice with collagen-induced arthritis. However, the mechanism of Bv8 regarding the onset of arthritis remains unknown. We examined whether Bv8 can recruit polymorphonuclear leukocytes (PMNs) or monocytes *in vitro* and induce inflammatory arthritis *in vivo*. Our data showed that Bv8 recruited PMNs *in vitro* and induced PMN-driven inflammatory arthritis *in vivo*. These results suggest that Bv8 contributes to the pathogenesis of RA. Targeting Bv8 may provide a new therapeutic strategy to treat inflammatory arthritis.

### Publications

**Yoshida K, Korchynski O, Tak PP, Isozaki T, Ruth JH, Campbell PL, Baeten DL, Gerlag DM, Amin MA, Koch AE.** Citrullination of epithelial neutrophil-activating peptide 78/CXCL5 results in conversion from a non-monocyte-recruiting chemokine to a monocyte-recruiting chemokine. *Arthritis Rheumatol.* 2014; **66**: 2716-27.

**Furuya K, Kaku Y, Yoshida K, Joh K (Sendai Shakai Hoken Hosp), Kurosaka D.** Therapeutic effects of sunitinib, one of the anti-angiogenic drugs, in a murine arthritis. *Mod Rheumatol.* 2014; **24**: 487-91.

**Hatano K, Ukichi T, Noda K, Furuya K, Hirai K, Kingetsu I, Kurosaka D.** A case of reaction arthritis developed after the intravesical BCG infu-

sion therapy (in Japanese). *Kanto Riumachi.* 2014; **47**: 143-50.

### Reviews and Books

**Kurosaka D.** Vaccination in rheumatic disease patients (in Japanese). *Seijinbyo to Seikatsushu-kanbyo.* 2014; **44**: 1453-5.

**Kurosaka D.** The importance of skin eruption in diagnosis of systemic disease (in Japanese). *Nihon Naika Gakkai Zasshi.* 2015; **104**: 335-9.

**Kingetsu I.** Approach to Sjögren's syndrome and the management (in Japanese). *Jibiinkoka Tenbo.* 2015; **58**: 43-9.