Update

Fractalkine: a new target molecule of rheumatoid arthritis

Chung-Jen Chen, Tien-Tsai Cheng

Division of Rheumatology, Allergy and Immunology
Department of Internal Medicine
Chang Gung Memorial Hospital-Kaohsiung Medical Center
Chang Gung University College of Medicine

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized with polyarticular involvement, which often results in joint deformity and disability in cases with inadequate treatment. Though lots of medications including DMARDs and biologic agents have been developed, there is no cure to date. Therefore, a further investigation upon the pathogenesis of RA is mandatory. Recently, a critical molecular, fractalkine has been found to be a critical molecule in the pathogenesis of RA. Activated fibroblast-like synoviocytes (FLS) express lots of fractalkine molecules, which attract CD4+CD28–CX3CR1+ T cells to be closely contacted. Thereafter, activated FLS works as an antigen presenting cell to send costimulatory signals to stimulate CD4+CD28–CX3CR1+ T cells, which then releasing lots of proinflammatory cytokines to cause proliferation of FLS. In addition, fractalkine is also known as an important angiogenetic factors to cause neovascularization in RA synovium. Furthermore, biologic agents to block fractalkine activity have been found to be able to attenuate the synovial inflammation in an animal RA model. Taken together, fractalkine and its receptor may be a new target molecule for treatment of RA.

Key words: Fractalkine, rheumatoid arthritis

Background

Rheumatoid arthritis (RA) a chronic inflammatory disease characterized with polyarticular involvement, which often results in joint deformity and disability in cases with inadequate treatment. Though a lot of medications including DMARDs and biologic agents have been developed, there is no cure to date. Therefore, a further investigation upon the pathogenesis of RA is mandatory.

Based upon pathologic studies of RA, lots of inflammatory cells infiltration in synovium, synovial hyperplasia and neovascularization are the well-known characters in RA pathology. We wonder which molecules are involved in this pathologic change. Based upon previous studies, it is realized that this pathologic pictures might be related with several factors rather than a single factor. However, among lots of factors, which is the key?

Chemokines, including IL-8, ENA-78, MCP-1, MIP-1alpha, and RANTES have been reported to be involved in immunopathogenesis of RA. However, application of their inhibitors in clinical trial is still very limited. Recently, a novel chemokine, the fractalkine, has been found to be strongly related with RA [1,2]. Here we make a brief review to discuss its potential in the future.

Identification of fractalkine and its receptor

In 1977, Bazan et al. reported the identification and characterization of a fourth human chemokine type, bearing the new CX3C fingerprint. They designed the gene fractalkine. This molecule can exist in 2 forms: as membrane-anchored or as a shed 95-kD glycoprotein. The
soluble fractalkine has potent chemoattractant activity for T cells and monocytes. The cell surface-bound protein, is induced on activated primary endothelial cells, promotes strong adhesion of those leukocytes [3].

In November 1997, a seven-transmembrane high-affinity receptor for fractalkine and show that it mediates both the adhesive and migratory functions of fractalkine, termed CX3CR1 was identified [4].

**Discovery of fractalkine involved in RA patients and rat model**

Till 2001, Ruth et al. examined the expression of fractalkine and its receptor (CX3CR1) in RA and rat adjuvant-induced arthritis (AIA), a model of RA [5]. In rat AIA, synovial tissue (ST) macrophages, fibroblasts, endothelial cells, and dendritic cells were fractalkine-immunopositive, but not lymphocytes. Significant staining for CX3CR1 was found in ST macrophages, fibroblasts, and dendritic cells in rat AIA. In human RA, fractalkine was found positive in RA ST macrophages, fibroblasts, endothelial cells, and dendritic cells. Intense ST macrophage and dendritic cell staining for CX3CR1 in RA ST. Besides, significantly elevated soluble fractalkine (sFkn) levels in RA SF was also noted compared with SF from patients with osteoarthritis or other forms of arthritis. They conclude that fractalkine and its receptor are both expressed in RA and in rat AIA, and that sFkn is up-regulated in RA SF. This initiation study suggests a new role for fractalkine and its receptor in the pathogenesis of inflamed RA joint.

**Fractalkine mediates T cell-dependent proliferation of synovial fibroblasts in RA**

In 2007, Sawai et al. investigated the interaction between T cell and fibroblast-like synoviocyte (FLS) in RA [6]. At first, they found that the proliferation of FLS was significantly increased in the presence of CD4 T cells from patients with RA compared with control T cells. Furthermore, CD4+CD28− T cells were found to be particularly effective in supporting FLS growth. Anti-CX3CR1 antibodies inhibited T cell production of tumor necrosis factor-alpha (TNF-α) and suppressed FLS proliferation. TNF-α was found to be able to amplify the expansion of FLS by enhancing their expression of CX3CR1 and fractalkine.

They conclude that the growth-promoting activity of CD4+CD28− T cells is mediated through CX3CR1; FLS stimulate autocrine growth by releasing fractalkine and triggering the activity of their own CX3CR1 and this growth-promotion loop is amplified by TNF-α produced by CX3CR1-expressing T cells upon stimulation by fractalkine-expressing FLS.

**Fractalkine is also a novel angiogenic chemokine in RA**

Angiogenesis is an important factor contributing towards the pannus formation in RA. Völín et al. reported that recombinant human fractalkine significantly induced migration of human dermal microvascular endothelial cells (HMVECs) and the formation of significantly more endothelial tubes on Matrigel [7]. Furthermore, they found that immunodepletion of fractalkine from six RA synovial fluids significantly inhibited their angiogenic activity in Matrigel plug assays. Their findings establish fractalkine may mediate angiogenesis in RA [7].

**Inhibition of fractalkine can ameliorate murine collagen-induced arthritis**

Nanki et al. examined the effect of fractalkine inhibition on murine collagen-induced arthritis. Anti-fractalkine mAb treatment was found to significantly lower clinical arthritis score compared with control Ab, and reduce infiltration of inflammatory cells and bone erosion in the synovium. This finding suggests that fractalkine can be a new target molecule for the treatment of RA [8].

**Perspective**

In brief, fractalkine and its receptor, has been found to be strongly related with not only inflammatory cells infiltration in synovium [5], but also synovial hyperplasia [6] and neovascularization in pannus [7]. More importantly, blockade of fractalkine has been reported to attenuate synovitis in an animal model of RA [8]. Taken together, fractalkine and its receptor may be a new target molecule for treatment of RA in the future.

**References**