EXTRACELLULAR MATRIX METALLOPROTEINASE INDUCER EXPRESSION AND LOCALIZATION IN DESTRUCTIVE JOINTS FROM PATIENTS WITH RHEUMATOID ARTHRITIS

**INTRODUCTION**

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by progressive joint destruction. At the site of joint destruction, abnormal expressions of matrix metalloproteinases (MMPs) are involved. MMPs degrade collagens, proteoglycans, and other matrix macromolecules in bone as well as in articular cartilage. Especially, collagenase (MMP-1) and stromelysin (MMP-3) are shown to be important in pathologic destruction of rheumatoid joint and produced by fibroblasts and macrophage-like cells in the synovium and pannus. Suppression of MMPs may be an alternative of potential therapeutic targets for treatment of RA. But the precise pathomechanism of production of MMPs at the site of joint destruction is still unknown. Extracellular matrix metalloproteinase inducer (EMMPRIN), formerly called tumor cell-derived collagenase stimulatory factor (TCSF), is a member of the Immunoglobulin superfamily which is located on the surface of human tumor cells and normal keratinocytes. EMMPRIN interacts with fibroblasts to stimulate the expressions of several MMPs which associate with tissue degradation and remodeling during tumor invasion and wound healing. But the contribution of EMMPRIN in joint destruction of RA is unknown. In this study, we investigated whether EMMPRIN may be involved at the site of joint destruction in RA.

**Materials and Methods**

Joint specimens were obtained from 10 patients with RA who met the revised American College of Rheumatology criteria, and 5 patients with osteoarthritis (OA) after informed consent. EMMPRIN mRNA expression in synovial tissue was examined by RT-PCR and at the site of joint destruction was examined by in situ hybridization (ISH). To identify the cells which expressed EMMPRIN mRNA in ISH, immunohistochemical stainings were performed. Antibodies against CD3, CD15, CD20, CD68 and prolin 4-hydroxylase, were used for the detection of T cells, granulocytes, B cells, macrophages and fibroblasts respectively. And to know whether the cells expressing EMMPRIN mRNA belong to the population of osteoclasts or osteoclast-like cells, tartrate resistant acid phosphatase (TRAP) staining were performed.

**Results**

EMMPRIN mRNA expression in synovium by RT-PCR

By RT-PCR, EMMPRIN mRNA expression in RA synovium was detected in 9 of 11 samples. However, EMMPRIN mRNA expression in OA synovium was detected only 1 of 5 samples.

Localization of EMMPRIN at the site of joint destruction

Marked expressions of EMMPRIN mRNA were detected in 30% of mononuclear cells and polymorphonuclear cells of invasive synovium, and 50–60% of fibroblast-like cells at the site of bone destruction in RA. However, no expression of EMMPRIN mRNA was detected in synovium obtained from patients with OA.

**Identification of the cells expressing EMMPRIN by immunohistochemistry**

The cells expressing EMMPRIN were identified as synovial fibroblast-like cells and polymorphonuclear cells, not as the infiltrating lymphocytes or synovial macrophages. The results of TRAP staining demonstrated that neither osteoclast, nor osteoclast-like cells in the synovium expressed EMMPRIN.

**Discussion**

In this study, we showed clearly the presence of mRNA encoding EMMPRIN in synovium at the site of joint destruction in RA. On the other hand, in osteoarthritic joint, no expression of EMMPRIN was confirmed. Even though the precise function of EMMPRIN is not known, recent experimental data have demonstrated that EMMPRIN stimulates the production of interstitial collagenase, stromelysin 1 and gelatinase A in fibroblast. These results are of particular interest regarding the implication of EMMPRIN in progressive joint destruction, because synovial cells derived from RA patients have been demonstrated to be the principal source of several MMPs.

The results in this study demonstrated that the location of EMMPRIN was specifically in the synovial fibroblast-like cells and CD15 positive cells, not in the infiltrating lymphocytes or macrophage like cells. EMMPRIN may play a role in the degradation of bone and cartilage associated with synovium invasion by stimulating the synthesis of several MMPs by synovial fibroblast-like cells.

**Conclusion**

In conclusion, the results in this study strongly support the hypothesis that EMMPRIN is an important factor in progressive joint destruction in RA.