Interleukin-4 inhibits interleukin-11 production by rheumatoid synovial cells

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Abstract

Objective. To examine the effect of interleukin-4 (IL-4) on IL-11 production by rheumatoid synovial cells.

Methods. Freshly isolated rheumatoid synovial cells (FRS) were obtained by collagenase digestion of rheumatoid arthritis (RA) synovial tissue specimens taken at the time of operation. Rheumatoid synovial cells at four to eight passages were used as cultured rheumatoid synovial fibroblasts (RSF). IL-11 concentration was measured by ELISA.

Results. IL-4 inhibited the production of IL-11 by FRS in a dose-dependent manner. This inhibition was observed in FRS obtained from six patients, and the mean inhibition was 46.5%. The inhibitory effect of IL-4 on IL-11 production was cancelled by the addition of anti-IL-4 antibody. IL-4 also inhibited IL-11 production by IL-1α-stimulated cultured RSF.

Conclusion. IL-4 inhibited IL-11 production by rheumatoid synovial cells. IL-4 has a protective effect on bone resorption. On the contrary, IL-11 participates in bone resorption via osteoclastogenesis. Therefore, IL-4 may exert its protective effect on bone resorption, at least in part, via inhibition of IL-11 production in rheumatoid joints.

KEY WORDS: Rheumatoid arthritis, Synoviocytes, Interleukin-4, Interleukin-11.
Rheumatoid synovial cells at four to eight passages were used as cultured rheumatoid synovial fibroblasts (RSF). RSF were seeded in 24-well dishes at $5 \times 10^4$ cells per well with 500 ml of DMEM/FCS. RSF were preincubated with IL-4 for 6 h. Media were exchanged with fresh DMEM/FCS, and cultured RSF were stimulated with IL-1a, kindly provided by Dainippon Pharmaceutical, in the absence or presence of IL-4.

**IL-11 measurement**

The concentration of human IL-11 was measured by ELISA using Quantikine Human IL-11 Immunoassay Kit (R & D Systems, Minneapolis, MN) according to the manufacturer’s instructions.

**Statistical analysis**

Values are presented as mean ± s.d. Data were analysed by Wilcoxon’s paired non-parametric test. Differences were considered significant at $P < 0.05$.

**Results and discussion**

We first examined whether IL-4 inhibited the spontaneous production of IL-11 by FRS. IL-4 inhibited IL-11 production in a dose-dependent manner with a maximal effect at 100 U/ml of IL-4 (Fig. 1a). This inhibitory effect was consistently observed in FRS obtained from six patients, resulting in a mean inhibition of 46.5% (Fig. 1b). Simultaneous addition of anti-IL-4 antibody to the culture medium prevented the inhibitory effect of IL-4 on IL-11 production (data not shown).

Although FRS produced a large amount of IL-11, cultured RSF produced only a small amount. As reported previously [27–29], IL-1α can stimulate IL-11 production by RSF. As shown in Fig. 2, IL-4 inhibited IL-11 production by IL-1α-stimulated RSF.

This is the first report demonstrating that IL-4 inhibits the production of IL-11 by rheumatoid synovial cells. The inhibition was specific because it was concentration-dependent and was completely abolished in the presence of anti-IL-4 antibody. However, we did not obtain a consistent result regarding the effect of IL-4 on IL-11 gene expression. This might have been due to partial suppression of IL-11.

In contrast to our study, Elias et al. [33] reported that IL-4 is a weak agonist for IL-11 production. This discrepancy might be explained either by (1) cell-specificity of the effect of IL-4 on IL-11 production, or (2) opposite effects of IL-4 in unstimulated and IL-1α-stimulated cells.

The role of IL-11 in the pathogenesis of RA has been a matter of controversy. Recent work has demonstrated that IL-11 ameliorates experimental arthritis in mice [34]. Although IL-11 was effective during the early phase, it did not affect disease activity during the late phase. Thus, the effect of IL-11 on RA may depend on the phase of inflammation.

Furthermore, IL-11 has been reported to inhibit TNFα production in human monocytes [35]. However, the effect was achieved only if the specific IL-11 receptor...
was provided. At present, little information is available about the expression of IL-11 receptors on monocytes and the existence of soluble IL-11 receptors in RA synovial fluid in vivo. The effect of IL-11 on TNFα production in RA synovia in vivo needs further elucidation.

It has also been reported that IL-11 is abundant in RA synovia and synovial fluid [26, 35]. Nevertheless, IL-11 present at the loci of inflammation does not restrict inflammation efficiently. IL-11 may protect RA synovia by inducing tissue inhibitors of metalloproteinases [28, 35] or inhibiting metalloproteinase production [35]. On the other hand, IL-11 promotes osteoclastogenesis [21, 22]. Therefore, we speculate that IL-11 is produced primarily to terminate inflammation in RA synovium, but that the effect of IL-11 may not be sufficient to terminate the local inflammation, and the persistence and excess of IL-11 production in the loci of inflammation may lead to bone resorption. Further studies are needed to elucidate the effect of IL-11 in RA.

The fact that IL-11 induced osteoclastogenesis [21] indicates that IL-11 might be involved in rheumatoid osteoporosis. On the contrary, IL-4 was reported to inhibit bone resorption [19, 20]. IL-4, scarcely detected in rheumatoid synovium [3, 4], inhibited IL-11 production in rheumatoid synovial cells. On the other hand, IL-1, which is abundant in rheumatoid synovium [1], induced IL-11 production. The imbalance between IL-4 and IL-1 might further explain the increased level of IL-11 in RA synovia, which might lead to inflammatory osteoporosis in patients with RA. Modulation of the cytokine network in inflamed synovium may reduce osteoporosis at the site.

References


