S-3 [11:20~11:50]

The Significance of the Mast Cell in Rheumatic Disease

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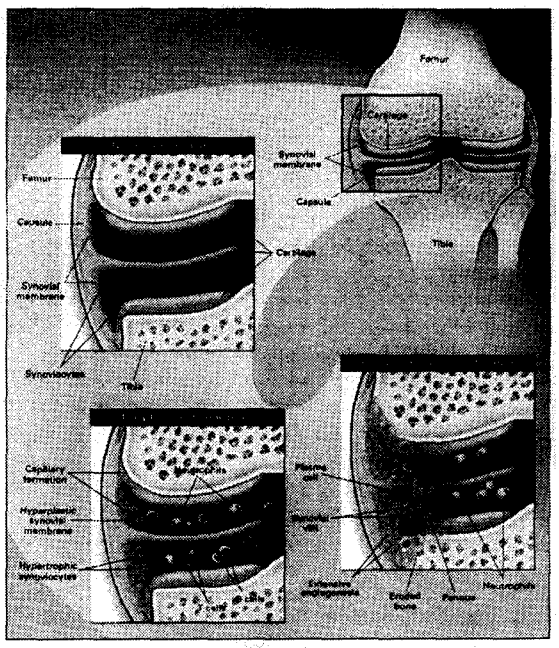
Rheumatoid arthritis (RA) is one of the most typical rheumatic diseases, and is characterized by chronic inflammation, cartilage destruction and joint deformity [1,2]. During this process, profound hypertrophic changes of the synovium with infiltration of immune cells, increased vascularity, and hyperplasia result in the formation of a synovial pannus that invades cartilage and bone [3]. In early stages of RA, the synovial membrane begins to invade the cartilage. In established RA, the synovial membrane becomes transformed into inflammatory tissue, the pannus (Fig. 1). The cell types that occupy cartilage-pannus junctions include synovial macrophages, fibroblasts, mast cells, polymorphonuclear lymphocytes (PMNs), and displaced, probably differentiated condrocytes [4-6]. Recent studies of rheumatoid synovial tissue have demonstrated localized accumulations of mast cells and evidence of their activation/degranulation [7]. Although mast cells have in the past been viewed primarily in the central role of immediate-type hypersensitivity reactions, there is recent growing evidence for a role of these cells in tissue homeostasis and in a variety of pathological reactions including tissue remodeling, wound repair, pathological fibrosis, arthritis, angiogenesis, and host reactions to neoplasia [8-10]. In several reports, synovial mast cells may contribute to the local inflammatory response of arthritis and produce a number of proinflammtory mediators that play a role in arthritis [11-14]. Increased numbers and activation of mast cells are found in the synovial tissue and fluid of patients with RA, and especially at sites of cartilage erosion. Mast cells play an important contributory role for mediating matrix degradation and oedematous changes within the rheumatoid lesion [15]. Because the mast cell contains potent mediators, including histamine, heparin, proteinases, leukotrienes and multifunctional cytokines, these have potential contributions to the processes of inflammation and matrix degradation. Therefore mast cell activation makes a significant contribution to the pathophysiological processes of the rheumatoid lesion.

The Proinflammatory cytokines TNF-α and IL-1 are reported to play important

roles in mediating the progression of many inflammatory joint diseases, including RA in human [16-18]. The major cell types and cytokine pathway believed to be involved in joint destruction mediated by TNF--α and IL-1 are shown in Fig.2. TNF-α reportedly plays a pivotal role in the pathogenesis of RA, especially cartilage and bone degradation, and this cytokine is highly up regulated in RA [19]. In recently report, the chemotactic effect of mast cells is mediated by SCF, augmentable by TNF-α, and may have implications for the pathogenesis of RA [20]. TNF-α is able to regulate IL-1β expression, this being important for induction of prostanoid and matrix metalloproteinase production by synovial fibroblasts and condrocytes [21]. So, the suppression of TNF-α release and anti-TNF therapy for RA have defined a molecular target and new approach for treating immuno-inflammatory disorders [22,23]. These therapies could dramatically change the treatment and outcomeof the disease.

To study of the migration of mast cells we used as a model the rat peritoneal mast cells (RPMCs). The result shows that stem cell factor (SCF) is a potent chemotactic factor for RPMCs in vitro. The addition of SCF resulted in a significant increase in the numbers of migrated RPMCs. In contrast, medium with DKHT+SCF had no effect on migration of RPMCs. This result shows that SCF clearly induced chemotactic movement of RPMCs, which was blocked pretreatment with DKHT (Fig. 3). 'Madi Madi' made from effective processing, fermentation, is a kind of alcohol made from water extracts of a prescription made up of five herb medicines. This wine is interesting from the viewpoint of an expectation of relieving RA. Plant medicines used in this wine have been applied to treat pains from various type of arthritis in far eastern countries including Korea as a folk medicine. But the mechanism and effect of this oriental medicine on RA regulation has not been examined at all. In our study, we investigated that 'Madi Madi' could inhibit the cytokine production of PMA- or A23187-stimulated human mast cell line, HMC-1, and of PHA-stimulated peripheral blood mononuclear cells (PBMC) of RA patients. Current slow-acting antirheumatic drugs have limited efficacy and many side effects. Moreover, they do not improve the long-tern prognosis of RA. But, this alcohol had no effect on cell viability and had not side effects, and inhibited the production of PMA-induced TNF-α secretion and of A23187-induced IL-1β secretion in HMC-1 cells (Fig. 4). The TNF-α mRNA expression (Fig. 5) was also regulated by 'Madi Madi' in PMA-stimulated HMC-1 cells. Table 1 showed the effect

of this alcohol on PHA-stimulated TNF-α and IL-1β secretion from PBMC of RA patients. These results suggest that 'Madi Madi' made from processing of five herb medicines have potential roles as therapeutic agent by regulation of TNF-α and IL-1β production in mast cells or lymphocytes. We believe that this traditional wine, 'Madi Madi', may be have functional roles for neighboring cells as well as mast cells in RA.



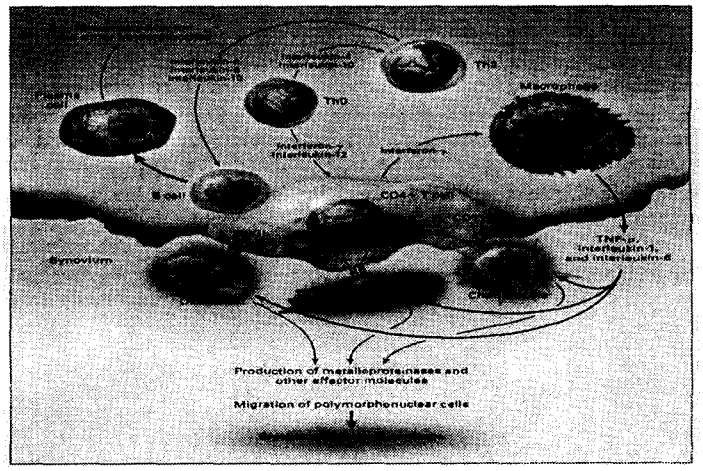


Fig. 1. The scheme of the pathogenesis of RA. (from ref. [18])

Fig. 2. Cytokine signaling pathways involved in inflammatory arthritis. The major cell types and joint destruction mediated by TNF-α and IL-1 are shown. (from ref. [18])

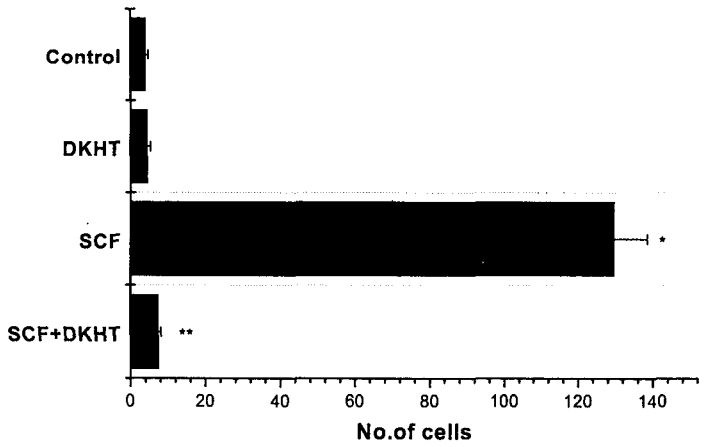


Figure 3. Inhibitory effect of DKHT in response to migration induced SCF. DKHT (1mg/ml) was added into 10 ng/ml rSCF, in the lower compartment. After incubation for 4 hours, migratory RPMCs were counted. *P < 0.05

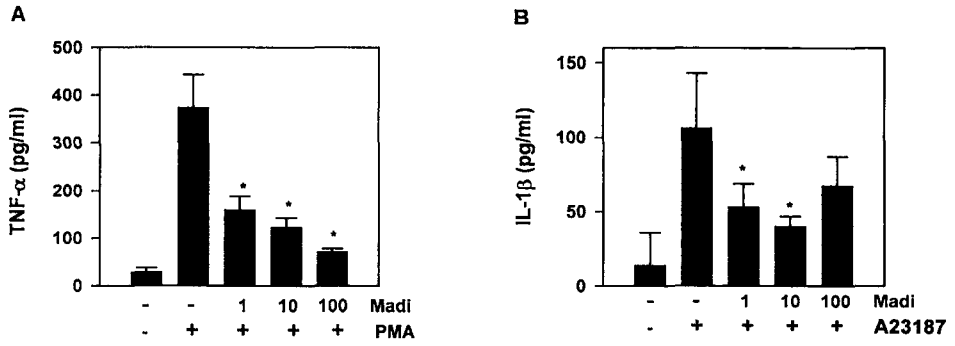


Fig. 4. PMA-induced TNF-α secretion (A) and A23187-induced IL-1β (B) from HMC-1 was measured by ELISA. HMC-1 cells were incubated in the absence or presence Madi (1-100 μg/ml) for 30 min prior to stimulation with PMA or A23187. TNF-α and IL-1β in supernatant were measured at 8 h and 6h incubation, respectively. *, $p < 0.05$ compared with PMA- and A23187-stimulated value.

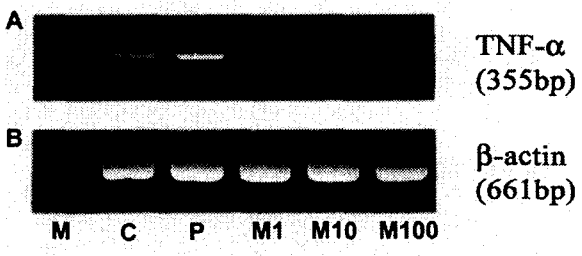


Fig. 5. TNF-α mRNA expressed in the absence or presence Madi (1-100 μg/ml) for 30 min prior to stimulation with PMA was determined by RT-PCR. A) Lane 1, 100 bp DNA marker; lane 2, control; lane 3, PMA treatment (20 nM); lane 4-6, 1-100 μg/ml Madi treatment prior to PMA stimulation, respectively. B) PCR using housekeeping gene β-actin was carried out in confirms equivalency of cDNA preparation.

Table 1. The inhibitory effects on cytokine secretion from PBMC of RA patients

Treatments		Secretion of cytokines	
Madi Madi (μg/ml)	PHA (25μg/ml)	TNF-α (ng/ml)	IL-1β (ng/ml)
-	-	0.34 ± 0.08	0.84 ± 0.09
-	+	1.52 ± 0.06	3.26 ± 0.42
0.1	+	0.01 ± 0.09*	2.65 ± 0.21
1.0	+	0.92 ± 0.19*	2.54 ± 0.12
10.0	+	0.81 ± 0.03*	1.88 ± 0.21*

PBMC (6×10^5 cells/ml) were stimulated with PHA (25μg/ml) for 24 hr in the absence or presence of Madi Madi. The amount of TNF-α and IL-1β produced from PBMC was measured by ELISA. Data were represented by mean ± SEM. Statistically significance assessed by Student's t-test of the means, $^*p < 0.05$, compared to PHA-treated alone value.

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