The Expression Levels Of Connexin 43 In Human Synovium Of Rheumatoid Arthritis

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Introduction: Rheumatoid arthritis (RA) is one of the most common articular diseases, characterized by hyperproliferation of synovial cells and bone destruction.
With the advent of biological agents which regulate inflammatory-cytokines such as TNF-α and Interleukin-6, treatment of RA has evolved.
However, biological agents may cause some side effects such as serious infectious desease, heart failure, and large amount of medical expenses are required.
Therefore, the new therapeutic drug which can control the condition of a patient of RA by the different mechanism conventionally is desired earnestly.
Gap junctions are cell-cell communication channels, consisting of multimeric proteins called connexins, that allow the exchange of ions, second messengers, and metabolites between adjacent cells.
The most widely expressed connexin gene is connexin 43 (Cx43), a protein expressed in the synovial cells and tissue[1]. It has recently been demonstrated that Cx43 regulates a variety of immune responses and inhibition of Cx43 expression can reduce inflammatory reactions.
Tsuchida et al demonstrated that small interfering RNA targeting for Cx43 (siCx43) had anti-inflammatory effects inhibition of Cx43 provided protection against the development of inflammation of RA[2]. These reports suggest the possibility that Cx43 expression in the synovial membrane contributes to the pathological condition of RA and inhibition of Cx43 expression can suppress synovitis in RA.
This aim of study is to evaluate a role of Cx 43 in human synovium of RA.

Methods: All human samples were obtained in accord with the Ethical Review Board on Clinical Research of Kyoto Prefectural University of Medicine. Synovial tissue was obtained from patients with RA or (15 RA patients were utilized) undergoing the operations such as total knee, elbow joint replacement and synovectomy.
As a control, I also gathered a synovial tissue at the time of an operation from 5 patients with osteoarthritis (OA) and analyzed it. Total RNA was extracted from the collected synovium by using ISOGEN (Nippopgene, Tokyo, Japan).
The gene expression levels of Cx43 in synovium was analyzed based on real-time RT-PCR method.
With a part of synovial tissue fixed by 4% paraformaldehyde, histological examination was performed by using immunohistochemical method on Cx43.

Results: The gene expression levels of Cx43 in human synovium of RA increased compared with that of OA, showing significant difference in the amount of expression.
In the immunohistochemical staining of Cx43, stainability was proved to be more intense in synovium of RA than that of OA.
In particular, intense stainability was observed on the synovial surface of RA.

Discussion: Connexins constitute a large family of trans-membrane proteins that allow intercellular communication and the transfer of ions and small signaling molecules between cells. Cx43 is the most highly expressed connexin in normal human synovial membranes. Cx43 has been reported to be upregulated in various tissue or cells by inflammatory stimuli. Recently, it has been reported that Cx43 in synovial fibroblast is activated by inflammatory stimulus and that inflammation is inhibited by controlling Cx43.
Tsuchida et al demonstrated that transfection of siCx43 significantly inhibited the expressions of TNF-α, IL-6 and IL-1β mRNAs upregulated by LPS on mouse in rat FLS. And synovitis is reduced by inhibiting Cx43 expression in a rat RA model with enhanced expression of Cx43 in synovium [2].
In this study, gene expressions and protein production of Cx43 were found to have increased in human synovium of RA compared with that of OA.
These indicate that Cx43 expression may have an important role in the pathological condition of synovitis in RA.
Cx43 may become the new target elucidating the pathogenesis of RA and controlling of Cx43 may become a new treatment for
RA.

**Significance:** Cx43 gene expressions and a stainability of immunostaining of Cx43 protein in human synovium of RA increased compared with that of OA.

It suggests that expression of Cx43 may have a potential to play a significant role in synovitis of RA.

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**References:**
2. Tsuchida S, et al.: JOR 2013; 31:525-

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**Figure 1.** Expression of Cx43 in OA and RA synovium.

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