Distribution Of Podoplanin In Synovial Tissues Of Rheumatoid Arthritis And Osteoarthritis

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Introduction: Podoplanin, known as platelet aggregation-inducing factor in the haematogenous metastasis of tumor cells [1] and mucin-type transmembrane glycoprotein, normally expressed on human lymphatic endothelia, basal epithelial keratinocytes, cancer cells [2] and possible potent molecule of inflammation. The expression of podoplanin on inflammatory cells, such as fibroblast-like synoviocytes, follicular dendritic cells and Th17 T cells, is up-regulated when stimulated by pro-inflammatory cytokines [3, 4]. The aim of this study was investigated to clarify its tissue and cellular distribution in the rheumatoid synovium, which was compared to OA synovium.

Methods: 1) Samples; The synovial tissue samples were obtained surgically from the patients with rheumatoid arthritis (RA) treated with biologic disease-modifying anti-rheumatic drug (DMARD) (BIO, n=25) or conventional DMARD (cDMARD, n=25) and osteoarthritis (OA, n=5). 2) Immunohistochemistry; Serial 5-μm-thick frozen tissue sections were cut and stained by rat monoclonal anti-human podoplanin (NZ-1) using the avidin-biotin-peroxidase complex (ABC) method. 3) Double-labeling; The sections were incubated with the mouse monoclonal antibody, anti-CD68, anti-fibroblast 5B5, rabbit polyclonal anti-IL17 and rabbit polyclonal anti-lymphatic endothelia LYVE-1 with the rat monoclonal anti-human podoplanin. The sections were then incubated with secondary antibodies, Alexa Fluor® 488 or 568 before mounting. 4) Scoring; Podoplanin+ cells were scored (3+: >50%/ area, 2+: 20%-50%, 1+: 5%-20%, 0: <5%) in the rheumatoid synovial tissues with analyses of inflammatory grading (0-3) and cell-typing. 5) Statistical analysis; Mann-Whitney U test and Spearman’s rank correlation coefficient analysis were performed using the PASW 18 software. Values of p<0.05 were considered to indicate statistical significance.

Results: Inflammatory grading score was 1.5 in both BIO and cDMARD, and 0.2 in OA. Podoplanin+ cells were expressed in the lining layer (BIO 1.5, cDMARD 1.2, OA 0.2) (Fig. 1) and lymphoid aggregation (BIO 0.6, cDMARD 0.7, OA 0.2), which correlated with grading of RA synovium in both BIO and cDMARD (r=0.7/0.9, p<0.05), not OA (r=0.2). Podoplanin was markedly expressed in CD68+ type A macrophages-like and 5B5+ type B fibroblast-like cells in the lining layer and partially IL-17+ cells in lymphoid aggregations of RA, slightly in LYVE-1+ lymphatic vessels.

Discussion: Podoplanin was markedly expressed in the immunologically inflamed synovium and correlated to inflammatory, which was surgically treated due to progressive arthritis against both BIO and cDMARD.

Significance: It indicates that podoplanin will be a possible new therapeutic target in the treatment of RA.