COLLAGEN TRIPLE HELIX REPEAT CONTAINING-1 (CTHRC1) REGULATES THE CELL MIGRATION VIA FOCAL ADHESIONS

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Introduction: Among other clinical symptoms rheumatoid arthritis is characterized by increased pathological cell migration and invasion, leading to the formation of hypertrophied synovium (also termed pannus). The exact mechanism of such increased cell motility remains largely unknown. We identified the Collagen Triple Helix Repeat Containing-1 (CTHRC1) as a promigratory biomarker of rheumatoid arthritis involved in the pathological migration of cells into the inflamed joints. CTHRC1 is an evolutionarily conserved secreted protein containing collagen like-motif with 12 Gly-X-Y repeats which was first discovered in injured rat arteries implicating a role in vascular remodeling. Here we studied the regulation of arthritic synoviocytes motility via upon treatment with CTHRC1, and its effects on cellular focal adhesions that are a part of the cellular migration machinery.

Methods: Activated synoviocytes were isolated form patients with rheumatoid arthritis (RA). Focal adhesion complexes were immunostained for vinculin and actin in RA-synoviocyes and murine NIH 3T3 cells. Further cells were treated with 100 ng/ml exogenous recombinant CTHRC1 and WNT5A. Focal adhesions were counted in immunostained cells as well as in living cells using time-lapse microscopy.

Results: We found that CTHRC1 regulates cell migration and adhesion in cells via focal adhesions. The subset of focal adhesions in the cell front provides the forward traction forces for the migrating cell and focal adhesion assembly and turnover is essential for productive forward movement. CTHRC1 induced the distribution of focal adhesions from the leading edges of the cells to the center. The prevalence of mature focal adhesions over young nascent focal contacts was apparent. In murine fibroblasts CTHRC1 facilitated the rapid turnover of focal adhesions leading to an increase in migration rate in samples treated with a combination of CTHRC1 and WNT5A.

Conclusions: The novel circulatory biomarker CTHRC1 acts as a WNT5A signaling moderator for activated synoviocytes and controlled synoviocyte invasiveness via assembly and disassembly of focal adhesion contacts. Thus, CTHRC1 is a promising diagnostic marker for early pannus formation.