Oncogenic properties of Rheumatoid synovial cells.

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Rheumatoid arthritis (RA) is one of the most common and critical articular diseases with synovial hyperplasia. However, the mechanism that regulate synovial cell outgrowth is not fully understood. To clarify the mechanism, we carried out immunoscreening using anti-rheumatoid synovial cell antibody and cloned a putative RING finger protein, designated “Synoviolin” (G&D, 2003). Synoviolin is an E3 ubiquitin ligase and located in endoreticulum. It was highly expressed in the rheumatoid synovium, and mice overexpressing this molecule developed spontaneous arthropathy.

In this regard, like rheumatoid synovial cells, the anti-apoptotic effect of Synoviolin was observed even for its expressed ectopically in NIH3T3 cells, which resulted in enhanced cell overgrowth in these cells (MCB, 2005). These results were confirmed also in fly system. Next, to identify the substrates for Synoviolin that may be involved in cell growth, we analyzed the comprehensive profile of protein expression in synoviolin null cells (JBC, 2005). Then, we found that Synoviolin targets tumor suppressor gene p53 for ubiquitination (EMBO J., 2007). Synoviolin sequestrated and metabolized p53 in the cytoplasm and negatively regulated its cellular level and biological functions, including transcription, cell cycle regulation and apoptosis. Furthermore, these p53 regulatory functions of Synoviolin were irrelevant to other E3 ubiquitin ligases for p53, such as MDM2, Pirh2 and Cop1, which form autoregulatory feedback loops. Our results provide novel insights into p53 signaling mediated by Synoviolin and clarify the molecular basis of synovial hyperplasia in RA.