Editorial

Association of autophagy to the phenotypic transformation of synovial fibroblasts in rheumatoid arthritis

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As an essential part of energy metabolism, autophagy plays a vital role in maintaining homeostasis (1). Through the processes of initiation, nucleation, elongation, maturation, and degradation, autophagy clears damaged and dysfunctional cells and proteins to maintain a healthy physiology. Autophagy also plays a protective role in cells under adverse environmental conditions, including hypoxia, hypoalimentation, and endoplasmic reticulum (ER) stress.

With aging, the basic autophagic ability of cells decreases, resulting in downregulated clearance efficiency. These reductions in the rates of autophagy are related to various age-related diseases (2). Autophagy also plays an important role in various autoimmune diseases, including rheumatoid arthritis (RA) (3-5). It was previously found that the levels of autophagy-related proteins [beclin1, Atg5, and light chain 3 (LC3)] were higher in the synovial tissues of patients with active RA than those in patients with osteoarthritis (OA) (6). However, the association between autophagy and the underlying mechanism of the phenotypic transformation of synovial fibroblasts (SFs) remains unclear.

RA is a systemic autoimmune disease characterized by multiple joint synovitis and erosive bone lesions (7,8). SFs are localized to the intimal lining of the synovium. Here, the phenotypically distinct RASFs produce cytokines and proteases that perpetuate inflammation and cartilage destruction (9). Kato *et al*. (10) reported a dual role for autophagy in the regulation of death pathways in RASFs. Under severe ER stress, such as that induced by thapsigargin, autophagy-linked FYVE protein (ALFY) expression is reduced. Furthermore, the formation of p62-positive polyubiquitinated protein aggregates promotes RASF cell death (10).

Protein accumulation in the ER lumen activates the unfolded protein response (UPR), which involves three master regulators: activating transcription factor 6 (ATF6), inositol-requiring enzyme 1 (IRE1), and protein kinase R-like endoplasmic reticulum kinase (PERK) (11). When binding immunoglobulin protein (BiP) is released, IRE1α activates endoribonuclease and X-box-binding protein 1 (XBP1) mRNA in the nucleus, and upregulates genes involved in mitigating the protein burden. XBP1—a central regulator of the ER stress response—is induced via the activation of the IRE1 stress sensor as part of the UPR and has been implicated in several pathologies. A recent study found that the expression of the active (spliced) form sXBP1 was higher in active RA patients than in healthy controls or patients in remission. sXBP1 is induced in SFs by toll-like receptor (TLR)-4 and TLR2 stimulation, resulting in sXBP1-dependent interleukin-6 and tumor necrosis factor (TNF) production, suggesting a link between TLR-dependent XBP1 activation and human inflammatory diseases (12).

Wang *et al*. (13) recently clarified the mechanism of autophagy under ER stress in the phenotypic transformation

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of RASFs. They showed that ER signature genes, such as *HSPA5* [the gene encoding glucose-regulated protein 78 (GRP78)], *ERN1* (IRE1), *EIF2AK3* (PERK), *MAPLC3* (LC3), *ATG5* (Atg5), and *ATG7* (Atg7), were higher in the synovium of patients with RA than those in patients with OA. In addition, ER stress-associated proteins, including GRP78, IRE1, PERK, and LC3, were upregulated in RASFs compared to OASFs. They concluded that the ER stress-autophagy pathway was prominently promoted in RA synovium and RASFs and that the phenotype transformation of RASFs was tightly regulated via the IRE1/c-Jun NH2-terminal kinase (JNK) pathway (13). These findings suggest that the IRE1/JNK pathway may be a therapeutic target in RA synovitis.

The survival of SFs is dependent on the continuous removal of proteins by both the lysosome/autophagy and ubiquitin/proteasome protein degradation pathways, both of which were more active in RASFs than in control fibroblasts (14). TNF-α stimulates SFs and increases the expression of ER stress markers. In RA, TNF-α stimulation increased the proliferation and invasion of RASFs, and led to the upregulation of IRE1 and JNK. This phenomenon was ameliorated by 4-PBA (an ER stress inhibitor) and 3-MA (an autophagy inhibitor). Short hairpin-RNA-ERN1-transfection inhibited the proliferation and invasion of RASFs via downregulation of IRE1 expression (13). In a mouse model, myeloid-specific deletion of IRE1α protected against inflammatory arthritis, and the IRE1α-specific inhibitor 4μ8c attenuated joint inflammation (15). Recent evidence also linked oxidative stress to autophagy/ER stress in the pathogenesis of RA (16-18). Therefore, the IRE1/JNK pathway might also be a therapeutic target for the regulation of oxidative stress in RA.

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