Autophagy in Rheumatic Diseases

Subjects: Rheumatology

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Autophagy is a lysosomal pathway for the degradation of damaged proteins and intracellular components that promotes cell survival under specific conditions. Apoptosis is, in contrast, a critical programmed cell death mechanism, and the relationship between these two processes influences cell fate. Recent evidence suggests that autophagy and apoptosis are involved in the self-tolerance promotion and in the regulatory mechanisms contributing to disease susceptibility and immune regulation in rheumatic diseases.

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1. Rheumatoid Arthritis

RA is a systemic autoimmune disease characterized by persistent synovitis, systemic inflammation, and autoantibodies production, such as rheumatoid factor and anticitrullinated peptides (ACPAs). ACPAs may be directly pathogenic thanks to their ability to promote synovitis, cartilage disruption, and bone loss via macrophage activation [1]. The contribution of autophagy to the presentation of citrullinated peptides and the generation of ACPAs is a critical step in RA. Several data suggest that increased autophagy leads to the production of citrullinated proteins in RA fibroblast-like synoviocytes (FLS) and that the level of LC3II in FLS positively correlates with the level of ACPAs [2]. As we know, protein citrullination is a post-translational modification catalyzed by the arginine deiminase-4 (PAD-4). It has been shown how, following treatment with a potent autophagy inducer, rapamycin, human synoviocytes exhibit activation of PAD-4 with consequent generation of citrullinated proteins [2]. The additional evidence that PAD-4 is detectable in LC3-II immunoprecipitates from FLS further supports the view that citrullination may occur in autophagosomes [2].

In RA patients, FLS do not represent the only cell type possibly affected by maladaptive activation of autophagy. As we know, RA is characterized by subchondral bone erosions promoted by reduced osteoblast-mediated bone formation and increased osteoclast-mediated bone reabsorption. Recent data suggest a possible link between osteoclastogenesis and the autophagy pathway. Specifically, increased expression of autophagy-related molecules, such as Beclin1 and Atg7, in osteoclasts from RA synovia has been observed [3]. Furthermore, in experimental mouse models of arthritis, a significant reduction in bone erosion has been demonstrated following treatment with autophagy inhibitors [3].

2. Systemic Lupus Erythematosus

SLE is a complex autoimmune disease with a strong genetic component. Genome-wide association studies have found that single-nucleotide polymorphisms (SNPs) in several autophagy-related genes (ATG5, ATG7, IRGM, DRAM1, CDKN1B, APOL1, and MTMR3) are associated with SLE susceptibility [4]. Specifically, at least five SNPs near the Atg5 locus seem associated with SLE initiation and development [4]. A different study also demonstrated that two specific SNPs in the ATG5 gene (rs6568431 and rs2245214, respectively) are associated, on the one hand, with anemia and renal involvement and, on the other hand, with a higher risk of producing anti-DNA autoantibodies. This finding further suggests that SNPs in autophagy-related genes likely have a role in SLE pathogenesis, determining not only disease susceptibility but also clinical phenotype [5].

Autophagy is reported to be crucial for monocyte differentiation and for the prevention of regular apoptosis and survival of monocytes. Inhibition of induced autophagy leads to apoptosis [6]. Of note, autophagy shows abnormalities in lupus macrophages, and autophagy-related genes are found to be upregulated in macrophages of lupus mice and SLE patients, suggesting that autophagy may be involved in SLE pathogenesis by influencing monocytes and macrophages [7]. Macrophages from patients with SLE exhibit increased levels of autophagy, and in mice with a lupus-like disease, inhibition of macrophage-induced autophagy leads to decreased B-cell maturation and reduced production of dsDNA [7]. Moreover, adoptive transfer of Beclin1 knockdown macrophages can significantly decrease anti-dsDNA antibody levels and immune complex deposition mitigating proteinuria and glomerulonephritis [7]. This protective effect seems to be associated with the significantly decreased production of IL-6 and TNF-α, indicating that abnormally activated autophagy in macrophages may contribute to lupus by promoting the production of TNF-α and IL-6 [7].

Emerging evidence demonstrates that autophagy is upregulated in SLE B cells during plasma cell differentiation [8]. B-cell-activating factor (BAFF) is one of the mean chemokines involved in SLE pathogenesis driving autoantibody production and is associated with an increased risk of SLE flare [9]. Interestingly, in SLE, BAFF seems to contribute to a dysregulation of B-cell autophagy [10][11]. Specifically, BAFF binding to its receptors (BAFF-R, TACI, and BCMA) results in activation of the noncanonical NFκB signaling pathway and the JNK1 pathway, which promote B-cell maturation and survival through concomitant activation of the autophagy pathway [11]. BAFF signaling through TACI and BCMA can also activate the inhibitor of NF-κB kinase, which in turn modulates downstream autophagy; this finding further suggests how autophagy pathways, promoted by BAFF, might be important for B-cell differentiation and survival in SLE [12].

B cells are not only relevant to SLE pathogenesis, as overactivation of T cells with increased cytokine and autoantigen-mediated signaling has been demonstrated. Interestingly, increased autophagic vesicle formation sustained by the evidence of increased production of LC3II and increased autophagic flux was identified in CD4+ T cells from patients with SLE compared to CD4+ T cells from healthy donors [13].

3. Sjögren’s Syndrome

Evidence on the role of autophagy in SS is still limited, although recent studies have demonstrated a potential pathogenic role in this condition too. Previous works from the reseachers' group demonstrated how dysregulation

of the autophagic process is detectable in T and B lymphocytes infiltrating SS minor salivary glands. Specifically, autophagic dysregulation has been detected in both infiltrating and circulating T lymphocytes [14]. The activation of autophagy resulted to be particularly relevant in CD4+ T, with an interesting association between its level of expression and disease histological severity; additionally, the level of autophagy in peripheral blood T lymphocytes positively correlated with patient disease activity and damage indexes [13]. By means of ultraselective methods allowing extracting lymphocyte infiltrates from minor salivary glands, the researchers then demonstrated how upregulation of autophagy is not a mere feature of infiltrating T cells. Specifically, concomitant upregulation of autophagy is detectable in B-cell-infiltrating minor salivary glands with interesting evidence of aberrant activation and a possible pathogenic effect in GC-like structures [15].

4. Autophagy Pathway Modulating Therapies

TNF-alpha inhibitors, whose prescription is largely diffused in patients with RA, seem also able to modulate the autophagy pathway. Indeed, it is well known that TNFα can induce autophagy in different cell types directly associated with RA pathogenesis and that TNFα-mediated autophagy may play a role in apoptosis resistance [16]. Indeed, Wang and colleagues showed that TNF-α can activate autophagy in FLS and that autophagy block may upregulate apoptosis and inhibit cell proliferation [16]. Thus, the block of autophagy by anti-TNF drugs in FLS may help in restoring this balance. Other evidence supports this hypothesis, demonstrating activation of synovial apoptosis after 8 weeks of treatment with two different classes of TNF-alpha inhibitors (etanercept and infliximab) [17]. In the previous work, Vomero et al. provided evidence of direct involvement of autophagy in the response to therapy in patients with RA [18]. Specifically, the researchers analyzed changes in spontaneous autophagy in peripheral cells from patients with RA treated with TNF inhibitors, demonstrating a reduction in autophagy only in patients responding to the therapy [18]. This finding leads to the hypothesis that the level of autophagy can not only be considered a measure of disease activity but can also be looked at as a measure to identify patients more likely to respond to TNFα inhibitors.

Increasing evidence in the literature also demonstrates a link between the autophagy pathway and the Jak-STAT pathway [19][20][21][22]. Janus kinases (JAKs) are a family of nonreceptor tyrosine kinases, composed of four members, JAK1, JAK2, JAK3, and TYK2. JAKs are involved in different inflammatory and autoimmune diseases, and tofacitinib and baricitinib are selective JAK inhibitors that preferentially inhibit JAK1 and JAK3 and JAK1 and JAK2, respectively. JAK inhibitors are indicated for the treatment of moderate to severe RA patients who respond inadequately to at least one DMARDs. As mentioned above, data from other studies seem to suggest a role for Jak-STAT inhibition in autophagy modulation. In this regard, in RA, very recent in vitro studies evaluated the connection between the regulation of homeostatic mechanisms and the Jak-STAT pathway [23]. In SS, the first evidence of a potential utility of the use of baricitinib has been speculated thanks to the additional capacity to interfere with the autophagy pathway; however, larger studies are needed to clarify this aspect [24].

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