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Editorial

Effects of autophagy on joint inflammation

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1. Introduction

The balance between cell survival and cell death is at the hub of the pathogenesis of autoimmune and autoinflammatory diseases. Immunogenic cell death and the accumulation of cellular debris constituting a reservoir of autoantigens promote abnormal inflammation. At the opposite, dysregulation of cell survival can trigger the release of proinflammatory cytokines and chronic activation of autoreactive immune cells. The choice between survival and the initiation of a cell death program results from the subtle integration of numerous signals. Metabolic cellular activity, environmental stress, and the effects of immune cells and inflammatory mediators must undergo integration to ensure tissue homeostasis. Macroautophagy, often referred to simply as autophagy, is a major contributor to the cell survival/death balance [1].

Autophagy involves the formation in the cytoplasm of double-membrane structures known as autophagosomes, which engulf either portions of the cytosol or, more selectively, protein aggregates or damaged organelles. Fusion of the autophagosomes with the lysosomes results in degradation of the autophagosome cargo by the lysosomal enzymes. Autophagy was initially described as a survival mechanism under conditions of metabolic stress, first in yeast and subsequently in superior eukaryotes. When nutrients are scarce, autophagy recycles cell components, which are used to generate new macromolecules and energy. Thus, autophagy promotes cell survival and often antagonizes apoptosis. Under normal conditions, the basal level of autophagy also makes a key contribution to the survival of long-lived cells, by eliminating nonfunctional organelles and protein aggregates. Finally, autophagy plays specialized roles in various physiological processes such as inflammation. Autophagy contributes to clear microorganisms and to regulate the production of proinflammatory cytokines and the survival and activation of lymphocytes (Fig. 1).

These properties suggest that autophagy may be involved in the development of autoimmunity and of autoinflammation in general. Polymorphisms of genes governing autophagy (autophagy-related [ATG] genes) are associated with the development of several diseases such as Crohn's disease, systemic lupus erythematosus (SLE), and rheumatoid arthritis (RA). Autophagy is induced by environmental stress due, for instance, to hypoxia, infection, or metabolic imbalances. Furthermore, the level of autophagy diminishes with advancing age. Thus, the development of joint diseases characterized by an age-related inflammatory component (e.g., osteoarthritis) and/or promoted by environmental stress (e.g., SLE and RA) is associated with autophagy dysregulation. Finally, several drugs used to treat inflammatory diseases can modulate autophagy, and we must therefore improve our understanding of how autophagy impacts chronic inflammation. Several studies have documented a functional link between autophagy dysregulation and cartilage autoinflammation.

2. Dysregulation of autophagy and loss of joint tissue homeostasis

Joint tissues are generated and degraded via the orchestrated effects of several cell types. Osteoblasts and the cells they differentiate into, i.e., osteocytes, ensure the generation and subsequent mineralization of the bone matrix. The fibroblasts in the synovial membrane and the chondrocytes, which are the only resident cells in the cartilage, generate the cartilage matrix. The bone and cartilage are also continuously degraded, according to a subtly regulated process in the healthy joint. Osteoclasts degrade both the bone and the directly overlying calcified cartilage [2]. The hyaline cartilage is degraded by metalloproteases released by either the synovial fibroblasts and macrophages or by the chondrocytes [3]. Thus, fibroblasts and chondrocytes contribute both to produce and to degrade the cartilage. Convincing evidence exists that autophagy regulation in these cell types is crucial to maintain joint tissue homeostasis. Osteoblasts can differentiate into osteocytes under the influence of several factors including the bone morphogenetic proteins (BMPs). Pancreatic cell stimulation by BMP2 induces autophagy. The existence of a similar effect on osteoblasts [4] would support a role for BMP2-induced autophagy in osteoblast differentiation. The Wnt/β-catenin is a key actor in osteoblast function and is overactivated in both RA and osteoarthritis. Autophagy negatively regulates Wnt signaling [5], and Wnt/β-catenin overactivation may therefore promote osteoblast death under stressful conditions. In osteoarthritis, autophagy is activated during the early stages of the disease and inhibited later on [6]. Thus, autophagy may help adapt to stress in early osteoarthritis by limiting cell

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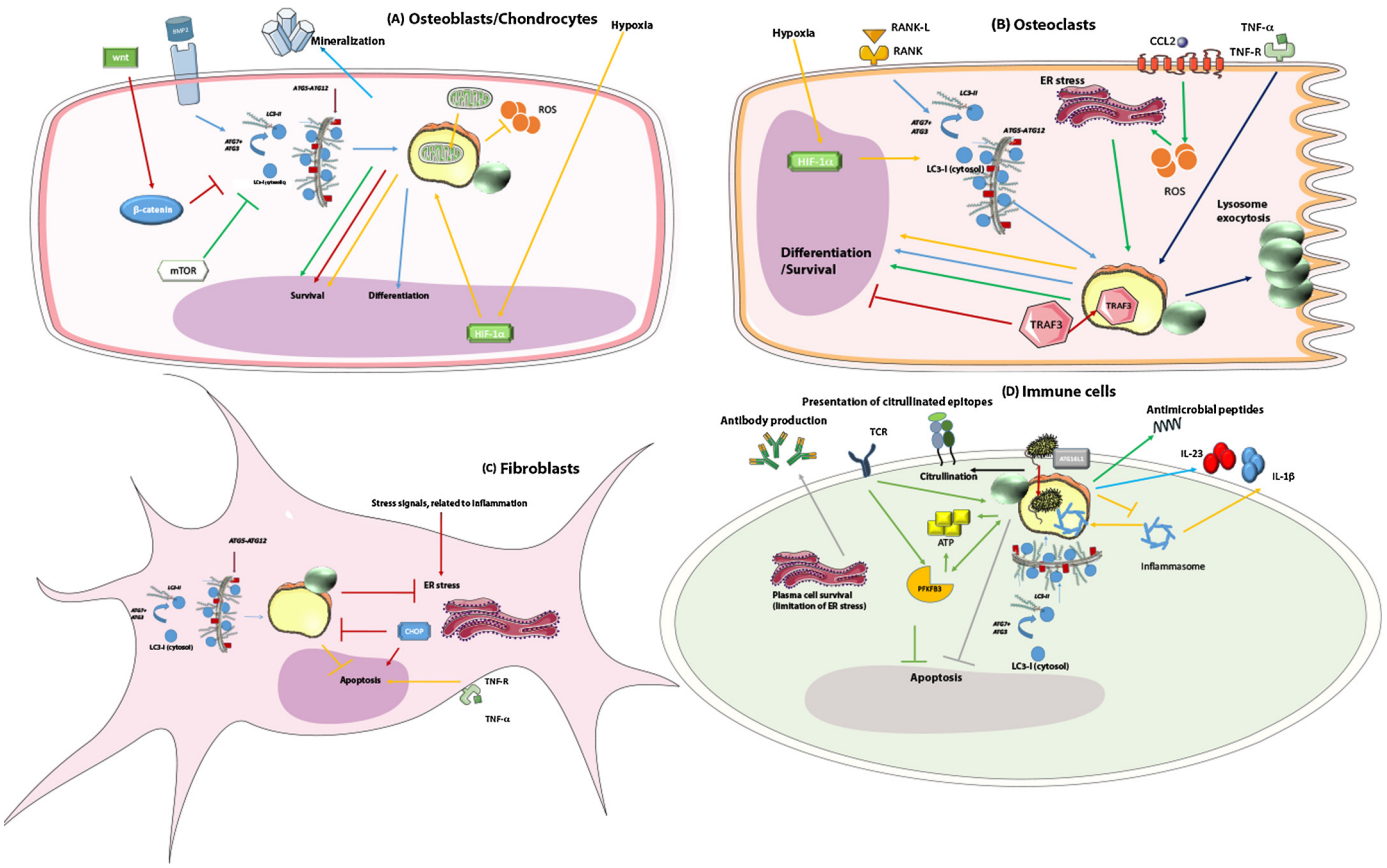

Fig. 1. Diagram of the autophagy process and its impact on cartilage inflammation. LC3-II (the lipid-bound form of LC3-I, formed after the action of the ATG3 and ATG7 proteins), as well as the ATG5-ATG12 conjugate, are indispensable to elongation of the autophagosome membrane. The autophagosome then fuses with the lysosomes, whose enzymes degrade the autophagosome contents. (A) Potential roles for osteoblast and chondrocyte autophagy in cartilage inflammation. Autophagy is induced in response to bone morphogenetic protein-2 (BMP2). Autophagy may promote the differentiation of osteoblasts to osteocytes and, more generally, participate in osteoblast survival under hypoxic conditions, by limiting the amount of reactive oxygen species (ROS) produced by dysfunctional mitochondria. In osteoarthritis, autophagy is suppressed by overactivation of the mTOR and Wnt/β-catenin pathways. Autophagy contributes to the mineralization process. (B) Role for osteoclast autophagy in inflammation. Autophagy contributes to osteoclast differentiation in response to the cytokine RANK-L and promotes osteoclast survival under hypoxic conditions. Autophagy is involved in the differentiation signals generated by the chemokine CCL2 after the induction of oxidative stress and endoplasmic reticulum (ER) stress. Autophagy degrades the protein TRAF3, thereby inhibiting osteoclast survival. Finally, the autophagic machinery is involved in lysosome exocytosis at resorption bays. (C) Synovial fibroblast autophagy limits apoptosis in response to proinflammatory signals, notably those mediated by TNF-α. Autophagy promotes the survival of rheumatoid arthritis synovial fibroblasts (RASFs) during ER stress and counterbalances the proapoptotic effect of the protein CHOP. (D) Immune cell autophagy and cartilage inflammation. Autophagy limits the inflammatory process by promoting the degradation of pathogenic organisms (directly or via a role in the release of antimicrobial peptides), limiting inflammasome activation and therefore IL-1β release, and modulating IL-23 release. In T cells, autophagy contributes to ATP production. In rheumatoid arthritis (RA), after T-cell receptor (TCR) triggering, deficient autophagy combined with deficient activity of the enzyme 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3 (PFKFB3) promotes cell apoptosis. In other conditions such as systemic lupus erythematosus (SLE), autophagy may contribute to the survival of autoreactive lymphocytes, notably those responsible for autoantibody production. Finally, autophagy participates in the presentation of citrullinated epitopes.

apoptosis. The declining autophagy level in more advanced stages of the disease may remove this protective mechanism, allowing degeneration of the cartilage and bone. Autophagy induction by expression of hypoxia-inducible factor (HIF)-1α in chondrocytes and osteoblasts is related to the constitutive hypoxia that characterizes the cartilage and bone [7]. Chondrocyte autophagy then limits the generation of reactive oxygen species (ROS) by preventing the accumulation of defective mitochondria and the resulting inflammation. In a recent study in mice, inhibiting chondrocyte autophagy accelerated the development of osteoarthritis and increased cartilage cell apoptosis [8]. The mammalian target of rapamycin (mTOR) pathway, a potent autophagy inhibitor, is overactivated in chondrocytes of joints with osteoarthritis, where the level of autophagy is diminished [9]. In vivo in mice, this mTOR pathway overactivation in the cartilage accelerates the development of osteoarthritis. Similarly, treatment of rats with the mTOR inhibitor rapamycin limits the development of osteoarthritis by restoring autophagic activity [10]. The induction of autophagy may also promote osteoblastic mineralization, as shown in murine models characterized by osteoblasts deficient in two ATG genes, *Atg5* and *Atg7* [11]. Thus, autophagy is involved in bone mineralization and in the osteoblast/osteocyte transition.

Osteoclasts are cells of monocyte lineage whose activity results in resorption of bone tissue and of calcified cartilage in direct contact with bone. Osteoclast differentiation and activation are strongly stimulated by proinflammatory signals produced in abnormally large amounts by the synovial membrane of rheumatoid joints. Autophagy was first shown to promote osteoclastogenesis in response to receptor activator of NF-κB ligand (RANK-L) [12]. A subsequent study demonstrated that autophagic activity degraded TNF receptor-associated receptor 3, a negative osteoclastogenesis regulator [13]. Interestingly, chloroquine – a drug widely used to inhibit lysosomal degradation – limited the osteoporosis induced by oophorectomy or hormone treatments. This study did not obtain definitive proof that the therapeutic effect of chloroquine was related to modulators of lysosomal catabolic processes such as autophagy. This possibility is worth considering, however, and suggests that inhibiting autophagy might hold promise as a treatment to prevent bone loss. Autophagy is also involved in autophagy induced by hypoxia in an HIF-1α-dependent manner [14] or by

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