Autophagy: A New Therapeutic Target in Cartilage Injury and Osteoarthritis

Martin Lotz, MD
Beatriz Caramés

Autophagy is a cellular homeostasis mechanism that plays an essential role in energy and nutrient regulation as well as in the removal of damaged and dysfunctional macromolecules and organelles.[1] Failure of autophagy results in the increased production of reactive oxygen species and to abnormal gene expression, and it can lead to cell death. Autophagy failure as observed in aging tissues and cells leads to neurodegeneration, cardiomyopathies, abnormal skeletal development, and premature death.[2] In human osteoarthritis (OA) and in a mouse model, autophagy proteins were expressed at reduced levels; this measure was associated with increased cell death and degradation in articular cartilage.[3]

An important suppressor of autophagy is the protein mammalian target of rapamycin (mTOR) as part of the complex mTORC1. Rapamycin is a lipophilic macrolide antibiotic that is used as an immunosuppressive drug in solid-organ transplantation for the management of renal cell carcinoma, and it is under evaluation for the treatment of certain types of cancer. It can induce autophagy in a variety of cell types.[4]

Rapamycin was tested for chondroprotective activities in an in vitro model of cartilage injury and in a mouse model of OA. Cartilage injury was induced by subjecting bovine tissue explants to single-impact loading, which results in cell death and extracellular matrix damage; single-impact loading was also associated with a suppression of autophagy regulators. Treatment of the explants with rapamycin improved cell viability and attenuated tissue damage.[5]

In the mouse model, OA was induced by transection of the medial meniscotibial ligament and the medial collateral ligament. Intraperitoneal administration of rapamycin affected the mTOR signaling pathway, as indicated by inhibition of phosphorylation of ribosomal protein S6, a target of mTORC1, and by activation of light chain 3 (LC3), a main marker of autophagy.[6] The severity of cartilage degradation was reduced in the rapamycin-treated group compared with the control group, and this reduction was associated with a decrease in synovitis.[6] Rapamycin treatment also maintained cartilage cellularity and decreased the expression of ADAMTS-5, an important enzyme in cartilage extracellular matrix degradation,[7] and of interleukin-1β, a potent inflammatory and catabolic stimulus in OA.[8] These results suggest that rapamycin reduces the severity of traumatic cartilage injury and of experimental OA at least in part by autophagy activation.

Drugs that inhibit one of a large number of extracellular matrix–degrading enzymes may not provide sufficient impact to change the overall course of the disease and failed in previous clinical trials.[9,10] By contrast, inhibiting the failure of a critical cellular homeostasis mechanism, such as autophagy, leads to global changes in gene expression and can ultimately cause cell death and extracellular matrix destruction,[2] two main features of OA-affected cartilage.[11] The in vitro and in vivo studies of rapamy-

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From the Scripps Research Institute, La Jolla, CA.

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cin establish proof of principle for chondroprotective effects of rapamycin. The two models are associated with the rapid development of cartilage lesions; it remains to be determined whether rapamycin is also effective in models of spontaneous or aging-associated OA. However, short-term use of rapamycin may be effective and feasible in clinical conditions associated with joint injury.[12]

One important limitation of rapamycin for long-term administration in humans is its immunosuppressive effect. This will certainly be a concern if the drug were to be used to slow progression of established disease. However, the clinical feasibility of using mTOR inhibitors for the management of OA is supported by recent advances in the development of new and safer rapamycin analogs. It can also be anticipated that, with more precise resolution of the different effector mechanisms that are regulated by mTOR, there will be new drugs with greater specificity.[13]

Recent observations on suppression of autophagy in aging and injured cartilage and chondroprotective activities of rapamycin suggest that pharmacologic enhancement of autophagy may be a promising new approach to prevent or manage OA.

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