Editorial

New therapeutic target for modulation of autophagy in osteoarthritis

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Autophagy is a normal intracellular mechanism for recycling unnecessary or dysfunctional cellular components and proteins, thus preserving energy and alleviating stress to promote cellular survival. Numerous recent studies have demonstrated the importance of autophagy in normal cartilage maintenance and implicated deregulation of autophagy in the pathogenesis of osteoarthritis (OA), which remains as the most common chronic joint disease and the leading cause of disability worldwide. Evidently, cartilage-specific deletion of autophagy protein Atg5 induced aging-associated OA (1), suggesting a crucial role of autophagy in normal cartilage homeostasis. Similarly, decreased autophagy activity is associated with OA progression, as key autophagy markers decreased significantly in late OA, followed by increased chondrocyte apoptosis (2). Consistently, several studies subsequently demonstrated that genetic ablation (3) or pharmacological inhibition (4) of mammalian target of rapamycin (mTOR), which is a key suppressor of autophagy, have protective effects against OA in mice. It is likely that mTOR signaling may also have other effects on OA that are independent of autophagy, but regardless, therapeutic approaches that help maintain or stimulate autophagy at the articular cartilage appear as a promising avenue in managing OA.

A recent study showed evidence that autophagy activity at the articular cartilage is modulated by microRNA(miR)-128a (5). In this new study, Lian and colleagues surgically induced knee OA in rat by anterior cruciate ligament transection (ACLT) and found significant downregulation of multiple autophagy markers during OA progression, including Atg12. Concomitantly, miR-128a, which they showed could directly target and suppress Atg12, was significantly upregulated in OA. Similar changes of ATG12 and miR-128a expressions were also found in cartilage specimens harvested from patients with end-stage knee OA. Importantly, they further demonstrated that intra-articular injection of miR-128a directly induced cartilage degradation, and conversely, lentivirus-delivered antisense oligonucleotide of miR-128a (miR-128a-AS) was able to alleviate ACLT-induced cartilage erosion. Atg12 is likely only one of the many gene targets by which miR-128a modulates OA progression, as one previous study identified miR-128 as the top upstream regulator of hypomethylated OA susceptibility genes (6). Nevertheless, these exciting new findings strongly hinted at the therapeutic potential of miR-128a-AS, or other similar molecules that could interfere with miR-128a to promote autophagy, in treating OA.

Interestingly, this new study by Lian *et al.* (5) also investigated the potential mechanisms by which miR-128a was upregulated in OA. To this end, they treated cultured primary chondrocytes with interleukin-1β (IL-1β) to mimic inflammation and found that IL-1β treatment led to upregulation of miR-128a and downregulation of Atg12, which were consistent with their *in vivo* model. Hypothesizing that miR-128a might be epigenetically regulated, they then tested and found IL-1β treatment

also decreased both the methylation of histone H3K27 and expression of enhancer zeste homology 2 (Ezh2), which is the histone methyltransferase driving H3K27 methylation. Finally, they demonstrated that overexpression or knockdown of Ezh2 reciprocally regulated the expression of miR-128a. Based on these findings, they proposed a working model to explain OA progression. Joint inflammation and upregulation of IL-1β results in downregulation of Eah2 and H3K27 methylation, which in turn upregulates miR-128a expression. miR-128a then suppresses Atg12 expression and autophagy in articular cartilage, thus driving chondrocyte apoptosis and cartilage erosion. While this working model is logically sound based on their observations alone, it is somewhat inconsistent with other previous studies in the field. Normal expression of Ezh2 is indeed required for proper cartilage development and normal chondrocyte functions during bone growth (7,8). However, it has been previously shown that EZH2 expression was upregulated, rather than downregulated, in both articular chondrocytes and synovial fibroblast in patients with OA (9,10). Importantly, intra-articular injection of Ezh2 inhibitor delayed OA development in mice (9), suggesting suppression of Ezh2 expression has protective effect against OA. This protective effect of Ezh2 inhibitor on OA is in part attributable to modulation of Wnt/β-catenin signaling. One of the many known genomic targets of Ezh2 is Sfrp1 (9,10), which encodes for a soluble inhibitor of Wnt signaling. Because activation of Wnt/β-catenin signaling is implicated in OA progression, and several preclinical studies have already demonstrated that Wnt inhibitors could ameliorate OA progression (11-13), inhibition of Ezh2 may similarly improve OA by derepression of Sfrp1 and consequent downregulation of Wnt signaling. Taken together, it is conceivable that the downregulation of Ezh2 observed by Lian *et al.* (5) in IL-1β treated chondrocytes is specific to the model they used, and whether or not pharmacological modulation of Ezh2 may have bone fide effects on autophagy in OA remain to be elucidated.

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