The dual role of autophagy in chondrocyte responses in the pathogenesis of articular cartilage degeneration in osteoarthritis

JUN CHANG¹, WEI WANG¹, HUI ZHANG¹, YONG HU¹, MINGLI WANG² and ZONGSHENG YIN¹

¹Department of Orthopaedics, Anhui Geriatric Institute, The First Affiliated Hospital of Anhui Medical University, ¹²Department of Microbiology, Anhui Medical University, Hefei, Anhui 230022, P.R. China

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Abstract. The present study aimed to analyze the responses to autophagy in osteoarthritis (OA) and aging chondrocytes in order to elucidate the role of autophagy in the pathogenesis of OA. We used multiple assays to confirm that autophagic activity was downregulated in chondrocytes of aged articular cartilage. Surprisingly, we found that the expression of autophagy-related proteins was not decreased in the tissues of patients with OA. We also observed that rapamycin-induced autophagy prevented the accumulation of subdiploid cells in young chondrocytes, while it induced cell death by autophagy in OA chondrocytes. Our results demonstrate that autophagic activity decreases with aging, and may be responsible for the cytoprotective effects in young cartilage. However, we found that autophagic activity in patients with OA was higher than in the aging group, and reported autophagic cell death in OA chondrocytes. These results suggest that autophagy plays both a cytoprotective and death-promoting role in the pathogenesis of OA.

Introduction

Osteoarthritis (OA), the most common chronic disability in older adults, is characterized by the degeneration of articular cartilage. With the aging of the population, it is estimated that the number of OA cases will double over the next 3 decades (1). Recent studies have suggested that aging plays an important role in the pathogenesis of OA (2,3). However, whether the aging process is responsible for the development of OA has not yet been fully elucidated. Considering that chondrocytes are the only type of cell type present in articular cartilage, the OA process is characterized by the changes that occur in these cells. Therefore, the understanding of the cellular processes that regulate aging-associated changes in chondrocytes is essential to the development of novel therapeutic interventions for progressive joint diseases.

Autophagy is a cellular response to various types of stress, whereby cellular organelles and macromolecules are engulfed and recycled to sustain cellular metabolism. Evidence indicates that autophagy is required for lifespan extension in various organisms, and that numerous autophagy-related proteins are directly regulated by longevity pathways (4). Autophagic dysfunction may contribute to the pathogenesis of numerous neurodegenerative diseases, including Parkinson's disease (5), Alzheimer's disease (6), Frontotemporal dementia (7), Lafora disease (8) and Huntington's disease (9). Constitutive autophagy is important for maintaining the quality of organelles and maintaining cell function. Autophagy degrades damaged organelles, cell membranes and proteins, and the failure of autophagy is thought to be one of the main causes of cell aging. Therefore, the level of autophagic activity decreases with aging, whereas the stimulation of autophagy may have potent anti-aging effects (10).

However, to date, little is known about the role of autophagy in articular cartilage. Roach et al (11) firstly described a peculiar variant of apoptotic cell death in articular cartilage, termed chondroptosis, a term that also included an autophagy component. Previous studies have suggested that autophagy is associated with OA. Caramés et al (12) demonstrated that aged and OA articular cartilage were associated with the reduced expression of Unc-51-like kinase 1 (ULK1), Beclin-1 and microtubule-associated protein 1 light chain 3 (LC3), and speculated that autophagy may play a protective role against chondrocyte death. In addition, hypoxia-inducible factor (HIF)-2α has been suggested to suppress autophagy in chondrocytes (13). Certainly, autophagy plays a dual role, and is involved in both cell survival and death (4,14). However, the potential role of autophagy in the initiation or the development of OA remains unknown. Therefore, further studies are required to elucidate the possible role of autophagy in OA and to understand the association between autophagy, cell survival and cell death.

In present study, we investigated the role of autophagy in chondrocyte responses in the pathogenesis of articular cartilage degeneration in OA. By intervening in autophagy, we assessed the differences among the chondrocytes and ultrastructural changes. Our results demonstrated that Beclin-1 and...
were incubated with biotinylated goat anti-rabbit secondary antibody for 30 min at room temperature, and then incubated using the Vectastain ABC-AP kit (Vector Laboratories, Burlingame, CA, USA) for 30 min. Finally, the sections were washed and incubated with 3,3-diaminobenzidine tetrahydrochloride (DAB) substrate for 2-8 min. Visual impressions of the staining intensity in the cytoplasm and the percentage of immunopositive chondrocytes were recorded by analyzing the digital photomicrographs using ImageJ software.

**Materials and methods**

**Human cartilage sampling.** All cartilage samples were collected from human donors who were undergoing surgery at the Department of Orthopaedics, the First Affiliated Hospital of Anhui Medical University, Hefei, China. The specimens were divided into 3 groups: group 1, young cartilage specimens were obtained from 9 patients undergoing lower limb amputation in severe trauma; group 2, 13 aging cartilage specimens, also having no history of joint disease, were harvested from patients with femoral neck fracture who were undergoing femoral head replacement and used as age-matched non-arthritic articular cartilage samples; and group 3, OA cartilage tissues were obtained from 12 patients with early-stage osteoarthritis undergoing total knee arthroplasty. Human tissues were obtained under the approval of the Hospital Ethics Committee of Anhui Medical University. The characteristics of the patients participating in this study are shown in Table I.

**Isolation and culture of primary chondrocytes.** The cartilage tissue was incubated with trypsin (0.5 mg/ml; Sigma-Aldrich, St. Louis, MO, USA) at 37°C for 10 min. After the trypsin solution was removed, the tissue slices were treated for 12-16 h with type II collagenase (2 mg/ml; Sigma-Aldrich, St. Louis, MO, USA) in Dulbecco's modified Eagle's medium (DMEM; Gibco-Life Technologies) with 5% fetal calf serum. The isolated chondrocytes were recovered in DMEM supplemented with 10% fetal calf serum. L-glutamine and antibiotics and were allowed to attach to the culture flasks. The cells were incubated at 37°C in a humidified gas mixture containing 5% CO₂ balanced with air. The chondrocytes were used in the experiments at confluency (2-3 weeks in primary culture).

**Histological and immunohistochemical analysis.** The serial sections were stained with hematoxylin and eosin (H&E) to observe histological changes in the articular cartilage. Immunohistochemistry (IHC) was performed according to the indirect immunoperoxidase method. In brief, following deparaffinization, hydration and blockage of endogenous peroxidase, the specimens were incubated for 20 min with 10% non-fat milk in phosphate-buffered saline (PBS) in order to block specific sites and then individually incubated at 4°C overnight with the following primary antibodies: rabbit polyclonal LC3 antibody (NB100-2220, 1:200; Novus Biologicals, LLC; Littleton, CO, USA) and rabbit polyclonal Beclin-1 antibody (ab55878, 1:400; Abcam, Cambridge, MA, USA). After rinsing, the slides were washed, and the sections were incubated with biotinylated goat anti-rabbit secondary antibody for 30 min at room temperature, and then incubated using the Vectastain ABC-AP kit (Vector Laboratories, Burlingame, CA, USA) for 30 min. Finally, the sections were washed and incubated with 3,3-diaminobenzidine tetrahydrochloride (DAB) substrate for 2-8 min. Visual impressions of the staining intensity in the cytoplasm and the percentage of immunopositive chondrocytes were recorded by analyzing the digital photomicrographs using ImageJ software.

**Western blot analysis.** The chondrocytes were isolated from confluent monolayer cultures. Before immunoblotting, protein was quantified using the Bradford method with a BCA detection kit (Thermo Scientific-Pierce, Rockford, IL, USA) and adjusted to equal concentrations across different samples. Equal amounts of protein were separated by SDS-PAGE on precise 10% polyacrylamide gels. Following electrophoresis, the proteins were transferred onto a polyvinylidene fluoride (PVDF) membranes (Millipore, Billerica, MA, USA). The membranes were then blocked with 5% non-fat milk in Tris-buffered saline containing 0.1% Tween-20 (TBST) at room temperature for 1 h, and then incubated overnight at 4°C with primary antibodies: rabbit polyclonal LC3 antibody (NB100-2220, 1:2,000; Novus) and rabbit polyclonal Beclin-1 antibody (ab55878, 1:2,000; Abcam). Following incubation, the membranes were washed in TBST buffer for 5 min and probed with anti-rabbit secondary antibody (401393 -2ML, 1:50,000; Millipore) or under normoxic conditions for 24 h, and examined under a confocal microscope. For quantification purposes, the proportion of chondrocytes that contain GFP-LC3 puncta (number of cells with green fluorescent puncta/total number of transfected cells) (15,16), at least 100 green fluorescent chondrocytes should be counted for each sample to obtain statistically significant results.

**Transmission electron microscopy (TEM).** TEM analysis was performed as previously described (17). The chondrocytes were harvested, and fixed in 2.5% glutaraldehyde in phosphate buffer, post-fixed in 2% osmium tetroxide and embedded in Luveak-812 (Nacalai Tesque, Inc., Kyoto, Japan). Ultrathin sections were stained with uranyl acetate for 1 h, washed, and incubated with 3% uranyl acetate for 30 min. Finally, the sections were washed and incubated with 3,3-diaminobenzidine tetrahydrochloride (DAB) substrate for 2-8 min. Visual impressions of the staining intensity in the cytoplasm and the percentage of immunopositive chondrocytes were recorded by analyzing the digital photomicrographs using ImageJ software.

**Monodansylcadaverine (MDC) staining.** Three groups of chondrocytes were seeded on coverslips overnight and then...
treated with rapamycin or 3-methyladenine (3-MA) (both from Sigma-Aldrich, Shanghai, China). After autophagy activation or inhibition, the cells were incubated with 0.05 mM MDC (Sigma-Aldrich, Shanghai, China) in PBS at 37˚C for 10 min, then washed 3 times with PBS and fixed with a solution of 4% paraformaldehyde for 30 min. The coverslips were examined under a fluorescence microscope (XSZ-D2; Olympus, Tokyo, Japan). To quantify autophagic cells after treatment, we counted the number of autophagic cells demonstrating MDC-labeled particles among 200 cells.

3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. AO is a widely used to visualize acidic vesicular organelles (A VOs) (18). AO is a fluorescent dye that stains DNA and the cytoplasm bright green. At low pH, AO emits red fluorescence with intensity proportional to the degree of acidity. To detect the cell death rate, following the pharmacological activation or inhibition of autophagy, the cells were washed twice with PBS, fixed with 4% paraformaldehyde and stained with AO (Molecular Probes, Eugene, OR, USA) at 1 µg/ml for 15 min. They were then washed with PBS to remove the unbound dye. AVO formation in the AO-stained cells was measured by flow cytometry, and the cells were analyzed on a flow cytometer using CellQuest software.

Acridine orange (AO) staining and quantification by flow cytometry. AO is a widely used to visualize acidic vesicular organelles (A VOs) (18). AO is a fluorescent dye that stains DNA and the cytoplasm bright green. At low pH, AO emits red fluorescence with intensity proportional to the degree of acidity. To detect the cell death rate, following the pharmacological activation or inhibition of autophagy, the cells were washed twice with PBS, fixed with 4% paraformaldehyde and stained with AO (Molecular Probes, Eugene, OR, USA) at 1 µg/ml for 15 min. They were then washed with PBS to remove the unbound dye. AVO formation in the AO-stained cells was measured by flow cytometry, and the cells were analyzed on a flow cytometer using CellQuest software.

Quantification of DNA hypoploidy and cell cycle phase analysis by flow cytometry. When the chondrocytes reached 60-70% confluency, we treated the cells with 3-MA or rapamycin (Sigma-Aldrich, Shanghai, China). Following treatment for the desired amount of time, the cells were harvested. The digested cells were then washed 3 times in PBS, fixed with ice cold 70% ethanol and then incubated at -20˚C overnight. Subsequently, the fixed cells were centrifuged and washed 3 times with PBS. The cells were resuspended in 250 µl propidium iodide (50 mg/ml) and incubated in the dark at room temperature for 3 h. The cells were then analyzed on a flow cytometer using CellQuest software.

Results

Differential expression of Beclin-1 and LC3 in human articular cartilage tissues. To determine the role of autophagy in the development of OA, we examined Beclin-1 and LC3 expression in young, aging and OA cartilage by IHC in the upper zone of the cartilage (including the superficial and middle zones). IHC analysis indicated that Beclin-1 and LC3 were ubiquitously expressed in the young cartilage group, but lower expression levels were observed in the aging cartilage. Cartilage samples were evaluated by staining with H&E (Fig. 1A-a-c) and Beclin-1 and LC3 expression levels were determine by IHC (Fig. 1A-d-g). The percentage of chondrocytes positive for Beclin-1 was substantially decreased in the aging group (21.5±6.1%) compared with the young group (64.8±4.4%), while the percentage of LC3-positive cells in the young and aging groups (57.2±5.6 and 24.3±5.7%, respectively) indicated a statistically significant decrease in aging cartilage (P<0.05) (Fig. 1B). These results indirectly suggest a decline in autophagic activity in aging tissue. Of note, we found that the expression of autophagic proteins was not reduced in patients with OA. In the OA group, the percentages of Beclin-1- and LC3-positive cells were 44.1±5.6 and 62.4±7.6%, respectively (Fig. 1B).

Differences in the autophagic response of cultured articular chondrocytes. We used human primary chondrocytes transiently expressing GFP-LC3 to quantify autophagosome formation. The results revealed that the percentage of chondrocytes with GFP-LC3 puncta structures was low (Fig. 2A). When comparing aging and OA chondrocytes, the percentage of chondrocytes with GFP-LC3 puncta structures did not differ. The results of electron microscopy also revealed few autophagosomes in these 3 groups of chondrocytes. Western
blot analysis also revealed no significant differences in the expression levels of autophagic proteins in the chondrocytes (Fig. 2C and D). Taken together, these results indicate that autophagic activity was low and did not differ between the 3 groups of cultured chondrocytes in vitro.

Hypoxia plays an essential role in autophagy in chondrocytes. Chondrocytes grow in a hypoxic environment in vivo (19). Thus, in this study, we further examined the role of hypoxia in autophagy in cultured chondrocytes. In the young and OA chondrocytes, the numbers of GFP-LC3 puncta structures were markedly increased, but in the aging group, no significant change was observed (Fig. 3A). Compared with the groups exposed to normoxic conditions, the percentage of cells with GFP-LC3 puncta structures in the aging group was significantly increased. We subsequently used electron microscopy to observe the changes in the ultrastructure of chondrocytes following hypoxia-induced autophagy. A large number of autophagosomes with degraded organelles was observed in the young chondrocytes (Fig. 3C-a). By contrast, the aging chondrocytes contained few autophagosomes. Of note, in the OA chondrocytes, we found characteristic structures of autophagic cell death (Fig. 3C-b); these cells with autophagic vacuoles contained cell fragments, autolysosomes and few or no chromatin was condensed. In addition, our results revealed a significant increase in the expression of LC3-II protein in the young and OA groups; however, no significant changes were observed in the aging group (Fig. 3D and E).

Effect of rapamycin and 3-MA on autophagic of chondrocytes. In this study, we demonstrated that autophagic activity was increased under hypoxic conditions compared with normoxic conditions. Thus, we induced autophagy under normoxic conditions and inhibited autophagy under hypoxic conditions. As illustrated in Fig. 4A-d-f, following the treatment of the chondrocytes with 10 μM rapamycin, which has been
reported to be a potent inducer of autophagy (13,20,21), under normoxic conditions, the number of vesicles was increased by MDC staining (Fig. 4B). Western blot analysis also indicated that the expression of LC3-II was significantly increased in the young and OA chondrocytes (Fig. 4C). This result indicated that autophagy in young and OA chondrocytes was more easily induced than in aging chondrocytes (Fig. 4D). Under hypoxic conditions, following the pre-treatment of the chondrocytes with rapamycin, MDC was concentrated in the spherical structures distributed in the cytoplasm. The chondrocytes have weak and diffuse MDC staining in untreated cells. To quantify autophagic cells after treatment, we counted the number of autophagic cells demonstrating MDC-labeled particles among 200 cells. Values are the means ± SD from at least 3 independent experiments. *P<0.05 vs. normoxia. (C and D) We evaluated the effect of rapamycin on light chain 3 (LC3)-II/LC3-I expression by western blot analysis. Densitometry analysis revealed a significant increase in LC3-II/LC3-I expression by 3.75-, 2.26- and 3.78-fold in the young, aging and osteoarthritis (OA), respectively in the rapamycin-treated chondrocytes under hypoxic conditions compared with normoxic conditions. Values are the means ± SD (P<0.05).
with 3-MA, which is one of the most commonly used inhibitors of autophagy (22,23), the number of autophagic vacuoles stained by MDC was much lower (Fig. 5A and B). Moreover, LC3-II and Beclin-1 expression significantly decreased in the young and OA chondrocytes (Fig. 5C and D).

Figure 5. Effect of 3-methyladenine (3-MA) on autophagy of chondrocytes. (A and B) Monodansylcadaverine (MDC) staining was used to quantify autophagic chondrocytes, arrows represent autophagic cells. The quantification results of MDC incorporation into the cells indicated that 3-MA decreased autophagy from 46.9±6.1 to 8.5±2.5% in osteoarthritis (OA) group, compared with the young and aging group (from 44.6±8.4 to 19.5±3.5%, from 18.6±4.8 to 12.0±2.9%, respectively). (C and D) We evaluated the effect of 3-MA on light chain 3 (LC3)-II/LC3-I expression by western blot analysis. Densitometry analysis revealed a significant decrease in LC3-II/LC3-I expression by 3.17-, 1.55- and 5.52-fold in the young, aging and OA groups, respectively under normoxic conditions compared with hypoxic conditions. Values are the means ± SD (*P<0.05).

Figure 6. Effect of autophagy on cell viability and cell cycle of chondrocytes. (A) Effect of rapamycin or 3-methyladenine (3-MA) on the viability of chondrocytes. Cell viability was determined by MTT assay. The cell survival rate changed from 51.57±6.92 to 88.27±3.15% in the young chondrocytes after the induction of autophagy, and the cell survival rate changed from 37.69±5.17 to 69.86±4.81% in osteoarthritis (OA) chondrocytes after the inhibition of autophagy (**P<0.05). (B) Flow cytometry was performed to detect cell death by acridine orange (AO) staining. (a) The cell death rate changed from 34.47 to 5.53% after the induction of autophagy in young chondrocytes. (b) The cell death rate changed from 40.16 to 9.61% after the inhibition of autophagy in OA chondrocytes. (C) Quantification of DNA hypoploidy and cell cycle phase analysis by flow cytometry. (a) Young chondrocytes under normoxic conditions: the majority of cells were in the G0/G1 phase. (b) Young chondrocytes under hypoxic conditions: the number of cells decreased in S phase. (c) Young chondrocytes following treatment with rapamycin under hypoxic conditions: the number of cells decreased in the S and G2 phase. (d) OA chondrocytes under normoxic conditions: many of the cells were in the G0/G1 phase. (e) OA chondrocytes under hypoxic conditions: the number of cells decreased in the S phase. (f) OA chondrocytes following treatment with 3-MA under hypoxic conditions: the number of cells was decreased in the S phase, and the number of cells in the sub-G1 phase declined.
Effects of autophagy on cell viability and cell cycle of chondrocytes. To extend our analysis, we intervened in the autophagic pathway to examine the effects on cell viability. In particular, we examined whether autophagy contributes to the cell survival or cell death process. Cell viability was determined by MTT assay. The cell survival rate increased significantly in the young chondrocytes after the induction of autophagy (P<0.05). In addition, the cell survival rate changed from 37.69±5.17 to 69.86±4.81% in the OA chondrocytes after the inhibition of autophagy (Fig. 6A). Flow cytometry was performed to detect cell death by AO staining. As shown in Fig. 6B-a, the cell death rate changed from 34.47 to 5.53% after the induction of autophagy in young chondrocytes. In the OA chondrocytes, by contrast, it changed from 40.16 to 9.61% after the inhibition of autophagy (Fig. 6B-b). These results demonstrated that autophagy was beneficial to cell survival in young chondrocytes but led to cell death in OA chondrocytes. To further clarify the possible mechanisms by which autophagy affected the viability of chondrocytes, we used flow cytometry for the quantification of DNA hypoploidy, analysis of the cell cycle and the measurement of cell sub-G1 peaks. In the young chondrocytes, the majority of cells were in the G0/G1 phase of the cell cycle (Fig. 6C-a). Flow cytometry demonstrated that rapamycin prevented the accumulation of subdiploid cells (Fig. 6C-b and c). These findings suggest that increased autophagosome formation is required for chondrocyte survival in young cartilage. As shown in Fig. 6C-e, autophagy was critical for the OA chondrocyte cycle progression from the G2/M to the G1 phase under hypoxic conditions. The sub-G1 population of the cell cycle is represented as total cell death, and we found that the sub-G1 population in the OA chondrocytes decreased from 16.24% to 4.47% following treatment with 3-MA under hypoxic conditions (Fig. 6C-e and f).

Discussion

The aim of this study was to confirm that autophagy plays a dual role in articular cartilage tissue. Firstly, we confirmed that autophagic activity was downregulated in the chondrocytes of aged articular cartilage. Surprisingly, we found that the expression of autophagy-related proteins was not decreased in the tissues of patients with OA. In addition, we also found that hypoxia may induce the autophagy of chondrocytes. Another observation was that rapamycin may activate autophagy, which plays a protective role in young chondrocytes. However, the excessive activation of autophagy led to autophagic cell death in OA chondrocytes in vitro.

The present study demonstrated that autophagic activity declined in the aging articular cartilage. We found that LC3-II conversion occurred more easily in young chondrocytes than in aging chondrocytes. In early autophagy, LC3-I is converted to LC3-II through lipidation by the ubiquitin-like system, which correlates with the extent of autophagosome formation (24,25). Therefore, decreased autophagic activity may participate in the pathological process of cartilage aging. Aging is one of the main factors in the pathogenesis of OA, and older patients who experience a joint injury develop OA much more rapidly than young patients with a similar knee injury (26). During aging, the efficiency of autophagic degradation is declined and intracellular waste products are accumulated. Furthermore, there is a general consensus that the function of autophagy is decreased during aging (27-29). This observation is consistent with the notion that basal autophagic activity is decreased with age, thus contributing to the accumulation of damaged macromolecules and susceptibility to aging-related diseases (30).

To our surprise, the autophagic markers were found to be increased in patients with OA. Beclin-1 and LC3 expression levels in OA cartilage were significantly increased in the upper zone compared with those in aging articular cartilage. These results are not completely consistent with those of Caramés et al (12). They reported that the expression of ULK1, Beclin-1 and LC3 in OA cartilage was significantly decreased in the superficial zone. We speculated that their results may be due to the wear and tear with the loss of chondrocytes in the superficial zone. However, we found the cell clusters which localized in the middle zone in OA cartilage showed a strong expression of Beclin-1 and LC3. In addition, the results of GFP-LC3 transfection indicated that the chondrocytes in OA were more easily susceptible to autophagy than those in the aging group, which further demonstrated that autophagic activity in OA was higher than the aging group.

We found that autophagy may play a protective role in young cartilage. In our experiments, rapamycin-induced autophagy protected chondrocytes in the young group from death under hypoxic conditions, to a certain extent. Autophagy is a mechanism for the turnover of proteins and elimination of damaged organelles to maintain cell homeostasis. The induction of autophagy under pathological conditions is generally considered to play a cytoprotective role in young cartilage. Recent studies provide compelling evidence that autophagy protects against diverse pathologies, such as neurodegenerative diseases (31), cancer (32), aging (33) and heart diseases (34). Therefore, we suggested that in young articular cartilage, autophagy was activated as an adaptive response to hypoxic conditions. These results indicate that compromised autophagy represents a novel mechanism in the development of cartilage degeneration.

The most intriguing finding of our study was that autophagic chondrocyte death occurred in OA. Roach et al (11) described a morphological change of cell death in articular cartilage which was similar to autophagic cell death. The present study first reported that this type of death is classic autophagy in chondrocytes. We detected cell death in the presence of autophagy, and demonstrated the reduction in cell death by the inhibition of autophagy. Such findings are consistent with most basic characteristics of autophagic cell death (35). Autophagic cell death is morphologically defined as a type of cell death. This autophagy-dependent non-apoptotic cell death is defined as autophagic cell death, or type II programmed cell death (PCD) (36). Therefore, our results provided a starting point to study autophagic chondrocyte death in OA.

In addition, although our results demonstrated that autophagy induced chondrocyte survival and death in different stages of OA progression. Certain studies have found that autophagy can promote cell survival or cell death, depending on the type of cellular stress (35). Autophagy has also been reported to play a role in cell survival under other types of stress, such as exposure to DNA-damaging reagents (37), endoplasmic reticulum stress (38) and radiation (39). Exposure to treatment...
conditions, such as hypoxia (40) and arsenic trioxide (41) have been reported to induce autophagic cell death.

In conclusion, the present study demonstrates that rapamycin-induced autophagy does not lead to chondrocyte death in young patients, while it can induce cell death by autophagy in the patients with OA. We described a novel and paradoxical role for autophagic cellular degradative pathways in OA cartilage. These results suggest that autophagy may play both a cytoprotective and death-promoting role in chondrocytes. Therefore, the dual role of autophagy in cytoprotection and cell death, as well as its impact on longevity is one of the most fascinating features of this process, which clearly has a direct impact on the age-related development of cartilage degeneration. Understanding the role of autophagy in chondrocyte responses should provide new targets for attenuating and preventing the development of OA.

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References