Editorial

Senolytic treatments applied to osteoarthritis: a step towards the end of orthopedic surgery?

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Osteoarthritis (OA) is the most common chronic degenerative disease of the joint for which more than 1/3 of the population after 60 years old have radiographic signs for knee OA (1). OA has pejorative consequences on quality of life and working abilities, leads to a social isolation in elderly and has a significant impact on the public health costs.

To date, no validated curative medical treatments for OA are available. New "symptomatic slow-acting drugs" such as glucosamine and visco-supplementation with hyaluronic acid are used in OA, but they still lack evidence for efficiency on long-term structural articular remodeling (2,3). Therefore, OA still shows a huge unmet need while symptomatic painkiller treatments and physiotherapy remain the main alternatives before prosthetic surgical joint replacement.

A range of clinical risk factors favors OA development. Next to local risk factors with overweight and life-driven repetitive or acute mechanical stresses, there are also systemic risk factors. Among them, the first one is ageing. Indeed, knee OA rate increases continuously with age, with the highest relative risk between 70–75 years old (4).

For long, OA was only considered as a degenerative disease of the cartilage *per se*. However, other joint structures play roles in OA etiology. Synovial membrane, that acquires inflammatory hypertrophic phenotype, contributes to symptoms severity, osteophytes formation and even articular erosion (5). Furthermore, remodeling of the subchondral bone is not only a consequence but also rather an active component of the disease, generating pain and articular loss of function (6). Thus, recent data teach us that OA is more a global and heterogeneous joint disease with both inflammatory and metabolic components. A new emerging theory linking age-related OA pathology and inflammation reveals the role of cellular senescence in OA onset, as recently demonstrated by Jeon *et al.* in *Nature Medicine* (7). Cellular senescence is a permanent cell proliferative arrest induced by intrinsic signals including telomere erosion but also extrinsic inappropriate stimuli such as free radicals or chronic exposure to inflammatory cytokines (8). Senescence is associated with dramatic changes in cell morphology, metabolism, epigenetic and genes expression (8). Several cyclin-dependent kinase inhibitors including the hallmark $p16^{INK4a}$ participate to senescence onset (9). Senescence program will thus trigger changes in cell functions pushing toward a terminal differentiated phenotype (10) meanwhile influencing tissue homeostasis through the establishment of one specific secretory phenotype so-called SASP for "senescence-associated secretory phenotype" (11).

Cellular senescence features on chondrocytes have been found for years in articular cartilage isolated from OA patients compared to matched-age non-OA donors (12). Indeed OA chondrocytes harbor premature telomeric shortening (12), DNA damage accumulation (13) meanwhile an increase in $p16^{ink4a}$ expression and $p16^{ink4a}$-dependent MMP-1 and MMP-13 metallo-proteases secretion (10). All these events seem to be deleterious for cartilage maintenance although still lack a causal demonstration for the role of cellular senescence in OA development

In the recent *Nature Medicine* volume, Jeon *et al.* demonstrate for the first time a clear correlation between OA onset and accumulation of senescent cells in joint of surgically induced OA murine models. They took advantage of two transgenic murine models allowing non-invasive detection of senescent cells and their specific elimination after pharmacological challenges. The first model, p16-3MR, consists in mice driving a luciferase fused with a truncated form of herpes simplex virus 1 thymidine kinase under the control of $p16^{INK4a}$ promoter. The second one INK-ATTAC mouse consists in $p16^{INK4a}$-driven expression of luciferase and caspase 8 suicide gene. Both models allow monitoring of $p16^{INK4a}$-positive senescent cells through luciferine delivery and their selective elimination in response to ganciclovir or AP20187 respectively. Jeon *et al.* first monitored the presence of articular senescent cells in 2-month-old p16-3MR mice following OA induction after anterior cruciate ligament transection. Using intra-articular luciferase injection, they could reveal a significant pick in senescent cells accumulation at 14 days post-surgery. Following immunohistochemistry staining, they detected $p16^{INK4a}$-positive senescent cells in activated synovium and in the superficial cartilage zones.

To determine whether articular $p16^{INK4a}$ senescent cells are responsible for OA onset, they elegantly eliminate these cells in the knee of animals that underwent surgery by intra-articular injections of ganciclovir. Local elimination of articular senescent cells was associated with less cartilage degradation, less cartilage expression of inflammatory markers such as IL-1β and less hypertrophic catabolic markers such as MMP-13. One of major interest of these studies was to find a higher expression level for two pro-chondrogenic markers namely collagen type IIB and aggrecan in treated mice. To bring further convincing argument, the authors used the second transgenic model to study spontaneous OA onset in older mice. Remarkably, treatment by AP20187, delivered in 12-months-old INK-ATTAC mice up to their natural death, maintains healthy cartilage and therefore reduces the appearance of spontaneous age-related OA signs.

Senescent cells are characterized by their resistance to apoptotic signals through up-regulation of anti-apoptotic BCL2-BCLX pathway (14). Several teams in the world have recently validated drugs that could specifically trigger cell death on senescent cells by targeting this anti-apoptotic axis. Thus, several of these so-called senolytic drugs, including UBX0101 (also known as ABT263), have already been validated as anti-senescent treatment in mice suffering from different age-related diseases (15): for instance, senolytics improved cardiac function in old mice (16), prevented osteoporosis (17), delayed loss of intervertebral disk proteoglycans in progeric $Ercc^{-/\Delta}$ mice (16), reversed irradiation-induced pulmonary fibrosis (18) and depleted senescent hematopoietic and muscle stem cells in old mice (19).

To test the efficacy of such senolytic drugs as new innovative OA treatment, Jeon *et al.* performed 6 intra-articular injections (every 2 days) of UBX0101 in 2-month-old mice, 14 days post-surgery when articular senescence was the highest. Results were impressive: UBX0101 significantly reduced $p16^{INK4a}$ senescent cells induced by surgery, but also cartilage degradation and OA-related pain after 28 days. Moreover, UBX0101 treatment reduced MMP-13, IL-6 and IL-1β expression in cartilage while promoting neo-cartilage formation, with an increase in collagen type II and aggrecan production. The authors concluded that UBX0101, by eliminating articular senescent cells, reduced experimental post-traumatic OA symptoms and disease severity in mice. Furthermore, UBX0101 stimulated new cartilage formation.

To translate these results from murine models to human OA patients, Jeon *et al.* offer convincing *in vitro* evidences. Using monolayer and 3D culture of human chondrocytes isolated from late-stage OA cartilage obtained after arthroplasty surgery, they showed that UBX0101 treatment reduced the expression of senescence- and OA-associated genes and even increased the proliferation rate of the remaining chondrocytes, indicating new cartilage growth. By eliminating senescent cells, UBX0101 not only removes a causative actor in OA process, but also restores a pro-chondrogenic environment. Thus, the authors add a new and promising category of drugs in the therapeutic arsenal of all physicians involving in OA management.

As for every new major step in medicine, several questions should be solved before UBX0101 human application in OA. First, UBX0101 is already used to treat cancer in phase I/II trials (20) and side effects, e.g., thrombocytopenia, have been described (21). The author's choice to inject locally the drug is reassuring: the systemic exposure in this case was very low (only 3,3% of the intra-articular dose) in mice. We can hypothesize that the systemic toxicity will be negligible in intra-articular treated patients. Nevertheless, the patient's fear for such molecules could become a problem. To circumvent this potential limitation, several other molecules less toxic (e.g., the flavonoid quercetin) have been screened for senolytic properties (16) and could be proposed as an alternative.

In daily practice, patients usually present late-stage disease with severe cartilage lesions. Jeon *et al.* also answered this question by injecting UBX0101 in young mice not only 14 but also 42 days after OA induction, when cartilage degradation was higher. They still observed an increase in cartilage staining and chondrogenic genes expression, suggesting that UBX0101 was also efficient in later-stage disease. However, UBX0101 was not able to reduce abnormal subchondral bone remodeling and osteophyte formation in these mouse models. The authors suggest that the local injection did not allow the drug to reach the bone. This could be a clinical limitation, as subchondral bone modifications are able to modulate OA severity (6).

Lastly, OA prevalence increases with ageing (4). To extrapolate their models to the elderly, 19 months old mice were used. The systemic removal of $p16^{INK4a}$ senescent cells markedly reduced the spontaneous age-related cartilage degradation, confirming that targeting senescence was also promising in older patients. However, in this case, intra-articular injection of UBX0101 alone had no impact on cartilage degradation and did not enhance chondrogenic genes expression in old mice. Thus, as discussed, intra-articular injection in aged patients would probably not be enough and a systemic treatment should be considered. The risk-benefit ratio of systemic administration of anti-cancer therapies to delay OA onset must therefore be carefully investigated.

In conclusion, evidences are accumulating that link cellular senescence features and numerous age-related pathologies including osteoporosis, sarcopenia or heart hypertrophy affecting elderly (15). Demonstrating that senescent cells are participating to OA onset is the major finding of this study paving thus the way to very promising innovative senolytic drugs-based treatments for OA. Nevertheless, one has to keep in mind that cellular senescence is also a physiological positive process implicated in wound healing, tumor suppression, immune and anti-viral responses, among others (22,23). We thus lack the perspectives on long-term effects and safety for senolytic treatments on human health. So the road is still long before celebrating the end of orthopedic surgery to treat OA.

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Footnote

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