Does Joint Injury Make Young Joints Old?

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Investigators studying the development of posttraumatic osteoarthritis (PTOA), such as Stephan Lohmander, have commented that joint injury makes young joints old. Clinical management of osteoarthritis (OA) would benefit from dissecting the complexity of this provocative statement. On the one hand, evidence from the heterogeneity of human OA progression and treatment response[1] and murine models[2] suggests that age-related OA and PTOA have at least some distinctive molecular features.[3] On the other hand, recent evidence indicates that at least two processes associated with aging, increased mitochondrial production of reactive oxygen species (ROS), and cellular senescence are important contributing factors to the development of both age-related OA and PTOA.

Increases in mitochondrial ROS have been proposed to disturb homeostatic cell signaling events to promote age-related diseases.[4] We have recently published data that demonstrates this may be true for OA as well.[5] Peroxiredoxins (Prxs) are a family of intracellular antioxidant proteins responsible for the removal of H_2O_2. Excessive levels of H_2O_2 seen during oxidative stress cause hyperoxidation and subsequent inactivation of Prxs. We found that hyperoxidation of the mitochondrial Prx3 was associated with inhibition of prosurvival Akt signaling and increased p38-induced cell death in articular chondrocytes.[5] Expression of catalase targeted to the mitochondria (mCAT) significantly decreased chondrocyte Prx3 hyperoxidation, restored Akt signaling, and abrogated p38-induced cell death. Of particular relevance was the finding that mCAT transgenic mice were protected from age-related OA compared to control mice.[5] These results agree with the hypothesis that targeted strategies aimed at restoring mitochondrial redox balance are of therapeutic benefit in age-related OA through attenuation of ROS-mediated catabolic signaling events.

New data from Coleman et al[6] suggest that targeting the mitochondria to reduce oxidative stress levels and preserve mitochondrial homeostasis may also be relevant for PTOA. The authors used the recently developed minipig intra-articular fracture (IAF) system[7] as a clinically relevant strategy to model PTOA in large animals. Immediately post-IAF, a subset of animals received intra-articular injections of amobarbital, a reversible complex I electron transport chain inhibitor hypothesized to decrease mitochondrial ROS, or N-acetylcysteine (NAC), a nonspecific antioxidant, and histological changes to the joint were assessed after 6 months. Both amobarbital and NAC reduced the severity of IAF-induced PTOA, effects which were attributed to reduced mitochondrial metabolic stress and oxidative stress levels.[6] Although amobarbital and NAC lack the specificity needed to determine the nature of the ROS contributing to PTOA, this study suggests that targeting mitochondrial ROS could be an approach for PTOA.

Cellular senescence is a complex phenotypic state that contributes to both beneficial processes (eg, tumor suppression, development, wound healing) and pathologic conditions

(eg, excess inflammation, reduced stem cell function, age-related disease progression).[8] Senescence is defined in part by a permanent cell cycle arrest as a result of the increased expression of the cell cycle inhibitor p16INK4a.[9] Senescent cells also produce inflammatory and matrix-degrading molecules known as the senescence-associated secretory phenotype (SASP).[10] We recently published that both human and murine chondrocytes express higher levels of p16INK4a with aging but that p16INK4a expression is not required for OA in either aging or PTOA settings.[11] This work suggests that senescence may drive OA through p16INK4a-independent secretion of SASP cytokines such as interleukin-6, interleukin-1β, and matrix metalloproteinase-13.

The concept that targeting senescent cells may be promising for treating age-related diseases has been developed from the finding that inducing apoptosis of p16-high (senescent) cells in a genetically engineered murine model can improve healthspan and increase longevity.[12] "Senolytic" compounds seek to mimic this effect by targeting antiapoptotic pathways that are specifically upregulated in senescent cells.[13] Repeated intra-articular injection of a proprietary senolytic (UBX0101; UNITY Biotechnology) or genetic clearance of p16-high cells mitigated the development of OA after anterior cruciate ligament transection in young mice.[14] The authors showed clearance of senescent cells and a reduction in SASP production despite a short half-life of the drug, supporting the concept that apoptosis of senescent cells was responsible for the effects. Interestingly, the clearance of senescent cells was less effective in older mice with anterior cruciate ligament transection but showed potential for reduced OA in a small set of mice with spontaneous age-related OA.[14] These results suggest a complex interplay of aging, joint injury, and the induction/clearance of cellular senescence. Further development of senolytic therapy for OA will require a better understanding of how senescence emerges, continued characterization of compounds with known molecular targets in senescent cells, and identification of the patients most likely to benefit from the clearance of these SASP-producing "bad neighbors."

These recent preclinical studies in animal models indicate that age-related OA and PTOA may share some common mechanisms. Although much more work needs to be done, including early-phase studies in humans, these studies provide hope that understanding shared mechanisms in OA associated with aging and joint injury could lead to novel disease-modifying therapies for both forms of OA.

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