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Targeting aging for disease modification in osteoarthritis

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Abstract

Purpose of review—Age is a key risk factor for the development of osteoarthritis and age-related changes within the joint might represent targets for therapy. The recent literature was reviewed to find studies that provide new insight into the role of aging in osteoarthritis, with a focus on the potential for disease modification.

Recent findings—Preclinical studies using isolated cells and animal models provide evidence that two hallmarks of aging (cellular senescence and mitochondrial dysfunction) contribute to the development of osteoarthritis. Senescent cells secrete pro-inflammatory mediators and matrix degrading enzymes, and killing these cells with ‘senolytic’ compounds has emerged as a potential disease-modifying therapy. Mitochondrial dysfunction is associated with increased levels of reactive oxygen species (ROS) that can promote osteoarthritis by disrupting homeostatic intracellular signaling. Reducing ROS production in the mitochondria, stimulating antioxidant gene expression through Nrf2 activation, or inhibiting specific redox-sensitive signaling proteins represent additional approaches to disease modification in osteoarthritis that require further investigation.

Summary—Although no human clinical trials for osteoarthritis have specifically targeted aging, preclinical studies suggest that targeting cellular senescence and/or mitochondrial dysfunction and the effects of excessive ROS may lead to novel interventions that could slow the progression of osteoarthritis.

Keywords

aging; cell senescence; cell signaling; mitochondria; reactive oxygen species

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Conflicts of interest

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INTRODUCTION

Osteoarthritis is one of the most common causes of pain and disability in older adults [1,2]. Management of osteoarthritis is limited to symptomatic treatments that many people with osteoarthritis find inadequate and there is a lack of any intervention proven to alter the natural course of OA. With the rapidly growing numbers of older adults in the United States and other developed countries, there is a significant need for research that will lead to new interventions that target both symptoms and disease progression.

It is well accepted that increasing age is a major risk factor for osteoarthritis and there is a growing body of evidence that aging processes within the joint, and perhaps systemically as well, contribute to the development and progression of osteoarthritis [3]. Therefore, a better understanding of how aging and osteoarthritis interrelate could lead to new targets or strategies for intervention. Geroscientists have suggested that similar age-related processes may contribute to multiple conditions associated with aging such as cardiovascular disease, cancer, neurocognitive disorders and musculoskeletal conditions [4]. Hallmarks of aging have been identified that represent the processes most likely to contribute to age-related conditions and include stem cell exhaustion, altered intercellular communication, genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, cellular senescence, and mitochondrial dysfunction [5]. For the purposes of this review, we will focus on the latter two, cellular senescence and mitochondrial dysfunction with its accompaniment of oxidative stress, where recent progress has been made that is contributing to the knowledge of mechanisms linking aging and osteoarthritis. We will include a review of preclinical studies that suggest targeting these age-related processes could be disease modifying.

CELLULAR SENESCENCE AND OSTEOARTHRITIS

Cellular senescence is a response to persistent stress that can be characterized by stable cell-cycle arrest, increased expression of the cell cycle inhibitor p16^{Ink4a}, and enhanced production of inflammatory cytokines and other factors known as the senescence-associated secretory phenotype (SASP) [6]. It has been well known for decades that cellular senescence occurs during the extended culture of cells in monolayer. The phenomenon of in-vitro senescence does have relevance to osteoarthritis therapies because it limits the capacity of patient-derived chondrocytes to be expanded for regenerative medicine applications [7]. There is also substantial evidence that cellular senescence develops with aging *in vivo* and plays an important role in driving age-related disease [8]. Recent developments in the ability to selectively induce apoptosis of senescent cells from within tissues have advanced basic science and generated excitement about the therapeutic potential of targeting senescent cells [9].

DEVELOPMENT OF THE 'SENOLYTIC' STRATEGY

The rationale for eliminating senescent cells was enhanced by studies with 'INK-ATTAC' mice in which senescent cells are killed by a tailored drug through expression of a transgene that is only expressed in cells with high levels of p16^{Ink4a} [10[■],11]. Although the effect on

osteoarthritis was not reported, a reduction in specific age-related pathologies occurred in both progeroid and naturally aged models [10[■],11]. The next development was to identify small molecules that achieve the same effects without requiring transgenic mice. One strategy for developing these ‘senolytic’ compounds has been to inhibit pathways that are upregulated in senescent cells, which is akin to the approach commonly used in developing chemotherapeutics. For example, the senolytic Navitoclax (ABT-263) inhibits Bcl-2 and Bcl-xL, which are part of the antiapoptotic machinery that allows senescent cells to survive in the context of persistent stress [12]. Delivery of Navitoclax was shown to specifically kill senescent cells *in vitro* and *in vivo*, promoting enhanced function of the remaining stem cells in the hematopoietic system and muscle [13].

THE RATIONALE FOR OSTEOARTHRITIS AS A POTENTIAL TARGET FOR SENOLYTIC THERAPY

The potential role for senescence during the pathogenesis of osteoarthritis has recently been reviewed [3,14], but published investigations have relied heavily on correlative evidence that cells with specific markers of senescence emerge with age and osteoarthritis. A recent example showed that osteoarthritis disease severity correlates with senescence-associated beta galactosidase activity [15[■]], a commonly used marker of senescence that represents high lysosomal activity. An alternative approach evaluated the general concept that exogenous cells secreting a potent SASP can drive osteoarthritis. In this study, delivery of irradiation-induced senescent ear fibroblasts directly to the joint caused cartilage degradation as compared to control cells [16[■]].

Senolytics provide a further opportunity to help determine the functional role of senescence by targeting senescent cells that arise spontaneously with age or in response to acute stress. Inducing apoptosis of chondrocytes may seem like a risky strategy given that articular chondrocytes are responsible for producing and maintaining the extracellular matrix. However, recent data demonstrate that killing chondrocytes that would otherwise secrete matrix-degrading factors such as matrix metalloproteinase 13 (MMP13) can protect the tissue in a posttraumatic osteoarthritis model [17[■]]. The tolerance for chondrocyte death in murine models may be partly because of the high cell density found within the cartilage of mice, and it remains to be seen whether the lower cell density in human cartilage alters the capability to withstand cell loss. The concept of inducing cell death during aging may also be feasible given the extraordinary stability of aggrecan and type II collagen [18], as maintaining the capacity for new matrix synthesis with aging may not be as essential as ensuring protection from matrix degrading enzymes that are produced by senescent cells. The potential negative effects of eliminating senescent cells (and potentially off-target cells) must be taken seriously for osteoarthritis, as the slow course of disease progression may necessitate periodic treatment over years to have the maximal therapeutic effect.

INTRA-ARTICULAR DELIVERY OF A NOVEL SENOLYTIC REDUCES POSTTRAUMATIC OSTEOARTHRITIS

Initial evidence that senolytics may improve the function of cartilaginous tissues came from the observation that weekly treatment with the senolytic combination of dasatinib and quercetin resulted in a higher glycosaminoglycan content in the intervertebral disc [19]. The direct application of a senolytic approach for osteoarthritis was explored using anterior cruciate ligament transection (ACLT) in both a transgenic model (p16-3MR mice in which p16-high cells are eliminated with ganciclovir) and using a proprietary senolytic compound that had not been previously described (UBX0101) [20[■]]. With repeated intra-articular injections beginning two weeks after ACLT, UBX0101 reduced the burden of senescent chondrocytes and production of SASP factors. The treatments also limited the development of osteoarthritis by histological analysis and improved the function of the injured joint as assessed by weight distribution. Inducing death of senescent cells showed a benefit despite the calculated intra-articular half-life of 1.5 h, which illustrates that this approach may have advantages over osteoarthritis therapies that require continuous biologic activity to mediate the intended effects. The authors also show protection from osteoarthritis in a small number of aged animals using senescence clearance in the previously described INK-ATTAC model, raising the exciting possibility that senescence may be a valid target for age-related osteoarthritis in addition to the posttraumatic setting [20[■]]. Finally, the authors provided evidence that UBX0101 targets senescent human chondrocytes using a pellet culture model, with the surrounding cells compensating for the death of senescent cells by enhanced proliferation and matrix synthesis.

REDOX SIGNALING PATHWAYS AS THERAPEUTIC TARGETS IN OSTEOARTHRITIS

It is becoming widely accepted that age-related increases in reactive oxygen species (ROS) levels, combined with a reduced intracellular antioxidant capacity, leads to oxidative stress-induced cellular damage that contributes to the progression of age-related diseases, including osteoarthritis [21]. The specific mechanisms linking oxidative stress to disease, however, remain poorly understood. Although some theories of aging suggest that oxidative stress contributes to age-related disease through random cellular damage, more recent theories align themselves with the concept that age-related oxidative stress leads to cellular dysfunction through disturbing normal homeostatic cell signaling pathways [21,22].

CYSTEINE SULFENYLATION REGULATES CHONDROCYTE SIGNALING

One proposed key mechanism by which ROS regulate cell signaling is through posttranslational oxidation of reactive cysteines by H₂O₂ (protein thiol oxidation). Thiol oxidation results in the formation of a cysteine sulfenic acid (Cys-SOH) termed S-sulfenylation, which can lead to either oxidative inhibition or activation of protein function that is dependent on the properties of the specific protein [23]. Recent data from Wood *et al.* [24] demonstrate that chondrocytes derived from osteoarthritis cartilage display increased levels of basal S-sulfenylation when compared to chondrocytes derived from non-

osteoarthritis cartilage. Treatment with fragments of fibronectin (FN-f) to induce physiological levels of H_2O_2 led to sulfenylation of the tyrosine-protein kinase Src (Src), which enhanced Src activity and MMP-13 production. Pre-treatment with dimedone, to block sulfenylation, or N-acetyl cysteine, to reduce levels of ROS, decreased Src sulfenylation and abrogated these effects. These data suggest that sulfenylation of cartilage proteins can significantly contribute to joint degradation by regulating redox-signaling events. Strategies aimed at reducing protein sulfenylation, either directly or through targeted antioxidant treatment, could restore homeostatic signaling to protect against osteoarthritis.

In contrast to physiologic levels of H_2O_2 , excessive levels can hyperoxidize cysteines to form sulfinic acid (Cys-SO₂H) or sulfonic acid (Cys-SO₃H). Hyperoxidation is most often irreversible and leads to inhibition of protein function, as has been observed with hyperoxidation of the peroxiredoxin (Prx) family of peroxidase enzymes [25].

MITOCHONDRIAL DYSFUNCTION AND REDOX SIGNALING IN OSTEOARTHRITIS

The mitochondrion is a key source of ROS. Mitochondrial function has been shown to decline with age and a causative link between age-related mitochondrial dysfunction, oxidative stress and disease has been put forth [5]. Mitochondrial Prx3 hyperoxidation was found to be greater in older human chondrocytes when compared to younger chondrocytes, both basally and in response to mitochondrial H_2O_2 induced by the redox cycling oxidant, menadione [26[■]]. Menadione-induced Prx3 hyperoxidation was associated with inhibition of prosurvival Akt signaling and activation of p38-mediated cell death. Expression of catalase targeted to the mitochondria (MCAT) abrogated these effects by preventing Prx hyperoxidation and restoring homeostatic signaling to maintain cell viability. Importantly, in an *in vivo* aging model, transgenic MCAT mice displayed reduced severity of age-related osteoarthritis when compared to wild-type mice [26[■]]. Similarly, in another recent study, treatment with the mitochondrial targeted antioxidant mitoTEMPO attenuated the severity of cholesterol-induced osteoarthritis in rats and mice [27[■]]. Mice deficient in Apolipoprotein E (ApoE) and rats with diet-induced hypercholesterolemia (DIHC) subjected to destabilization of the medial meniscus (DMM) surgery displayed enhanced severity of osteoarthritis symptoms when compared to animals fed a control diet or animals subjected to sham operations. A daily regimen of MitoTEMPO for 5 weeks beginning 1-week after DMM surgery significantly reduced osteoarthritis severity as assessed by the Mankin score. *In vitro* studies showed that Mito-TEMPO reduced cholesterol-induced ROS generation, partially restored ATP levels, and decreased MMP13 expression and markers of apoptosis in primary human articular cartilage chondrocyte pellets [27[■]].

As further evidence for a role of mitochondrial ROS in osteoarthritis, deletion of superoxide dismutase 2 (Sod2), enhanced the severity of osteoarthritis in mice [28]. This suggests that this mitochondrial antioxidant, which catalyzes the detoxification of mitochondrial superoxide, may also be of importance in the pathogenesis of osteoarthritis. Fu *et al.* [29[■]] recently conducted an in-depth analysis of the antioxidant network from the cartilage of adult (10 month-old) and aging (30-month-old) rats and showed that, although mitochondrial

Sod2 levels in aging rats increased compared with adult rats, specific Sod2 activity was reduced. Sod2 activity is impaired by posttranslational acetylation in many cell types and this process is finely regulated by the mitochondrial deacetylase enzyme sirtuin3 (Sirt3) [30]. Accordingly, reduced Sod2 activity in aging rats was associated with an increase in Sod2 acetylation and a reduction in Sirt3 protein abundance. Incubation of cartilage homogenates with recombinant Sirt3 and its cofactor, NAD⁺, led to increased Sod2 enzymatic activity [29[■]]. This effect was greater in homogenates from aged rats, suggesting that an age-related decline in Sirt3 levels may underlie impaired Sod2 function in aging cartilage. Taken together, these studies suggest that targeting the mitochondria to counter age-associated, oxidative stress-induced disturbances in redox signaling pathways could represent a novel therapeutic strategy to slow or stop the progression of OA.

MITOCHONDRIAL GENETICS INFLUENCE REDOX SENSITIVITY AND OA

In addition to mitochondrial dysfunction, mitochondrial genetics may also play a role in osteoarthritis incidence and progression [31]. Fernández-Moreno *et al.* [32[■]] investigated human subjects from the osteoarthritis initiative (OAI) and the cohort hip and cohort knee studies to demonstrate that mitochondrial DNA haplogroup J associates with a reduced risk of incident knee osteoarthritis when compared to mitochondrial DNA haplogroup H. To identify specific differences between these haplogroups, transmitochondrial cybrids harboring haplogroup J or H were constructed and metabolic and redox parameters were analyzed. Haplogroup H cybrids displayed enhanced glycolysis and mitochondrial respiration, which led to increased ATP production when compared to haplogroup J cybrids. Haplogroup H cybrids also exhibited higher production of peroxynitrite, peroxide, and mitochondrial superoxide, and an increased susceptibility to cell death in response to H₂O₂. Thus, it appears that metabolic dysfunction and redox imbalance are closely related to osteoarthritis prevalence. Therapeutic drugs aimed at targeting these specific parameters, or to more closely mimic those of haplogroup J, may be of value in osteoarthritis therapy.

REGULATION OF NUCLEAR RECEPTOR ERYTHROID 2-RELATED FACTOR 2 SIGNALING IN OSTEOARTHRITIS

Nuclear receptor erythroid 2-related factor 2 (Nrf2) represents an important transcription factor that regulates the expression of a wide array of phase II antioxidant genes relevant to maintaining cellular redox homeostasis [33,34]. There is evidence for decline in Nrf2 protein levels in human osteoarthritis chondrocytes when compared to healthy controls [35]. Recent data from Cai *et al.* [36[■]] demonstrate that treatment with trichostatin A (TSA), a broad-spectrum histone deacetylase inhibitor (HDACi), reduces the severity of osteoarthritis in both a posttraumatic mouse model (DMM surgery) and an inflammatory mouse model of osteoarthritis [monosodium iodoacetate (MIA) injection]. Analysis of cartilage from the joints of these mice showed that treatment with TSA enhanced acetylation-induced Nrf2 activation and the expression of the Nrf2 antioxidant target genes heme oxygenase-1 (HO-1) and NAD(P)H: quinone oxidoreductase 1 (NQO-1). This was associated with reduced catabolic cytokine production and decreased MMP release. Treatment with TSA was unable to offer protection against DMM and MIA-induced osteoarthritis in Nrf2

knockout mice suggesting that the protective effect of HDACi on osteoarthritis severity was Nrf2 dependent.

In addition, several recent studies have assessed the role of active Nrf2 to regulate chondrocyte inflammatory signaling pathways. For example, Vaamonde-Garcia *et al.* [37] demonstrate that pharmacological activation of Nrf2 or its downstream target, HO-1, leads to a reduction in interleukin (IL)-1 β induced ROS generation and IL-6 production in murine chondrocytes. The purported antioxidant compounds Wogonin [38], pterostilbene [39], protandim and 6-gingerol [40] have also been shown to exert chondroprotective effects through ROS-induced activation of the Nrf2 pathway and suppression of inflammatory mediators such as PGE2 and nitric oxide production. Thus, strategies aimed at maintaining active Nrf2 in aging cartilage may hold promise for osteoarthritis therapy but the precise mechanisms underlying Nrf2 regulation in aging human joint tissues requires further characterization.

CONCLUSION AND FUTURE DIRECTION

Advances in the understanding of how senescence and oxidative stress develops in the joint and how this contributes to osteoarthritis will help in the design of more targeted senolytic and antioxidant therapies that could be used to slow or stop osteoarthritis from progressing. One key question related to senolytics is determining if other cell types other than chondrocytes would be important to target. Cells from the synovium and infrapatellar fat pad could potentially secrete SASP factors directly into the joint space and drive the inflammatory cascades that can occur with osteoarthritis. Given the relationship between cartilage and the health of underlying bone in osteoarthritis development, it is of interest that markers of senescence and the SASP also increase with age in osteocytes [41]. Innovative methods to measure multiple indicators of senescence on a single-cell basis [42] may be helpful for quantifying the senescence burden in particular cell types. Indeed, it is feasible that senescence may emerge as a biomarker to help phenotype the particular forms of osteoarthritis and that senolytic therapies would be most effective in a subset of patients [43].

The studies reviewed above provide evidence that oxidative stress can contribute to the development and progression of age-related osteoarthritis through disturbing homeostatic redox signaling pathways. Anabolic and cell survival pathways appear to be more susceptible to inhibition during conditions of oxidative stress whereas catabolic and cell death pathways are more active. This altered balance in signaling pathways may result from attempted degradation and removal of proteins that have been damaged by oxidative stress, with cell death occurring if homeostasis cannot be restored. The design of disease modifying osteoarthritis drugs aimed at maintaining antioxidant signaling pathways in aging, such as those governed by the Prx's, Sod's, Sirt's, and Nrf2, hold novel therapeutic value in the prevention or treatment of osteoarthritis. Such therapeutics will replace the current untargeted antioxidant approach with disease modifying osteoarthritis drugs that target specific signal transduction pathways that contribute to osteoarthritis.

The connection between oxidative stress and the promotion of cellular senescence has not been fully explored in the context of cartilage and osteoarthritis. A recent study in mice with deletion of the antioxidant gene superoxide dismutase found evidence for increased accumulation of senescent cells in the kidney [44]. Future studies investigating whether increased oxidative stress with aging plays a causal role in the development of the senescent phenotype in the joint will be important to designing effective therapeutic strategies. Preventing the emergence of senescence with targeted antioxidant therapies may be one strategy to delay the onset of osteoarthritis before severe matrix degradation and inflammatory pathways are established.

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KEY POINTS

- There is mounting evidence that cellular senescence and mitochondrial dysfunction, two of the hallmarks of aging, contribute to the development of osteoarthritis.
- Targeting cellular senescence in joint tissues by killing senescent cells has been shown in a preclinical study in mice to reduce the severity of age-related osteoarthritis, and osteoarthritis induced by ACLT.
- Mitochondrial dysfunction results in increased levels of ROS that disrupt homeostatic cell signaling through protein thiol oxidation.
- Increasing the antioxidant capacity of joint tissue cells through transgenic overexpression of catalase targeted to the mitochondria reduced the severity of age-related osteoarthritis in mice. Treatment with a small molecule mitochondrial antioxidant, MitoTempo, reduced the severity of osteoarthritis in rats on a high cholesterol diet that also underwent DMM surgery to induce osteoarthritis.
- Further work is necessary to move promising approaches that alter aging processes in osteoarthritis from preclinical models to humans, including identifying the tissues and particular forms of osteoarthritis that should be targeted.