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Invited Review

Senescence in Osteoarthritis: Overview of Mechanisms and Therapeutics

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Abstract

Osteoarthritis is a morbid and costly condition affecting an increasingly larger segment of the population with a lack of effective treatment options. The pathophysiology of osteoarthritis is poorly understood; cell senescence is deemed to be contributory. Senescence of joint tissues particularly chondrocytes, synoviocytes (fibroblasts), and adipocytes is implicated in the pathogenesis through the production of senescence-associated proteins. Senescence-associated proteins are cytokines, matrix degradation enzymes, and chemokines that contribute to an inflammatory milieu which leads to the propagation of senescence. Senescence-modifying therapies include senolytics which eliminate senescent cells and senomorphics which inhibit the senescence-associated protein production of senescent cells. Treatments being investigated include novel agents as well as agents previously used in other conditions in rheumatology and other fields.

Keywords: Osteoarthritis, senescence, senolytic therapy, senolytics, senomorphics, chondrocyte senescence

Introduction

Numerous risk factors such as older age, female sex, genetics, obesity, and prior trauma have been associated with osteoarthritis (OA). Of these, aging is recognized as one of the most prevalent risk factors, due both to the biological age-related joint structure changes and the cumulative exposure to various risk factors for OA with age.[1] At the same time, it is projected that the number of older persons will double to 1.5 billion in 2050.[2] The incidence of knee and hip OA increases continuously after the age of 40 years and peaks at age 75-80 years.[3] Given the connection between age and OA, it is not surprising that the global prevalence of OA is increasing across all countries and is estimated to be between 2090 and 6128 per 100 000 people. Many countries have a high economic burden as a consequence of the overwhelming proportion of older people suffering from OA. The medical costs related to OA are an estimated 1%-2.5% of national gross domestic products in high-income countries and OA is one of the leading causes of years lived with disability globally.[4]

While OA causes significant disability and imposes high societal economic costs, there are not yet approved medications able to stop or reverse the progression of OA, in part due to the complexity of its pathologic mechanisms. Nevertheless, there is ongoing research focusing on the effect of aging on the development of OA. Some of the promising mechanistic pathways that are being studied include aging-associated inflammation, cellular senescence, senescence-associated secretory proteins (SASPs), oxidative stress and mitochondrial dysfunction, dysregulated nutrient sensing, and extracellular matrix changes. Cellular senescence is of particular interest as it provides potential targets for treatment in the form of senescence-modulating drugs (Table 1). A better understanding of the mechanisms implicated in OA will allow us to find the precise therapeutic targets of this common, morbid, and costly disease. This review will provide an understanding of the role of senescence in OA and senescence-modifying therapies being explored to date.

The Role of Senescence in Osteoarthritis

Senescence or cell senescence was first described by Hayflick and Moorhead[5] in 1961 as the process of eventual cell growth arrest noted in fibroblast cells grown in cell culture. Cell senescence has since been postulated to be a response to damaging stimuli and is defined broadly as the process of the irreversible arrest of cell growth and replication. Numerous pathways for the development of cell senescence have been described, including DNA damage, cell cycle arrest, activation of inflammatory molecules, resistance to cell apoptosis, and alteration of metabolic processes. The presence of senescent cells in tissues creates a pro-inflammatory environment that contributes to age-related diseases. On the other hand, the

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Table 1. Potential Experimental Drugs Targeting Senescence in Osteoarthritis

Senolytics	Senomorphics
Tyrosine kinase inhibitors (dasatinib)	Biologics (TNF-alpha inhibitors, IL-1 blockers, IL-6 blockers)
BCL anti-apoptotic protein inhibitors (navitoclax)	Non-steroidal anti-inflammatory drugs (celecoxib)
p53 activators (UBX0101)	Rapamycin
Sirtuin-activating compounds (fisetin)	Ruxolitinib
PPAR-alpha agonist (fenofibrate)	Metformin, simvastatin

BCL, B-cell lymphoma; IL, interleukin; PPAR, peroxisome proliferator-activated receptor; TNF, tumor necrosis factor.

main benefit of cellular senescence is that of tumor suppression; additionally, senescence has been studied in relation to wound healing, fertility, and response to organ injury.[6]

In OA, cellular senescence has been studied in relation to chondrocytes, although senescence of other cells of the joint such as synoviocytes (also known as fibroblasts) and adipocytes has also been implicated. Various cell senescence markers including beta-galactosidase expression, telomere length, and mitotic activity have been used to study senescence in OA.[7] However, none of these have been shown to be specific to this process. It is important to note that SASPs may be another potential biomarker of cell senescence. While SASPs are found in synovial fluid, these factors' levels may be reflected in the peripheral circulation, suggesting its use as another potential diagnostic biomarker of cartilage damage.[8]

Main Points

- Osteoarthritis is a highly prevalent condition associated with high morbidity and societal economic cost.
- Cellular senescence is defined by a state of replicative arrest. In the joint, senescence has been studied in the context of chondrocyte, synoviocyte, and adipocyte senescence.
- Chondrocyte senescence is initiated by external stressors leading to gene activation with subsequent nuclear factor kappa B activation leading to increased senescence-associated secretory protein production. This leads to extensive intercellular signaling and changes to the extracellular matrix that further promote chondrocyte senescence.
- Therapeutics to mitigate senescence in osteoarthritis include senolytic and senomorphic approaches. While existing rheumatologic therapies have been disappointing to date, research is ongoing regarding finding new or repurposing existing medications for mitigating senescence in osteoarthritis.

Chondrocyte Senescence

Chondrocytes are cells of the joint typically responsible for the maintenance of the extracellular matrix. Several mechanisms for the development of chondrocyte senescence have been posited (Figure 1). Chondrocytes can experience stress through shear forces, increased reactive oxygen species, and erosion of telomere length.[9] During periods of stress, chondrocytes undergo activation of several tumor suppressor genes (particularly p53/p21CIP1 and p16INK4A), which leads to a premature cell cycle arrest. Stress also leads to the activation of a stress-inducible kinase, the p38MAPK, which increases nuclear factor kappa B (NF-kB) transcriptional activity which stimulates production of SASPs.[10] The SASPs act in an autocrine and paracrine manner to promote surrounding cell senescence.[11] The SASPs include cytokines [interleukin (IL)-1b, IL-6, and tumor necrosis factor (TNF)-alpha], matrix degradation enzymes (metalloproteinases), and chemokines such as CCL2 and MCP1. The presence of SASPs leads to further degradation of the extracellular matrix, with the buildup of advanced glycation end products causing increased crosslinking between collagen fibers, inhibiting proteoglycan formation, and increasing TGF-beta signaling; this further leads to cell cycle arrest in the surrounding tissue.[12]

Role of Synoviocytes

Cell-to-cell interactions between chondrocytes and synoviocytes (fibroblasts) can result in cell aging. In 1 genomic study, synoviocytes were found to produce 55% of OA-related cytokines, particularly IL-1a, IL-1b, IL-6, TNF, CCL2, and CCL3, whereas chondrocytes only produced 16% of OA-related cytokines. Given that synovitis is a feature of early OA, targeting synoviocytes may be another pathway for intervention.[13] The causal link between synoviocyte (fibroblast) senescence and OA has been shown in animal models. In a study by Xu et al.[14] senescent fibroblasts were transplanted into non-OA joints of experimental mouse models. The senescent fibroblasts exhibited higher expression of tumor suppression genes p16INK4A and p21CIP1 and higher levels of IL-6 and other inflammatory markers. Implanting senescent fibroblasts induced OA symptoms in mice, with documented higher measures of pain and decreased locomotion in the treated joint, whereas transplanting non-senescent fibroblasts did not have such effects in the animal model.

Role of Adipocytes

Adipose cells also play a role in OA development, as adipokine (adipose tissue-derived cytokine) receptors are found in all cells within the joint. In a mouse model with lipodystrophy (completely lacking adipose tissue), increased weight and joint trauma were not associated with the development of OA. However, implanting adipose tissue into the lipodystrophy mouse model restored the development of OA. The mechanism of this is deemed to be due to the production of leptin by adipose tissue.[15] Within the joint, adipose tissue in the form of fat pads (most famous being Hoffa's fat pad of the knee) is being investigated as a mediator of OA. While the function of the fat pad in the maintenance of healthy joints is poorly understood, it is postulated that adipocytes in fat pads secrete leptin, adiponectin, and resistin which may support a pro-inflammatory environment.[16]

Senescence-Modifying Therapies

Therapeutic strategies to counteract senescence have been examined with various levels of success. The 2 most common approaches used are senolytic and senomorphic agents. Senolytics focus on inducing apoptosis of senescent cells to eliminate the production of inflammatory proteins, whereas senomorphics inhibit the inflammatory output of senescent

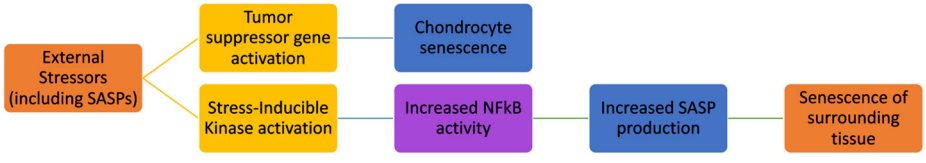


Figure 1. Development of chondrocyte senescence.

cells without inducing apoptosis. Importantly, either senomorphic or synolytic approach is limited by the undue toxicities of potential treatments on surrounding non-senescent tissues.[17]

Senolytic Therapies

Senolytics being investigated have included the following: inhibitors of tyrosine kinase such as dasatinib, inhibitors of the BCL anti-apoptotic proteins, promoters of p53 activation, as well as agonists of peroxisome proliferator-activated receptor alpha (PPARa). Dasatinib is a tyrosine kinase inhibitor currently used for the treatment of chronic myeloid leukemia. A combination of this drug with quercetin, a plant flavonol which inhibits PI3K, is under investigation. This cocktail in animal models lowered the percentage of senescent osteocytes in bone, overall improving spine trabecular bone microarchitecture compared to the control.[18] Another naturally occurring flavonoid, fisetin, a sirtuin 1 activator that inhibits IL-1beta-induced inflammation, was associated with a decreased progression of OA in mouse models.[19] Inhibitors of BCL anti-apoptotic proteins include navitoclax (ABT-263) which inhibits heterodimerization of BCL-2/BCL-XL, thereby allowing the progression of cell apoptosis. In mouse cartilage tissue, navitoclax reduced the number of senescent cells by reducing chondrocytes expressing p16, thus promoting apoptosis.[20]

Another novel senolytic agent is UBX0101, which blocks the interaction between p53 and MDM2, causing p53-mediated clearance of senescent cells. In post-traumatic OA in mice treated with intra-articular UBX0101, there was a reduced expression of senescent chondrocytes as well as decreased OA symptomatology in treated animals. More importantly, UBX0101 was found to eliminate senescent cells in human cartilage with OA.[21] Phase I clinical trials are ongoing to evaluate UBX0101 use in patients with OA (NCT03513016, NCT04129944, and NCT04229225). Another potential senolytic agent, found during cell-based high throughput screening of human chondrocytes, is the PPARa agonist already used in lipid management in humans—fenofibrate. Fenofibrate increases PPARa expression leading to an increase in apoptosis of senescent cells in the context of IL-6-mediated induction of senescence. Interestingly, improved physical function was observed in patients with OA receiving fenofibrate.[22]

Senomorphic Therapies

Senomorphic drugs inhibit SASPs without causing cell apoptosis. The armamentarium of agents included in this group is extensively used in the management of autoimmune diseases, such as TNF-alpha inhibitors, IL-6, and IL-1 blockers, albeit the success in OA has been limited.[23]

TNF-alpha promotes senescence by inducing p21 and p53 expression and causing cell cycle arrest, yet the use of etanercept (TNF-alpha inhibitor) did not show any benefit in knee OA. IL-6 is deemed to cause degradation of cartilage matrix proteins via the production of metalloproteinases. Blockade of IL-6 with tocilizumab, an effective therapy of rheumatoid arthritis, has been considered in the management of OA; a phase III trial for hand OA is ongoing (NCT02477059).[24] Celecoxib, a drug commonly used for the treatment of OA, was recently noted to attenuate the TNF-alpha effect on chondrocytes and reduce senescence.[25] However, the clinical significance of this finding is unclear. Canakinumab, an IL-1b monoclonal antibody, decreases the expression of matrix metalloproteinases (MMPs) in human OA chondrocytes cultured with TNF-alpha.[26] While an exploratory clinical trial revealed reduced rates of knee or hip arthroplasty in patients with OA who received canakinumab compared to those who did not, more studies are needed to confirm this finding.[27]

Senomorphics also include medications aimed to block SASP regulatory pathways without the use of biological molecules. Rapamycin, a mammalian target of rapamycin inhibitor frequently used in transplant medicine, has been found to suppress IL-1 expression by downstream inhibition of the NF-kB pathway.[28] In a murine model of OA, treatment with rapamycin decreased the pro-inflammatory activity of IL-18 and showed a chondroprotective effect linked to autophagy activation.[29] Conversely to rapamycin's mechanism of action, metformin, an anti-diabetic drug, activates mTOR signaling consequently downregulating metalloproteinase production, and slowing down cartilage degeneration.[30] Another commonly used drug, simvastatin—a lipid lowering medication—has been shown in animal models to reduce MMP-13 and IL-1b levels in chondrocytes after an intra-articular administration.[31] Ruxolitinib, a JAK1/2 inhibitor, has been found in mouse models to decrease components of the SASP by 40%-60% within days of initiation and decrease systemic inflammation leading to better physical function in aged mice.[32] Further evaluation of ruxolitinib in OA may be a future direction of research.

Conclusion

A better understanding of the complex interconnections between external stressors, senescence development, and OA is needed given the aging global population and increased prevalence of OA. Evaluating SASP as the mechanistic connection between the 3 is an important task as it provides targetable molecules which may have therapeutic implications. Investigating novel agents, as well as reassessing existing agents, are future steps to better understanding and treating cellular senescence as a cause of OA.

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