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Ageing and the pathogenesis of osteoarthritis

Richard F. Loeser[1], **John A. Collins**[1], and **Brian O. Diekman**[2]

[1]Thurston Arthritis Research Center, Division of Rheumatology, Allergy, and Immunology, 3300 Thurston Building, Campus Box 7280, University of North Carolina School of Medicine, Chapel Hill, North Carolina 27599-7280, USA

[2]Lineberger Comprehensive Cancer Center, University of North Carolina School of Medicine, 450 West Drive, Campus Box 7295, Chapel Hill, North Carolina 27599-7295, USA

Abstract

Ageing-associated changes that affect articular tissues promote the development of osteoarthritis (OA). Although ageing and OA are closely linked, they are independent processes. Several potential mechanisms by which ageing contributes to OA have been elucidated. This Review focuses on the contributions of the following factors: age-related inflammation (also referred to as ‘inflammaging’); cellular senescence (including the senescence-associated secretory phenotype (SASP)); mitochondrial dysfunction and oxidative stress; dysfunction in energy metabolism due to reduced activity of 5′-AMP-activated protein kinase (AMPK), which is associated with reduced autophagy; and alterations in cell signalling due to age-related changes in the extracellular matrix. These various processes contribute to the development of OA by promoting a proinflammatory, catabolic state accompanied by increased susceptibility to cell death that together lead to increased joint tissue destruction and defective repair of damaged matrix. The majority of studies to date have focused on articular cartilage, and it will be important to determine whether similar mechanisms occur in other joint tissues. Improved understanding of ageing-related mechanisms that promote OA could lead to the discovery of new targets for therapies that aim to slow or stop the progression of this chronic and disabling condition.

A number of risk factors for the development of osteoarthritis (OA) exist, including prior joint injury, obesity, genetics, sex, and anatomical factors related to joint shape and alignment; however, the most prominent risk factor is increasing age[1]. A Spanish study published in 2014, which included more than 3 million individuals, examined the incidence of clinically diagnosed OA and reported that incident hand OA in women peaked between

Correspondence to R.F.L. richard_loeser@med.unc.edu.

Author contributions

All authors researched data for the article and contributed to discussion of content, writing the article, and reviewing and editing the manuscript before submission.

Competing interests statement

The authors declare no competing interests.

Review criteria

The authors searched the PubMed database for articles using the search terms “ageing”, “cellular senescence”, “oxidative stress”, “AMPK”, “autophagy” and “sirtuin”, combined with “chondrocyte”, “cartilage” or “osteoarthritis”, and years starting at 2010. Full-length original manuscripts published in English were selected for further review. Key references from identified manuscripts that reported important earlier studies of interest were also reviewed.

the ages of 60 and 64 years, whereas that of the hip and knee continued to increase with increasing age[2]. A US study using data from the National Health Interview Survey reported that incident symptomatic knee OA peaked between the ages of 55 and 64, whereas prevalent disease increased with age, such that at age 85 years and older, prevalence ranged from ~13% in nonobese men to 32% in obese women[3].

Musculoskeletal conditions, including OA, are a major cause of disability worldwide[4] and have a substantial contribution to health-care costs, accounting for an estimated 1.0–2.5% of the gross domestic product in the USA, Canada, the UK, France and Australia[5]. Advanced OA often requires joint replacement to reduce pain and disability, and the number of knee replacement surgeries has substantially increased over the past 20 years[6]. The ageing of our population will compound the number of older adults disabled by OA and in need of joint replacement. Improved understanding of how ageing contributes to the development of OA could lead to new therapies that slow or stop the progression of the disease, which would have a major impact on public health.

OA that occurs in young adults is most often caused by a prior joint injury, a process known as post-traumatic OA[1], whereas in older adults a number of factors related to ageing can contribute to the development of OA (BOX 1). These ‘ageing factors’ probably work in concert with other OA risk factors. Important differences between joint ageing and OA demonstrate that they are distinct processes (BOX 2). Although OA is a condition that affects the entire joint[7] and results in joint failure, the majority of research to date has focused on ageing-associated changes in the articular cartilage. However, studies on the meniscus[8], anterior cruciate ligament[9] and bone[10] have shown age-related changes similar to those observed in articular cartilage — including loss of cellularity, and disruption and degeneration of the extracellular matrix — suggesting that common processes could be involved.

In 2013, nine cellular and molecular hallmarks of ageing were proposed[11] to highlight the underlying causes of age-related dysfunction and assist with research into potential therapeutic interventions. These hallmarks include genomic instability, `telomere attrition`, epigenetic alterations, loss of `proteostasis`, dysregulated nutrient sensing, mitochondrial dysfunction, `cellular senescence, stem cell exhaustion` and altered intercellular communication. This Review covers selected aspects of ageing that are relevant to OA and, where possible, relates these studies to the hallmarks of ageing.

Ageing, inflammation and OA

Mounting evidence suggests that OA is associated with low-grade systemic and local inflammation[12,13]. Ageing has likewise been associated with chronic low-grade inflammation, sometimes referred to as ‘inflammaging’ (REF.[14]), which could promote OA, although studies to date have not identified the precise mechanisms. Several of the hallmarks of ageing could also have a role in OA, including epigenetic alterations, dysregulated nutrient sensing, mitochondrial dysfunction, cellular senescence and altered intercellular communication. As discussed further below, increased production of proinflammatory

mediators is a feature of the senescence-associated secretory phenotype (SASP) and could be an important mechanism in OA.

A key cytokine associated with ageing and age-related disease is IL-6. Levels of IL-6 in the systemic circulation increase with age[15,16] and are strongly associated with the risk of OA progression[17,18]. IL-6 is important in the pathogenesis of rheumatoid arthritis, and IL-6 inhibition is an effective therapy approved for clinical use in this setting[19]. However, a causal role for IL-6 in age-related OA has not been established, as mice with deletion of the *Il6* gene have more severe (rather than less severe) age-related OA[20], suggesting that other mediators could be involved. In addition, the levels of multiple proinflammatory and anti-inflammatory mediators change with age[16], and so it is unlikely that the association between age and OA is driven by a single factor.

Inflammaging is probably attributable, at least in part, to the age-related increase in visceral fat mass that is associated with a decline in muscle mass[21]. Obesity is a well-accepted risk factor for OA in all age-groups[3]. Reviews published elsewhere[22,23] have detailed the potential mechanisms by which obesity leads to OA, and so here we will only summarize the key findings most relevant to age-related OA. The increase in fat mass with ageing is associated with increased numbers of adipocytes and proinflammatory macrophages in adipose tissue, and these cells produce a number of cytokines and adipokines that could contribute to OA[24,25], although the importance of these mediators in OA remains unclear. Obesity and increased fat mass can also contribute to OA through metabolic alterations that are sometimes referred to as ‘meta-inflammation’ (REFS 22,23). In addition to increased levels of cytokines and adipokines, meta-inflammation is associated with increased levels of circulating free fatty acids, hyperglycaemia and oxidative stress, which can all negatively influence joint tissues to promote matrix destruction[22,23]. Furthermore, obesity associated with low muscle mass (that is, sarcopenic obesity) has been associated with knee OA[26] and could contribute to joint instability and an increased risk of falls in older adults, particularly in women[27].

In addition to an age-related increase in visceral fat, local fat depots such as the infrapatellar fat pad increase with age[28]. Given that this fat pad is proximal to the knee joint and produces the adipokines adiponectin and leptin, as well as basic fibroblast growth factor (bFGF; also known as FGF-2), vascular endothelial growth factor, TNF and IL-6 (REF. 29), it is plausible that an age-related increase in fat pad volume could contribute to OA. However, *in vitro* studies of conditioned media from infrapatellar fat pads removed from patients with end-stage knee OA found a protective rather than catabolic effect on bovine cartilage explants[30].

Cellular senescence and the SASP

Cellular senescence is one of the hallmarks of ageing, and chondrocytes have many features that are characteristic of senescent cells during ageing and during OA[31,32]. The observation that OA catalyses the development of senescence indicates that cellular stresses probably have a key role in establishing this phenotypic state. A key challenge has been deciding how to best define chondrocyte senescence and determine the underlying mechanisms that might

be targeted therapeutically (FIG. 1). Morphological changes and permanent replicative arrest after monolayer expansion have defined cellular senescence for *in vitro* settings, but defining cellular senescence *in vivo* has proved more difficult[33].

Two distinguishing characteristics of senescent cells are stress-induced permanent proliferative arrest and resistance to both mitogenic and oncogenic stimuli[33], both of which are challenging to assess in chondrocytes. Chondrocytes exhibit low proliferation rates, which hinders the measurement and interpretation of the functional impact of a further reduction in proliferation[34]. Lineage-tracing experiments in mice indicate that proliferation of particular chondrocyte subpopulations could help to maintain cartilage tissue[35], suggesting, therefore, that the loss of proliferation in these cells due to senescence could contribute to OA progression. The other defining feature of senescence is a beneficial function of preventing the division of transformed cells[36]. Chondrosarcomas typically derive from the growth plate and perichondrium but not from articular cartilage[37], suggesting that articular cartilage might be inherently unlikely to undergo uncontrolled growth. This characteristic presents a challenge for the identification of senescent chondrocytes on the basis of an increased resistance to oncogenic transformation.

Cellular senescence could have other functional roles aside from inhibition of proliferation, as the SASP is defined by the production of high levels of proinflammatory cytokines and matrix-degrading enzymes[38]. Indeed, the SASP seems to be regulated independently from cell cycle arrest[39,40]. Some of the most highly upregulated SASP-related factors, such as IL-1α, IL-6 and monocyte chemoattractant protein 1 (MCP-1, also known as CC chemokine ligand 2 (CCL2)) are found in OA cartilage[41], hindering efforts to determine whether the level of a particular mediator is due to senescence or a result of OA. The cell type responsible for producing these cytokines is also difficult to determine. As these factors are also found in the synovial fluid, they could be produced by cells other than chondrocytes, such as cells in the meniscus, synovium or bone[7]. Future work is needed to determine whether any of these cell types display other features of senescence.

The induction of chondrocyte senescence

A detailed understanding of how chondrocytes enter the senescent state might enable the development of therapies designed to prevent such a phenotypic switch during OA. One model proposes that senescence occurs during conditions characterized by simultaneous signals for cell cycle arrest and cell growth[7,42], and aged cartilage tissue has the potential to provide both these cues.

The cumulative DNA damage and oxidative stress that occurs with ageing and in the OA tissue microenvironment alters gene expression patterns in chondrocytes[7,43] and could cause telomere attrition due to targeted DNA damage[41,44]. Notably, stem cells and postmitotic cells such as neurons and chondrocytes can be particularly susceptible to the accumulation of cellular damage during the long interval between replicative events[45,46]. One common consequence of accumulating DNA damage is the upregulation of cell cycle inhibitors, such as cyclin-dependent kinase inhibitor 2A (also known as $p16^{INK4A}$) and cyclin-dependent kinase inhibitor 1 (also known as p21), which mediate the stable arrest that is associated with senescence[33]. Evidence correlating increasing age and OA with increased *CDKN2A*

($p16^{INK4A}$) gene expression in chondrocytes has been complemented by mechanistic work showing that the suppression of $p16^{INK4A}$ expression by the microRNA miR-24 serves to prevent features of chondrocyte senescence[47]. These observations in chondrocytes seem to be aligned with a model explored in mouse muscle stem cells, in which increased $p16^{INK4A}$ expression with age made cells more likely to undergo senescence during subsequent proliferation after injury[48].

The second signal required for establishing senescence, a strong growth signal, can be provided in the form of growth factors that are either directly released from damaged cartilage or synthesized at high levels by chondrocytes during OA. For example, bFGF is released from damaged cartilage tissue[49], and can be detected in focal clusters of chondrocyte proliferation that develop near areas of cartilage damage[50]. As a downstream result of signalling by inflammatory cytokines associated with OA, expression of bone morphogenetic protein 2 (BMP-2) is increased,[51] thereby stimulating enhanced turnover of extracellular matrix[52]. Although their competence for proliferation indicates that these chondrocytes are not senescent, cells that enter the cell cycle in the context of potentially damaging stimuli have an increased likelihood of entering senescence as opposed to returning to quiescence[53,54]. Observations that senescence occurs after monolayer expansion of chondrocytes (reviewed elsewhere[55]) provide further evidence that contexts of increased proliferation correlate with emergence of the senescent phenotype.

The role of circadian signals

Also of potential interest is the finding that chondrocytes have an intrinsic circadian clock which is disrupted in cartilage from aged mice[56]. A decline in expression of the circadian clock gene *BMAL1* (also known as *ARNTL*) has been associated with stress-induced senescence in fibroblasts[57] and has been noted to occur in human OA chondrocytes and in the cartilage of aged mice[58]. Mice with cartilage-specific deletion of *Bmal1* developed premature knee cartilage lesions that appeared at 2 months of age and became progressively more severe in adult animals[58]. However, no other OA-associated changes in the bone, ligaments or synovium were evident in these mice, and the finding that the cartilage changes were detectable before the mice were skeletally mature suggests that the phenotype is the result of a developmental defect rather than OA. Further work is needed to determine the role of *BMAL1* and the circadian clock in age-related human OA.

Therapeutic targeting of senescence

One emerging therapeutic strategy for age-related diseases is to specifically kill senescent cells in order to prevent detrimental secretion of SASP-related factors. Although this approach has not yet been explored in OA, the concept builds on studies that eliminated $p16^{INK4A}$-positive cells in mouse models of premature[59] and natural ageing[60]. Drugs that eliminate senescent cells in aged tissue would ideally mimic the efficient clearance of senescent cells that occurs after wound repair[61]. The ‘senolytic’ compounds dasatanib and quercetin target senescent cells by inhibiting the anti-apoptotic pathways that are upregulated in senescent cells[62]. One anti-ageing effect of this treatment was protection from proteoglycan loss in the intervertebral disc of *Ercc1*-mutant mice (a model of accelerated ageing based on compromised DNA damage repair). Although articular cartilage

was not investigated in this study, other work has shown that *ERCC1*-mediated DNA repair helped to restrain senescence in human articular chondrocytes[63]. A separate study further supports the strategy of inhibiting anti-apoptotic pathways by identifying navitoclax as an inhibitor of B-cell lymphoma family proteins that specifically targets senescent human fibroblasts *in vitro* and mouse stem cells *in vivo*[64].

Another therapeutic approach could be to interfere with inflammatory pathways active in senescent chondrocytes. Rapamycin inhibits the translation of SASP proteins in human fibroblasts through decreasing the rate of IL-1α translation, which is regulated by serine/threonine-protein kinase mTOR (also known as mammalian target of rapamycin)[65]. With increased progress in the understanding of how senescence is regulated in chondrocytes, particular cellular features could provide other novel drug targets for OA.

Oxidative stress and the mitochondria

Mitochondrial dysfunction is a hallmark of ageing that has attracted particular attention in the context of OA. The free radical theory proposes that cellular damage occurring as a result of excessive levels of reactive oxygen species (ROS) substantially contributes to the development of the ageing phenotype and to the progression of age-related diseases[66]. However, in addition to cellular damage, elevated levels of ROS produced as a result of age-associated oxidative stress also promote disease by disturbing homeostatic physiological cell signalling[66–68].

Mitochondrial function has long been recognized to decline during ageing, and a causative link between mitochondrial dysfunction, oxidative stress and the ageing phenotype has been proposed[66,69]. Evidence from a 2015 study[70] demonstrates that, compared with normal chondrocytes, chondrocytes from patients with OA have reduced mitochondrial mass and mitochondrial DNA content along with reduced levels of electron transport chain proteins and proteins involved in mitochondrial biogenesis. The researchers confirmed that some of these changes occurred during ageing and were independent of OA by analysing mouse cartilage tissue sections. Interestingly, protein levels of nuclear receptor erythroid 2-related factors 1 and 2 (also known as NFE2-related factor 1 and NFE2-related factor 2, respectively), which confer cellular protection through regulation of antioxidant gene expression, were also decreased in chondrocytes from patients with OA compared with those from healthy controls[70].

As mitochondria are an important source of ROS, age-related mitochondrial dysfunction that leads to an imbalance between the production of ROS and the antioxidant capacity of the cell has been identified as a contributing factor in the development of OA[68,71,72] (FIG. 2). Mice with post-traumatic OA showed elevated intracellular and mitochondrial superoxide generation, which was associated with downregulation of mitochondrial superoxide dismutase 2 (SOD2) expression[73]. Furthermore, in this same model, SOD2 loss resulted in greatly increased age-related cartilage degeneration[73]. *In vitro* studies using paraquat to induce mitochondrial superoxide generation in primary mouse articular chondrocytes led to substantial mitochondrial dysfunction, along with reduced expression of both antioxidant genes (including *Sod2*) and anabolic genes in cartilage, whereas catabolic gene expression

was upregulated[73]. These data are in accordance with other studies demonstrating downregulation of SOD2 expression at the mRNA and protein levels in cartilage from both humans[74–76] and animals[76] with OA, and support the hypothesis that mitochondrial dysfunction and the associated redox imbalance is a key mechanism contributing to cartilage degeneration and the pathogenesis of OA.

Consistent with the concept that age-related oxidative stress alters cell signalling, studies have demonstrated an age-related disruption in human chondrocyte insulin-like growth factor 1 (IGF-1) signalling that results in reduced extracellular matrix gene expression and protein synthesis[77,78]. In human chondrocytes from older adults, this effect was associated with an increased sensitivity to oxidative stress, which resulted in inhibition of IGF-1-mediated activation of RACα serine/threonine-protein kinase (AKT) and increased activation of catabolic mitogen-activated protein kinase (MAPK) signalling pathways[78].

A key mechanism by which ROS regulate cell signalling is through oxidative post-translational modifications of specific thiol groups in proteins that contain reactive cysteines[79]. Cysteine oxidation initially results in the formation of a cysteine sulfenic acid (Cys-SOH) in a process known as *S*-sulfenylation. In a 2016 study, chondrocytes from patients with OA had an increased basal level of *S*-sulfenylation compared with those from healthy controls[80]. ROS induced sulfenylation of multiple chondrocyte proteins including the tyrosine kinase SRC, the activity of which promoted an increase in the production of matrix metalloproteinase 13 (MMP-13)[80]. These data suggest that ROS-induced sulfenylation of chondrocyte proteins can alter signalling pathways that can promote cartilage degradation.

In the presence of excessive levels of ROS, cysteine oxidation can proceed from cysteine sulfenic acid to sulfinic ($Cys\text{-}SO_2H$) or sulfonic ($Cys\text{-}SO_3H$) acid; this so-called hyperoxidation can lead to inactivation of redox-sensitive proteins. Hyperoxidation of the peroxiredoxin family of antioxidant enzymes has been demonstrated in cartilage samples from older adult humans and patients with OA[81]. Conditions of oxidative stress (induced *in vitro* with the ROS generator menadione) led to an age-related increase in peroxiredoxin hyperoxidation, which was associated with both inhibition of pro-survival cell signalling and p38 MAPK-induced chondrocyte cell death[81]. Importantly, reduction of ROS levels by mitochondrion-specific overexpression of the antioxidant enzyme catalase prevented peroxiredoxin hyperoxidation *in vitro*, and reduced the severity of age-related OA in mice *in vivo*[81]. Collectively, these studies highlight ROS as crucial secondary signalling molecules in chondrocytes that warrant further study in the context of ageing and OA.

Dysfunctional energy metabolism

Another hallmark of ageing is dysregulated nutrient sensing. 5′-AMP activated protein kinase (AMPK) is a key regulator of cellular metabolism and energy balance that is activated by stressors that enhance the cellular AMP:ATP ratio[82]. The activity of AMPK and its regulatory upstream kinase, serine/threonine-protein kinase STK11 (also known as liver kinase B1 (LKB1)), is reduced in cartilage from aged mice and mice with OA, as well as in bovine chondrocytes after dynamic compression-induced biomechanical injury[83]. Similarly,

OA-associated reductions in AMPK activity have been observed in human chondrocytes and cartilage[84], and this reduced activity has been associated with substantially reduced mitochondrial biogenesis[70].

Importantly, AMPK might also modulate key homeostatic signalling pathways through regulation of autophagy, a cellular process that removes damaged and dysfunctional organelles and proteins[82,85]. Autophagy is relevant to another hallmark of ageing: loss of proteostasis. Transgenic overexpression of AMPK delays the onset of the ageing phenotype through direct upregulation of autophagy in *Drosophila melanogaster*, which ultimately increases the lifespan of these organisms[86]. Consistent with this observation, the expression of key autophagy proteins was considerably reduced in cartilage from aged mice compared with that from young mice, and these changes were associated with increased levels of apoptosis and cartilage degeneration[87]. Similar results were also found in a mouse model of post-traumatic OA[88], implicating dysfunctional autophagy as a key mechanism in both ageing and OA. Although AMPK levels were not measured in these post-traumatic OA studies, other work has demonstrated that AMPK signalling stimulates autophagy in chondrocytes[89]. As inhibition of mTOR signalling is a widely investigated strategy to prevent age-related disease[90], the fact that cartilage-specific loss of mTOR increased AMPK levels and autophagy, and was sufficient to protect mice from OA following surgery, is of particular interest[91]. Taken together, a plausible interpretation of these findings is that age-related and OA-related reductions in AMPK signalling reduce autophagy and contribute to the cellular dysfunction observed in OA cartilage, a connection that is worthy of future investigation.

In addition to AMPK, many lines of evidence suggest that the evolutionarily conserved sirtuin (SIRT) family of NAD^+-dependent deacetylase proteins also contributes to cellular homeostasis through regulation of energy balance. This regulation is achieved via direct nutrient sensing, which can contribute to increased lifespan in model organisms, such as worms and flies[92]. However, whether overexpression of sirtuins can have a direct longevity-promoting effect remains unclear[93]. SIRT6 has been identified as a crucial regulator of processes that are hypothesized to be directly involved in ageing, including metabolic homeostasis, genome stability and transcription[94]. *Sirt6*-knockout mice display reduced IGF-1 levels and accelerated ageing-like degenerative processes that ultimately lead to premature death, which suggests a role for SIRT6 in ageing[95]. Similarly, male transgenic mice overexpressing *Sirt6* had an increased lifespan, in part due to regulation of IGF-1 signalling[96], which suggests that age-related loss of SIRT6 activity could contribute to ageing by disturbing normal cell signalling pathways.

In cartilage, research has predominantly focused on the role of SIRT1 (reviewed elsewhere[97]). As such, there is a paucity of research on how other sirtuins regulate chondrocyte function. However, depletion of SIRT6 in human chondrocytes (achieved using RNA interference) resulted in substantially increased DNA damage and telomere dysfunction, which was associated with premature senescence[98]. SIRT6 depletion also increased expression of *MMP1* and *MMP13*, which are implicated in the pathogenesis of OA. Compared with cells from normal human tissue, human OA chondrocytes show reduced expression of SIRT6 at both the mRNA and protein level, and lentivirus-induced

overexpression of SIRT6 in the knee joint protects young mice from surgically induced OA[99]. These studies highlight a potential role for SIRT6 in cartilage homeostasis that warrants further investigation.

Changes in the extracellular matrix

Articular cartilage is a load-bearing tissue, and the ability of chondrocytes to sense and respond to mechanical signals is essential for maintaining joint homeostasis (reviewed elsewhere[100]). Accumulation of `advanced glycation end-products (AGEs)` with ageing causes non-enzymatic collagen crosslinking that directly alters the mechanical properties of the extracellular matrix[101]. However, a canine model using ribose and threose injections to increase AGE levels in young animals to match those of aged controls was insufficient to initiate OA[102]. Nevertheless, chondrocytes did synthesize fewer proteoglycans in the highly crosslinked tissue, which might indicate that compromised cellular function would prevent sufficient tissue maintenance in the context of ageing or injury. This possibility is supported by a study in rabbits, in which forced exercise in combination with ribose injections did induce OA, through AGE-mediated suppression of protective chondrocyte signalling[103].

Whether limiting AGE accumulation would be sufficient to prevent age-related OA remains unclear, but genetic deletion of lysyl oxidase (an enzymatic collagen crosslinker that is upregulated by joint injury) protected mice from injury-induced OA[104]. The potential relevance of this finding to AGEs and thus ageing was suggested by the finding that collagen crosslinking induced by AGEs and by lysyl oxidase had similar effects on chondrocyte signalling in collagen gels and on the development of OA after injury.

Chondrocytes integrate signals from mechanotransduction pathways that sense changes in the extracellular matrix and those initiated by soluble factors, and both types of signals are affected by ageing. Mechanical compression of bovine cartilage stimulates increased expression of the gene encoding transforming growth factor-β (TGF-β) and the subsequent phosphorylation of SMAD2 and SMAD3 through TGFR-1 (TGF-β receptor type-1), which increases matrix synthesis and limits catabolic signalling[105]. However, ageing causes a significant loss in expression of TGFR-1, resulting in a shift that favours TGF-β signalling through serine/threonine-protein kinase receptor R3 (SKR3, also known as TGF-β superfamily receptor type I). SKR3-mediated signalling leads to phosphorylation of SMAD1, SMAD5 and SMAD8, which is associated with an increase in catabolic signalling and increased production of MMP-13 (REF. 106). In a 2016 study of bovine cartilage explants subjected to `anabolic dynamic compression`, tissues from aged animals had deficient phosphorylation of SMAD2 and SMAD3 in response to loading compared with explants from young animals[105]. The exact mechanism responsible for this effect is difficult to deduce because, compared with young explants subjected to the same load, aged tissue showed less deformation, exhibited less upregulation of growth factors and also had lower levels of TGFR-1 on the cell surface. However, previous work using a hydrogel system with varied stiffness revealed that mouse chondrocytes show a maximal response to exogenous TGF-β at a physiologically relevant stiffness of 500 kPa[107], indicating that the age-related

increase in matrix stiffness probably contributes to the reduced phosphorylation of SMAD2 and SMAD3 in aged tissue.

Conclusions

Researchers are becoming increasingly interested in elucidating the mechanisms by which ageing promotes the development and progression of OA. Studies in the early 2000s detailed age-related changes in the extracellular matrix, such as the accumulation of AGEs, which could promote OA by altering the mechanical properties of joint tissues. Subsequent research has focused on age-related cellular changes that include not only an accumulation of damaged proteins, lipids and DNA, but also alterations in mitochondrial function, levels of ROS and energy metabolism that disrupt signalling and associated cell functions. These changes promote catabolic activity over anabolic activity and eventually result in cell death. We can easily envision how these changes could result in joint tissue degeneration and matrix loss, but the precise mechanisms need to be clarified. The concept of hallmarks of ageing suggests that common mechanisms will drive dysfunction in various tissues and organ systems that are most affected by ageing. These hallmarks represent areas for further research into elucidating the connections between ageing and OA. Although the majority of research into the effects of ageing continues to focus on articular chondrocytes, further studies are needed to determine whether similar mechanisms are at play in cartilage as well as other joint tissues affected by OA, in order to find common targets for intervention.

A primary goal of ageing research is to better understand common mechanisms that could be targeted with the intent of delaying loss of function in more than a single system, which would result in improved ‘healthspan’ rather than simply extending lifespan. Heterochronic parabiosis experiments, in which the circulatory systems of young and old animals are joined, have revealed systemic factors that alter the ageing phenotype, including growth and differentiation factor 11 (GDF11), oxytocin and IL-15, which might be able to reduce ageing in multiple organ systems[108]. An important aim of future studies will be to determine whether these ageing-associated factors influence the development of OA.

Another emerging approach is the development of senolytic agents that would target and remove senescent cells[62,64]. These and other therapies that target ageing processes could be developed into novel treatments for OA (BOX 3). Given the prevalence of conditions such as OA in older adults and the importance of the musculoskeletal system in physical function, achieving improvements in healthspan will certainly require interventions that benefit the musculoskeletal system.

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Biographies

Richard Loeser is the Herman and Lousie Smith Distiguished Professor in the Division of Rheumatology, Allergy and Immunology at the University of North Carolina School of

Medicine and the Director of Basic and Translational Research in the Thurston Arthritis Research Center, Chapel Hill, North Carolina, USA. He trained in both rheumatology and geriatrics at the Wake Forest School of Medicine in Winston-Salem, North Carolina, and has spent more than 25 years carrying out research in the field of cartilage biology and osteoarthritis (OA) with a major interest in how ageing contributes to OA.

John Collins is a postdoctoral research fellow at the University of North Carolina Thurston Arthritis Research Center, Chapel Hill, North Carolina, USA. He earned his PhD in 2014 from the Institute of Ageing and Chronic Disease, University of Liverpool, UK, for his research in the field of musculoskeletal biology. Under the mentorship of Dr Richard Loeser, he is currently investigating the role of oxidative stress in ageing and osteoarthritic joint tissues, with a focus on how age-related oxidative stress disrupts cell signalling.

Brian Diekman is currently investigating ageing and cellular senescence as a postdoctoral research associate in the University of North Carolina Lineberger Comprehensive Cancer Center, Chapel Hill, North Carolina, USA, under the direction of Dr Norman Sharpless. After earning a BSE in Biomedical Engineering from Duke University, Durham, North Carolina, in 2005, he received a Fulbright Student Grant to perform stem cell research at the Regenerative Medicine Institute in Galway, Ireland. Dr Diekman earned his PhD in Biomedical Engineering from Duke University in 2012 after performing a series of projects in the field of cartilage tissue engineering in the Orthopaedic Bioengineering Laboratory directed by Dr Farshid Guilak.

Glossary

Telomere attrition	The shortening and deterioration of the protective caps on the ends of chromosomes associated with ageing.

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Key points

- Ageing-associated changes promote the development of osteoarthritis (OA), but ageing and OA are independent processes
- Several hallmarks of ageing could contribute to OA: genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, dysregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication
- The increase in fat mass and related metabolic changes that occur with ageing can result in ageing-related inflammation (referred to as ‘inflammaging’), a chronic low-grade systemic proinflammatory state
- Elevated levels of reactive oxygen species can contribute to OA by causing oxidative damage and disrupting normal cell signalling, leading to imbalanced anabolic and catabolic activity and ultimately cell death
- Chondrocytes can undergo cellular senescence with age and OA in response to growth signals released as a result of underlying cellular damage
- The non-enzymatic crosslinking of collagen that occurs with ageing alters the mechanical properties of cartilage, and the resulting changes to mechanotransduction pathways reduce extracellular matrix synthesis by chondrocytes

Box 1

Age-related factors that contribute to osteoarthritis development

- Reduced muscle mass and increased fat mass alter joint loading and are associated with an increase in adipokine and cytokine production, resulting in low-grade systemic inflammation[109].
- Changes in the extracellular matrix, including accumulation of advanced glycation end-products, reduced aggrecan size, reduced hydration, and increased collagen cleavage alter the mechanical properties of cartilage and make it more susceptible to degeneration[31].
- Extracellular matrix disruption and reduced cell density in the meniscus and ligaments promote degeneration and can potentially alter joint mechanics[8,9].
- Impairment in the function of subchondral bone due to reduced numbers of osteocytes and altered mineral composition[10].
- Mitochondrial dysfunction, oxidative stress and reduced autophagy in chondrocytes alters their function, promoting catabolic processes and cell death over anabolic processes[31].

Box 2

Differences between normal joint ageing and osteoarthritis

- With normal joint ageing, articular cartilage remains intact but loses thickness and has a reduced glycosaminoglycan (GAG) content. With osteoarthritis (OA), fibrillation of the cartilage surface occurs in focal areas and can be associated with a complete loss of staining for GAGs[31,110].
- Non-enzymatic crosslinking of collagen by advanced glycation end-products (AGEs) increases in cartilage with age. A mouse model of injury-induced OA demonstrated that collagen crosslinking occurs through a distinct mechanism involving lysyl oxidase[104].
- The density of chondrocytes in cartilage decreases with age, but chondrocyte ‘clusters’ emerge during the development of OA near sites of tissue damage and may indicate attempted repair or altered cellular signals[31,110].
- Aged chondrocytes have reduced levels of extracellular matrix gene expression and synthesis, whereas during OA chondrocytes become highly active with increases in both anabolic processes (for example, matrix synthesis) and catabolic pathways (for example, those induced by inflammatory cytokines)[31,110].
- Synovial inflammation and hypertrophy occur in OA but have not been described in normal joint ageing[7].
- Bone mass and density decrease with ageing, whereas subchondral bone thickening is seen in patients with OA[7].

Box 3

Therapeutic targeting of ageing-related processes in osteoarthritis

- Interventions designed to extend ‘healthspan’ by targeting systemic ageing-related processes could potentially delay or prevent various chronic diseases, including osteoarthritis[111,112].
- Senolytics, such as dasatanib and quercetin, are being designed to specifically kill senescent cells; removal of these cells might alleviate their harmful effects on neighbouring cells, including the release of proinflammatory factors that characterize the senescence-associated secretory phenotype (SASP)[62].
- Agents that activate 5′-AMP-activated protein kinase (AMPK), such as metformin, could restore physiological levels of autophagy and promote proteostasis[112].
- Sirtuin activators could restore normal nutrient sensing and energy metabolism[112].
- Antioxidants targeted to the mitochondria or designed to restore homeostatic redox signalling could counteract mitochondrial dysfunction and altered intracellular signalling[113].

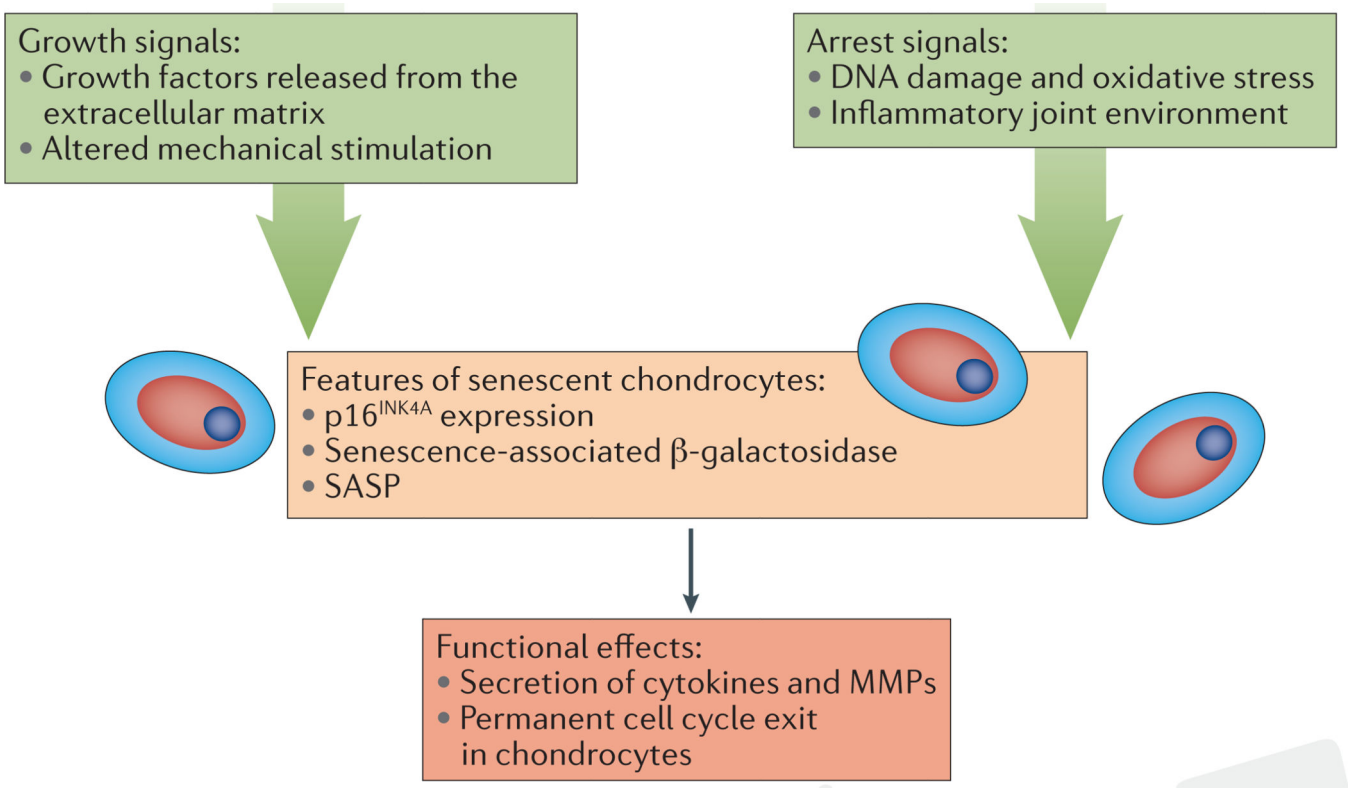

Figure 1. Chondrocytes exhibit features of cellular senescence in the contexts of ageing and osteoarthritis

Senescence is often caused by the combination of growth and arrest signals, conditions that can occur in cartilage during ageing. Features of senescence include expression of *CDKN2A* (encoding $p16^{INK4A}$) and positive staining for senescence-associated β-galactosidase. The functional effects of chondrocyte senescence are challenging to measure because of the low proliferation rate of chondrocytes and the overlap between features of the senescence-associated secretory phenotype (SASP) and those associated with the development of osteoarthritis (OA). Understanding the mechanism of senescence could yield therapeutic interventions to prevent development of the SASP or specifically eliminate senescent cells from joint tissues. MMPs, matrix metalloproteinases.

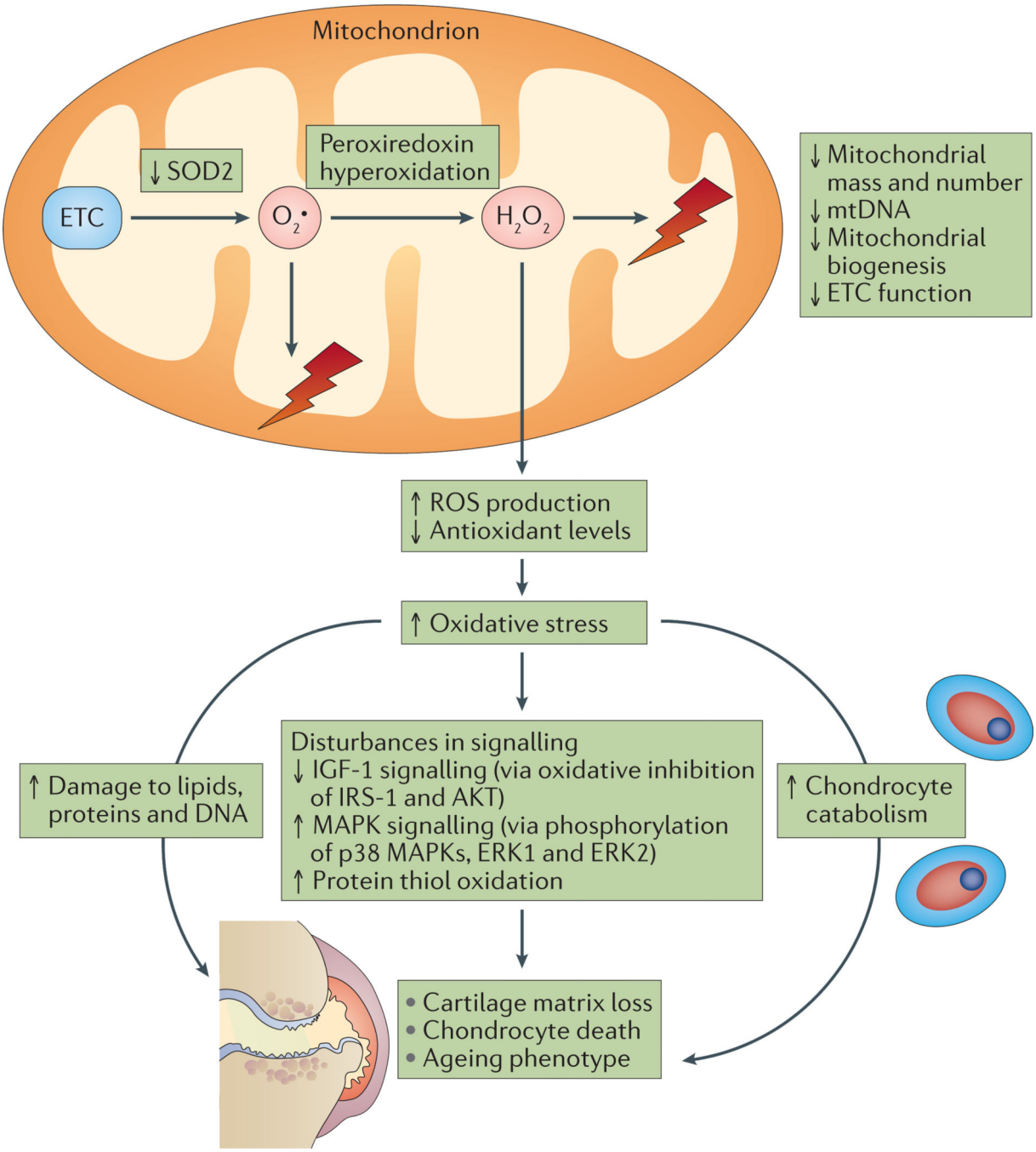

Figure 2. Mitochondrial dysfunction, oxidative stress and changes in normal cell signalling in ageing and osteoarthritis

Mitochondrial dysfunction in both ageing and osteoarthritis (OA) is characterized by reduced mitochondrial integrity (mass, number and DNA content) and impaired electron transport chain (ETC) function. These features contribute to increased production of reactive oxygen species (ROS). Concomitant reductions in mitochondrial antioxidant capacity — including reduced mitochondrial superoxide dismutase 2 (SOD2) levels and peroxiredoxin (PRX) hyperoxidation — lead to enhanced oxidative stress and ROS-mediated damage in the mitochondria (indicated by red lightning bolts). Extra-mitochondrial antioxidant systems

(namely, SOD1, catalase and glutathione synthetase; not shown) are also considerably less active in ageing and OA, which exacerbates oxidative stress. ROS cause damage to proteins, lipids and DNA, increase chondrocyte catabolism and, importantly, lead to disturbances in normal cell signalling. These disturbances can include inhibition of pro-survival IGF-1 signalling and increased catabolic mitogen-activated protein kinase (MAPK) signalling. Increased levels of ROS can also result in increased protein thiol oxidation, resulting in *S*-sulfenylation or, when excessive, hyperoxidation of reactive protein cysteines, which might contribute to altered cell signalling. mtDNA; mitochondrial DNA; ERK, extracellular signal-regulated kinase; IGFR, insulin-like growth factor receptor; IRS-1, insulin receptor substrate 1.