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Age and frailty as risk factors for the development of osteoarthritis

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ABSTRACT

Osteoarthritis (OA) is a degenerative joint disease that increases in prevalence with advanced age. While a multitude of factors contribute to the development of OA, ageing has been implicated as a major driving force leading to an inability of the joint to repair itself and maintain normal health. In aged individuals, changes in joint cellular composition and signalling mechanisms have been observed which could lead to the development of degenerative joint disease. Senescent cells found in both aged and OA joints release senescent-associated mediators which can destroy articular tissues. These changes in addition to the chronic pro-inflammatory environment associated with ageing may hinder the ability of the joint to repair culminating in OA. We hypothesise that frailty may also drive OA development by creating an inflammatory environment that can interfere with normal tissue health. The molecular and biochemical changes associated with OA may in turn promote frailty resulting in an exorable deterioration of the joint. Frailty may therefore be considered an additional risk factor for the development of OA.

1. Introduction

Throughout our lifetime, our joints are subjected to repetitive loading which can invariably lead to tissue failure and progressive damage. The body's inability to repair this damage ultimately leads to the manifestation of degenerative joint diseases of which osteoarthritis (OA) is the most prevalent (McDougall et al., 2009). Once thought of as simply 'wear and tear' of an ageing joint, the etiology of OA is now known to be far more complex and involves a multitude of risk factors such as sex, obesity and a prior history of joint trauma (Loeser et al., 2016). Frailty may also play a role in OA since an individual with OA has an increased likelihood of becoming frail (Castell et al., 2015; Meessen et al., 2018; Misra et al., 2015; Veronese et al., 2017; Wise et al., 2014). Here, we hypothesise that frailty may also drive the development of OA as a number of systemic factors in a frail person have the potential to cause joint damage. This review will highlight the cellular and molecular processes that occur during joint ageing and their contribution to OA. The relationship between age, frailty and OA will also be discussed.

2. Anatomy of a normal joint

Synovial joints are complex organs that allow us to move and interact with our environment. The specialized tissues found in joints ensure that this movement is coordinated, occurs in a defined plane, and is almost frictionless (Fig. 1A). Understanding the biochemical composition of normal joint tissues is important when considering the contribution of age and frailty to joint disease.

The chemical composition of articular cartilage allows for the almost frictionless movement associated with joints. This hyaline cartilage is aneural and avascular and derives its nutrition from surrounding synovial fluid. The tissue is comprised of metabolically-active chondrocytes embedded in an extra-cellular matrix (ECM) of collagen and proteoglycans (Fox et al., 2009). The ECM is bathed in water which in a normal joint accounts for approximately 80% of the tissue (Fox et al., 2009). Collagen fibrils occur in various orientations and aggregate proteoglycans and water molecules. The distinct architecture of the ECM combined with the high water content protects the underlying subchondral bone from the relatively high loads encountered during movement. Chondrocytes are responsible for the development, maintenance and repair of cartilage and respond to a variety of stimuli, including sheer stress, growth factors, and cytokines.

Abbreviations: OA, osteoarthritis; ECM, extra-cellular matrix; AGE, advanced glycation end-product; IGF-1, insulin-growth factor 1; MMP, matrix metalloproteinases; SnCs, senescent cells

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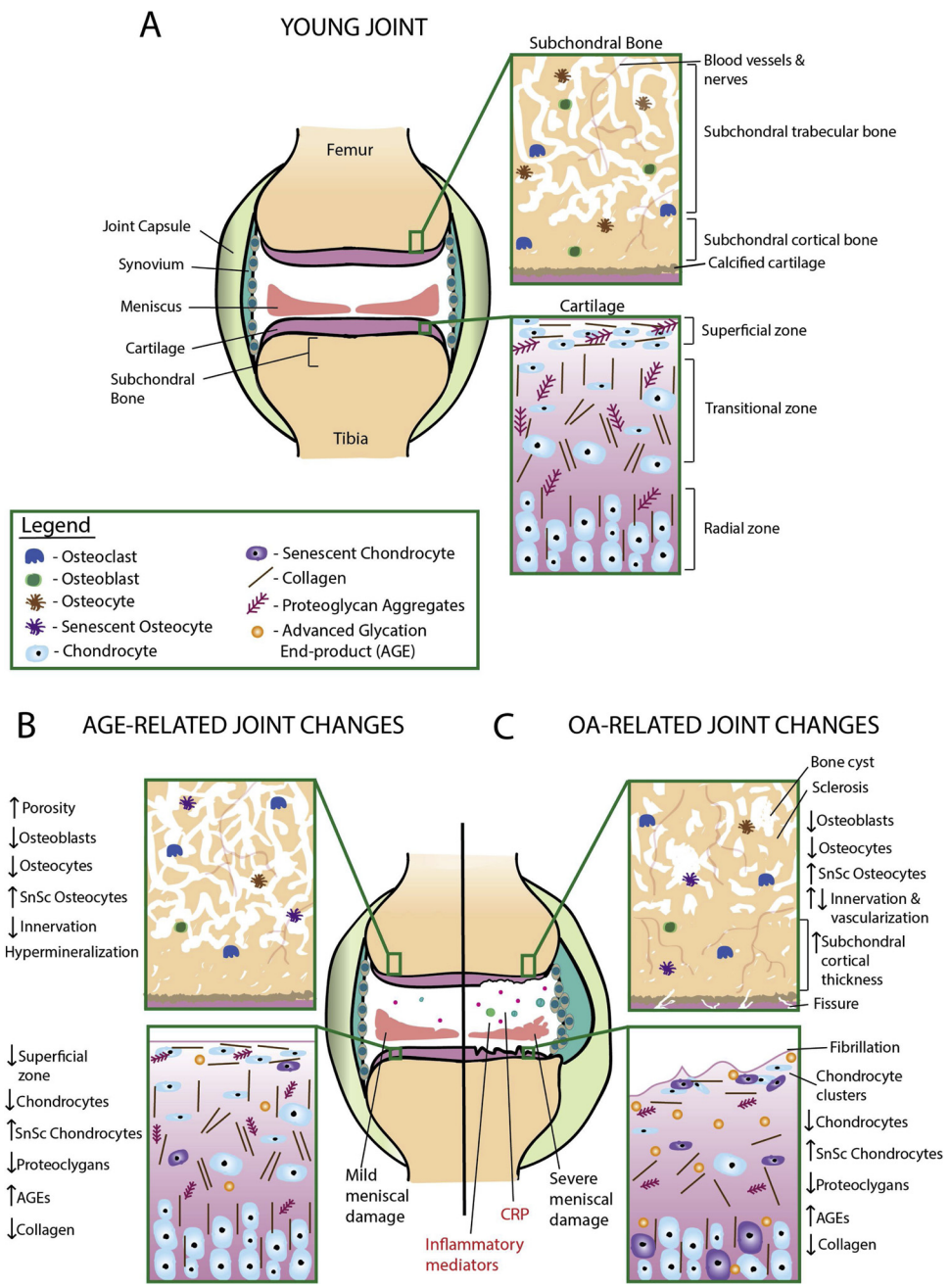

Fig. 1. Structural Changes in Young, Aged, and OA Knee Joints. A, The structural anatomy of a young, healthy knee. B, Age-related changes to the joint including decreased subchondral bone density and increased porosity caused by a decline in the number of osteoblasts and osteocytes. The presence of senescent osteocytes likely contributes to a pro-inflammatory environment. Hypermineralization is also observed in aged bone which results in increased bone stiffness with a heightened susceptibility to joint damage. Cartilage in older individuals is characterized by a thinned superficial zone, and a decrease in extracellular matrix proteoglycans, collagen, and chondrocytes. Advanced glycation end-products (AGEs) are also observed in aged cartilage and contribute to non-enzymatic crosslinking of collagen fibres. Senescent chondrocytes are also present which create a pro-inflammatory environment that leads to further cartilage degeneration. C, Osteoarthritis-related joint changes share similarities with age-related joint changes including decreases in osteoblasts and osteocytes, and increased senescent osteocytes that contribute to abnormal bone remodelling. In contrast to age-related changes, subchondral OA bone is characteristically thicker with sites of sclerosis and the manifestation of cysts. Bone fissuring is also present. OA cartilage has many similarities to aged cartilage, but with the addition of greater fibrillation and cartilage degeneration. Chondrocytes in OA joints cluster at the sites of fibrillation which is not observed in aged cartilage. Systemic factors that are elevated in frail individuals which may drive the development of OA are shown in red (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

Juxtaposed onto the articular cartilage is the subchondral bone which is also important for maintaining joint integrity and function. Two of the main actions of the subchondral bone are to (1) provide nutrients to the articular cartilage, and (2) provide shock-absorption during joint loading (Li et al., 2013). Adjacent to a zone of calcified cartilage lies the superficial subchondral plate (cortical bone) which progresses into the deeper lying subchondral trabecular (cancellous) bone. The articular cartilage and subchondral bone are intrinsically interconnected by channels linking the calcified cartilage to both the subchondral plate and trabecular bone. Within these channels are nerves and blood vessels that respond to excessive mechanical forces to promote subchondral bone thickening, angiogenesis, and pain.

The menisci of the knee joint are crescent-shaped fibrocartilaginous structures that are positioned on the tibial plateau and act as cushions to distribute and absorb compressive and sheer forces between the bones (Tsujii et al., 2017). Only the outer third of the meniscus is innervated and vascularized which allows the remaining inner two thirds of the tissue to bear mechanical loads. Meniscal tears are common initiators of post-traumatic OA; however, age-related damage can also contribute to degenerative joint disease.

Intra-articular and extra-articular ligaments provide mechanical stability to the joint and prevent movement in abnormal planes. These connective tissues consist of long collagen fibres with significant tensile strength. Blood vessels and nerves occur in the superficial epiligament and tend to congregate at the entheses (McDougall et al., 1997). The main functions of ligamentous nerves are for vasomotor control and proprioception which enables safe, coordinated movement of the joint.

Finally, the entire joint is enclosed by a fibrous capsule on the inside of which lies the synovium. This membrane is normally only 1–2 cells thick, but can become hypertrophied in arthritis. The synovium is highly innervated and vascularized and consists of synoviocytes that secrete a viscous fluid that lubricates and nourishes the inside of the joint.

3. Age-related changes to joint structures

It is likely that all tissues in a joint undergo age-related changes; however, the preponderance of current research has focused on bone, meniscus and cartilage. Age-related changes to the synovium, infrapatellar fat pad and articular ligaments may also conspire to weaken joint integrity rendering the joint vulnerable to disease. Here, we summarize the effect of age on the most studied joint structures.

3.1. Cartilage

Age-related changes in cartilage are thought to be major contributors to the etiology of OA (Fig. 1B). With advancing age, articular cartilage loses water content, undergoes modifications in the composition of the ECM, and a depletion of chondrocytes (Buckwalter et al., 1993; Grogan and D'Lima, 2010; Venn, 1978). With respect to the ECM, the number and size of hydrophilic aggregating proteoglycans decreases with age which is responsible for the loss of cartilagenous water. A significant increase in the number of advanced glycation end-products (AGEs) are also present in aged cartilage which can contribute to the development of OA (Steenvoorden et al., 2006). AGEs are produced by non-enzymatic glycation of proteins by reducing sugars and subsequently cause non-enzymatic cross-linking of collagen fibres. The long half-life of collagen and thus its low turn-over rate, renders cartilage particularly susceptible to the accumulation of AGEs (Lotz and Loeser, 2012). The combination of water loss, aggrecan destruction, and non-enzymatic cross-linking of collagen results in cartilage that is stiff and brittle, less compliant in response to joint loading, and more likely to become damaged with joint use (Lotz and Loeser, 2012; Verzijl et al., 2002). The reduced capacity of aged cartilage to dissipate compressive forces can ultimately result in the formation of subchondral bone lesions (Fox et al., 2009).

An additional action of AGEs in cartilage is the modification of chondrocyte signalling to promote ECM destruction via catabolic processes (Loeser et al., 2005; Steenvoorden et al., 2006). The receptor for advanced glycation end-products (RAGE) is expressed on chondrocytes and its levels increase with age (Loeser et al., 2005). Treating monkey and human articular chondrocytes with the RAGE natural ligands S100B or HMGB-1 in culture caused an increase in the production of cartilage-destroying matrix metalloproteinases (MMPs) (Loeser et al., 2005). Thus, the elevated levels of MMPs found in articular cartilage and synovial fluid of OA patients may in part be due to the accumulation of AGEs.

Chondrocyte density in the superficial zone of normal, undamaged cartilage of the femoral head decreases by up to 50% in adults over the age of 80 compared to adults aged 40 and under (Quintero et al., 1984). Cell density in the superficial zone of cartilage is especially important because it protects deeper zones from mechanical stress and is also the area of cartilage most susceptible to damage (Fox et al., 2009; Lotz and Loeser, 2012). When areas of articular cartilage fibrillation are examined, chondrocyte loss is apparent in the damaged regions suggesting that aged cartilage is unable to repair itself (Vignon et al., 1976). In OA cartilage, there is an overall loss of chondrocytes which cluster together at sites of fibrillation in an attempt to mend the damage (Lotz et al., 2010). Since chondrocytes exhibit poor replication properties, cartilage is unable to regenerate and irreparable damage is inevitable (Fox et al., 2009).

In addition to a reduction in the total numbers of chondrocytes, senescent cells also become less responsive to growth factors involved in anabolism. Cultured chondrocytes from aged cartilage produce less proteoglycans and collagen when treated with insulin-like growth factor 1 (IGF-1) or transforming growth factor-β (TGFβ), compared to chondrocytes from young individuals (Guerne et al., 1995; Loeser et al., 2014; Lotz and Loeser, 2012). In particular, IGF-1 is an important inducer of ECM regeneration while also acting as an anti-catabolic mediator by decreasing MMP-13 production in chondrocytes (Lotz and Loeser, 2012). An aberrant response to IGF-1 is also observed in OA, where chondrocytes are less responsive to IGF-1 compared to chondrocytes from non-OA cartilage (Doré et al., 1994). Further evidence from aged chondrocytes suggests that catabolic signalling is enhanced. Compared to chondrocytes from young individuals, those from aged donors produce increased levels of MMPs when incubated with IL-7 (Long et al., 2008). The skewed response towards catabolic rather than anabolic signalling demonstrates another mechanism by which repair and maintenance of articular cartilage is diminished with age.

3.2. Meniscus

Changes in the ECM of the meniscus have also been described. Post-traumatic meniscal damage has long been associated with OA, but there is also increasing research suggesting that age-related changes to the meniscus contribute to the disease as well. Pauli et al. compared the menisci of donors between the ages of 23–92 years old (Pauli et al., 2011). They discovered that in aged patients devoid of OA, meniscal tissue exhibited increased levels of proteoglycans, decreased cell density with the appearance of focal acellular zones, and evidence of degeneration (Pauli et al., 2011). Changes in collagen fibre organization was also observed which may be linked to accumulation of meniscal AGEs (Pauli et al., 2011; Takahashi et al., 1998). Similar to articular cartilage, a pro-inflammatory environment is observed in meniscal tissue where there is an age-related increase in IL-7 (Tsujii et al., 2017). In OA patients, the menisci typically exhibit severe fibrillation and tears at the periphery whereas in aged individuals who have never suffered joint trauma the tissue exhibits very mild internal lesioning. There is also a loss of proteoglycan in the superficial zone of OA menisci, whereas aged tissues demonstrate an overal increase in proteoglycan levels. These observations suggest that degeneration of the meniscus that results from normal ageing begins as a break-down of the internal meniscal structure rather than at the surface of the tissue (Pauli et al., 2011). While the exact mechanism responsible for age-related degeneration of the meniscus is unknown, this type of damage is common and presents as internal tears of the tissue rather than the acute perimeter tears that are associated with sports injuries. Age-related changes in the composition of the ECM and loss of meniscal fibrochondrocytes causes the meniscus to become more vulnerable and prone to tears which become more difficult to repair with age (Tsujii et al., 2017).

3.3. Bone

Age also has a profound impact on the skeleton which becomes less robust, less able to repair itself and therefore more likely to succumb to OA (Fig. 1B) (Li et al., 2013). Adult bone is continuously remodeled by the activity of osteoclasts and osteoblasts (Almeida and OBrien, 2013). Osteoclasts are derived from hematopoietic stem cells and are responsible for the breakdown or resorption of bone. Osteoblasts are derived from mesenchymal stem cells and produce new bone matrix. With ageing, an imbalance exists whereby the amount of bone resorbed by osteoclasts is not fully restored by the generation of new bone from osteoblasts. This ultimately leads to a loss of bone mass and strength as well as increased porosity (Almeida and OBrien, 2013; Zebaze et al., 2010). The inability to form sufficient bone is primarily due to a decrease in the number of osteoblasts present in bone with age. Two potential factors leading to the depletion of osteoblasts are an age-related decline in the number of mesenchymal stem cells as well as an increased likelihood of the progenitor cells to adopt an adipocyte-like phenotype instead of osteoblast characteristics (Zhou et al., 2008). In addition to the decrease in osteoblast population, a concomitant decline in the production of osteocytes is observed. Osteocytes, the third type of bone cell which are derived from osteoblasts, are found inside lacunae within the bone matrix where they signal with osteoclasts and osteoblasts to regulate bone remodeling (Bonewald, 2011a). A loss of these cells with ageing impairs the remodeling process and contributes to

bone damage. Enhanced osteocyte apoptosis is also observed in OA. Following microdamage to the subchondral bone, proapoptotic regulators are elevated in osteocytes which trigger the recruitment of osteoclasts to begin bone resorption (Bonewald, 2011b). Importantly, in the context of aged bone, the loss of osteoblasts hinders subsequent bone formation, thus contributing to a loss of bone mass in the early stages of OA.

A number of mediators contribute to bone damage with age. IGF-1, for example, acts as an anabolic mediator within the bone stimulating osteoblast activity (Bonewald, 2011b; Martel-Pelletier et al., 1998). In aged bone, the levels of IGF-1 decrease dramatically and this is associated with a reduction in bone mass and an increased incidence of fractures (Almeida and OBrien, 2013). A striking difference between age-related and OA-related changes in the bone occurs at the subchondral plate where a mild decrease in thickness has been observed in aged bone whereas OA bone increases in thickness. IGF-1 also appears to be one of the mediators responsible for the sclerosis observed in OA (Dequeker et al., 1993; Hilal et al., 1998). Osteoblasts from OA subchondral bone release significantly higher levels of IGF-1 compared to osteoblasts from normal bone (Hilal et al., 1998). When osteoblasts were harvested from sclerotic and non-sclerotic regions of OA subchondral bone, it was discovered that IGF-1 was increased in the cell supernatant from sclerotic osteoblasts. This suggests that IGF-1 is involved in the enhanced bone density associated with end-stage OA (Sanchez et al., 2008).

The lacunae in aged bone become hypermineralized in a process called micropetrosis. This decrease in lacunal size makes the bone more stiff and less able to deform under load (Busse et al., 2010). The inability of the rigid subchondral bone to distribute load slowly is a contributing factor to joint soft tissue damage and bone fracture (Goldring and Goldring, 2016). The exact causes of micropetrosis are unknown, but osteocyte death has been implicated. Osteocytes reside within lacunae, but maintain a pericellular space that allows the movement of nutrient rich fluid. Following osteocyte death, if a replacement cell is not generated quickly then the pericellular space can become mineralized in its absence. It is hypothesized that these age-related changes in bone mineralization can create a joint that is less compliant and more prone to damage which may progress to OA (Busse et al., 2010).

4. Cellular senescence and ageing

Cellular senescence is a signal transduction process that results in cells entering a state of growth arrest while remaining metabolically active (Hayflick and Moorhead, 1961). While senescence has important physiological roles in tissue homeostasis and tumor suppression, it is also central to the ageing process and is thought to contribute to a gradual functional decline (Toh et al., 2016). In the context of ageing, cellular senescence thought to be a result of age-associated damage and progresses due to several factors such as telomere erosion, DNA damage, and mitochondrial dysfunction (McHugh and Gil, 2018). Senescent cells (SnCs) can be identified by the expression of senescence-associated β-galactosidase (SA-β-Gal) and the tumor suppressor genes $p16^{INK4a}$ and $p53/p21^{CIP1}$. In addition to growth arrest, SnCs also produce and secrete a mixture of potent pro-inflammatory mediators which include cytokines, chemokines, and proteinases and is called the 'senescence-associated secretory phenotype' (SASP). The release of the SASP in turn results in a pro-inflammatory micro-environment that elicits an adaptive and innate immune response aimed at removing the SnCs (Toh et al., 2016).

4.1. Chondrocytes

An increase of SnCs has been observed in aged chondrocytes as evidenced by shortened telomere lengths and SA-β-Gal staining (Lotz and Loeser, 2012; Martin and Buckwalter, 2001). Moreover, chondrocytes from individuals with OA also show signs of senescence with DNA damage, $p16^{INK4a}$ expression, and telomere attrition (Harbo et al., 2012; Price et al., 2002; Rose et al., 2012). The levels of $p16^{INK4a}$ expression in chondrocytes correlate with the severity of disease (McHugh and Gil, 2018; Rose et al., 2012). Chondrocytes are rarely known to replicate in adult cartilage, thus the most important contribution of SnCs to the development of OA may be the SASP. Freund et al. identified 83 components of the SASP from different SnCs and grouped them based on their increased levels of expression (high, intermediate, and low) (Freund et al., 2010). Many of the SASP mediators were found to have intermediate and high increases in expression (2–4 fold and > 4 fold) in OA joints which could contribute to the pathogenesis of the disease. These include interleukins (IL-1β, IL-6, IL-7, and IL-8), matrix metalloproteinases (MMP-1, MMP-3, MMP-10, and MMP-13), insulin-like growth factors and adipokines. The effects of these SASP factors in joints include cartilage destruction, autocrine signalling to promote growth-arrest of senescent chondrocytes, and the recruitment of immune cells, which overall will promote a catabolic state (Greene and Loeser, 2015).

Persuasive evidence to support the ability of the SASP to contribute to the development of OA was provided by a recent study by Xu et al., where transplanted SnCs induced knee OA in normal mice (Xu et al., 2016). Following an intra-articular injection of senescent fibroblasts, mice developed severe cartilage degeneration, meniscal damage, subchondral bone remodeling, formation of osteophytes, referred pain, and impaired mobility. The SnCs were characterized by their SASP and expressed elevated levels of 23 pro-inflammatory mediators including IL-1α, IL-1β, IL-6, and TNF-α. These data elucidate how SnCs observed in the joints of older individuals may also drive the development of OA.

4.2. Bone

SnCs have also been identified in bone. Farr et al. have recently shown that SnCs and SASP factors accumulate over time in the bone and bone marrow of mice (Farr et al., 2016). When the expression of $p16^{INK4a}$ was examined in bone samples from young (6 month) and old (24 month) mice, the levels of the senescence marker were significantly higher in B cells, T cells, myeloid cells, osteoblast progenitors, osteoblasts, and osteocytes in the older animals. The osteocytes and myeloid cells from aged mice also had significantly higher expression of SASP factors including pro-inflammatory cytokines IL-1α, IL-6, TNFα, as well as a number of MMPs. In a human study, needle biopsies from a small number of young and old healthy volunteers were taken and similar results were observed where $p16^{INK4a}$ and 12 SASP factors were elevated in the bone tissue from older individuals. The study found that several cell types are affected by age-related senescence and the inferred consequence is that the SASP is promoting a pro-inflammatory microenvironment in the bone which may drive age-related bone diseases such as osteoporosis and OA (Farr et al., 2016). Further studies are needed to understand exactly how SnCs and the SASP are contributing to altered bone remodeling with age ultimately leading to OA.

5. Age-related changes in joint biomechanics

Joint movement is regulated by coordinated muscle contractions under the guidance of proprioceptive feedback and motor control. Disruption to these kinematic processes can predispose an individual to abnormal joint loading and misalignment which likely will culminate in OA (Roos et al., 2011). A decline in muscle mass (sarcopenia) is observed with advancing age such that muscle function is compromised in the aged individuals (Wilkinson et al., 2018). In young adults, muscles respond to anabolic stimuli such as mechanical stimulation and nutrition to promote mTOR (mammalian target of rapamycin) signalling and subsequent muscle protein synthesis. In older adults, anabolic arrest produces a shift towards muscle protein breakdown (reviewed in Wilkinson et al., 2018) which contributes to a loss of muscle mass and

strength. Muscle loss and weakness is also observed in OA patients and has been shown to contribute to the development of the disease. During the early stages of OA, quadricep strength declines which renders the knee joint less stable thereby potentiating the progression of joint damage and cartilage loss (De Ceuninck et al., 2014; Knoop et al., 2012; Toda et al., 2000). Unfortunately, longitudinal clinical studies demonstrating that this muscle atrophy precedes OA are lacking, but animal models provide compelling evidence to support this hypothesis. In rabbits, administration of *Botulinum* toxin type-A into the quadriceps muscle caused a decrease in muscle mass and strength that led to cartilage degeneration (Youssefy et al., 2009). Another study in rabbits demonstrated that denervation of the vastus lateralis muscle prevented knee extensor activity and caused significant cartilage destruction at the end of a 90-day time course (Egloff et al., 2014). The cartilage degeneration in both studies was focal suggesting that the damage was caused by abnormal joint biomechanics as a result of the muscle weakness (Egloff et al., 2014; Youssefy et al., 2009).

6. Age-related changes in joint innervation

Proprioception also deteriorates in normal ageing and has been highlighted as a causal factor for OA development. In a study comparing knee proprioception in young, aged, and OA volunteers, it was found that joint position sense was negatively correlated with age (Pai et al., 1997). When those with OA were compared to age-matched controls, the proprioceptive capacity of the knee decreased further in those with arthritis. Furthermore, proprioceptive impairment in OA patients was proportional to the severity of the disease. The fact that proprioceptive decline preceded OA in a group of these individuals suggests that this age-related loss of sensory feedback may contribute to OA (Pai et al., 1997). A decline in proprioception leads to abnormal joint loading resulting in local cartilage lesioning and bone deformation consistent with OA. Animal models of ageing provide further evidence to support proprioceptive loss and the development of OA. C57BL/6 mice commonly develop knee OA with increasing age and histological analysis reveals that there is an age-related decline in large-diameter sensory fibres innervating the knee joint (Salo and Tatton, 1993). The loss of mechanosensitive nerves is observed in both the subclinical phase of OA as well as in animals with radiographic evidence of OA. Elsewhere, it has been found that there is a decrease in joint sensory nerves in old Dunkin Hartley guinea pigs and horses with advanced OA (McDougall et al., 2009; Pujol et al., 2018). Furthermore, peripheral sensitization due to the algogenic neurotransmitter substance P is diminished in old animals indicating an impairment of normal nociception and an incapacity for corrective joint loading (McDougall and Schuelert, 2007). Thus, a loss of proprioceptors and altered nociception likely contribute to the development of age-related OA.

7. Ageing and inflammation

A chronic, low-grade pro-inflammatory state occurs as we get older and this process has been termed 'inflamm-ageing' (Franceschi et al., 2000). This systemic and local inflammation observed with ageing is found in joints and has the potential, therefore, to contribute to the development and progression of OA. The proposed mechanism for inflamm-ageing is the combined accumulation of antigenic load, cell senescence, an increase in adiposity, and changes in the endocrine system (Greene and Loeser, 2015). Serum levels of pro-inflammatory mediators such as TNF-α, IL-6, and C-reactive protein (CRP), become elevated as we age and are known to be involved in the inflamm-ageing process (Singh and Newman, 2011). In the context of OA, levels of IL-6 and CRP have been found to be higher in individuals with knee OA than in age-matched non-arthritic subjects (Livshits et al., 2009; Spector et al., 1997). The elevated levels persist and continue to progress with the disease even at 5–15 years following initial diagnosis. In another longitudinal study, Stannus et al. discovered that the levels of TNF-α and CRP correlated with pain in OA and it was subsequently found that levels of the soluble TNF-α receptor were inversely associated with levels of physical function in individuals with OA, possibly because of debilitating pain (Penninx et al., 2004; Stannus et al., 2013).

The increase in adiposity with age is a compelling factor in the development of OA because it affects several potential mechanisms. Obesity is a risk factor for OA and the increased fat-content and loss of muscle in ageing adults can contribute to altered biomechanics of joints (De Ceuninck et al., 2014; Godziuk et al., 2018; Runhaar et al., 2011; Toda et al., 2000). In addition to an increase in joint loading associated with obesity, the greater amounts of adipose tissue can create a pro-inflammatory state both systemically and locally in the joint which can expedite OA development (Greene and Loeser, 2015). The relationship between adipose tissue hypertrophy, inflammatory markers, and joint loading was assessed in older adults with OA in the IDEA clinical trial (Messier et al., 2013). Also assessed was whether exercise and diet affected any of these parameters. It was found that serum IL-6 correlated with the level of adipose tissue and that diet and exercise significantly decreased both. Weight loss led to decreased IL-6 concentrations in the circulation and reduced reported pain levels suggesting that adiposity is an important factor in inflamm-ageing and in the promotion of OA symptoms.

The adipokine, adiponectin has also been found to be significantly elevated in the serum of older individuals (Laughlin et al., 2007) as well as in patients with end-stage OA (de Boer et al., 2012). Patients undergoing total knee replacement surgery had elevated levels of adiponectin that correlated with the degree of synovitis (de Boer et al., 2012). A recent study by Conde et al. suggests that the infrapatellar fat pad and synovium may be local sources of pro-inflammatory molecules (Conde et al., 2014). This study found that levels of leptin and chemerin mRNA are higher in OA patients compared to tissues from healthy controls. Both of these adipokines have been found to cause MMP and prostaglandin release when added to chondrocyte cultures. Other research into the potential role of the fat pad in knee OA demonstrated a surprising anti-catabolic effect when fat pad media was co-cultured with chondrocytes; however, further research is needed to understand the exact contribution of the infrapatellar fat pad to OA pathogenesis (Bastiaansen-Jenniskens et al., 2012).

8. Frailty and osteoarthritis

A compelling new field of research centres around the relationship between frailty and OA. Frailty is defined as an increased vulnerability to stressors which enhances the risk of dependency on others and/or death (Rockwood and Mitnitski, 2007). It can be assessed clinically using either the 'Frailty Index' which dynamically quantifies a broad spectrum of health deficits of an individual, or the 'Frailty Phenotype' which characterizes frailty on the basis of five factors (unintentional weight loss, self-reported exhaustion, weakness, slow walking speed and low physical activity) (Fried et al., 2001; Rockwood and Mitnitski, 2007). Frailty, like OA, is commonly observed with increasing age and the pro-inflammatory markers implicated in inflamm-ageing, IL-6, TNF-α, and CRP, are also elevated in frail individuals (Giovannini et al., 2011). It is conceivable that these inflammatory factors found in frail individuals could drive OA development (Fig. 1C).

Within the past five years, six clinical studies have been published where the primary aim of the study was to assess the relationship between frailty and OA (Bindawas et al., 2018; Castell et al., 2015; Meessen et al., 2018; Misra et al., 2015; Veronese et al., 2017; Wise et al., 2014). Despite using different methodologies to assess frailty, all of these studies demonstrated that suffering from OA was significantly associated with the likelihood of being considered frail (Table 1). The percentage of people with OA that were considered frail ranged from 24 to 60%. When multiple sites of OA were considered it was found that arthritis affecting the hip had an increased risk of frailty compared to arthritis of the knee, perhaps due to greater disability associated with

Table 1
Summary of clinical studies assessing the relationship between osteoarthritis and frailty.

Author (Year)	Type of OA	Sex	Summary of Results
Wise et al. (2014)	Hip	Male	• Participants with OA or have undergone a hip-replacement surgery are 1.26 times more likely to be frail compared to non-arthritic participants • Clinical OA was strongly associated with the progression of frailty • Hip pain was associated with frailty
Misra et al. (2015)	Knee	Male & Female	• Knee OA associated with greater prevalence and risk of developing frailty • Participants with OA had a 60% higher prevalence of frailty • The severity of OA, as determined by the Kellegren & Lawerence score, was significantly correlated with prevalence of frailty
Castell et al. (2015)	Hand, Hip, and/or Knee	Male & Female	• The presence of OA (in any joint) is significantly associated with frailty (odds ratio: 2.96) • The odds of frailty were four times higher when the hip was the affected joint (odds ratio: 4.41) • The odds of frailty were over eight times higher when the participant had OA in the hand, knee, and hip (odds Ratio: 8.95)
Bindawas et al. (2018)	Knee	Male & Female	• The presence of unilateral knee pain at baseline was associated with an increased chance of developing frailty (odds ratio = 1.89) over the 6 year longitudinal study period • Pain in both knees at baseline increased risk of developing frailty even further (odds ratio = 2.21)
Veronese et al. (2017)	Hand, Hip, and/or Knee	Male & Female	• Women were more likely to be considered frail than men • Participants that suffered from OA pain had a higher incidence of frailty than those without OA pain
Meessen et al. (2018)	Hip or Knee	Male & Female	• Women were more likely to be considered frail than men • 35% of participants with hip OA were considered frail • 24% of participants with knee OA were considered frail • 84% of frail participants had a serious comorbidity (undefined)

hip OA. Several studies also concluded that women were more likely to be frail which may be linked to a sex-related differences in disease presentation corroborating the observation that OA rates are higher in older women than men (Meessen et al., 2018; Veronese et al., 2017).

Additionally, OA pain is associated with enhanced risks for frailty where people with sore joints were more likely to be considered frail compared to those without significant joint pain (Veronese et al., 2017; Wise et al., 2014). Individuals with OA pain were also more likely to become frail as the disease progressed (Bindawas et al., 2018). Pain is the primary concern of people living with OA and it is the main reason patients seek medical assistance. It is directly linked to a loss of physical function and is often associated with poor mental health both of which are observed in frail individuals (van Dijk et al., 2008).

Research aimed at elucidating the underlying mechanisms linking OA and frailty has been scarce. Potential links include elevated levels of pro-inflammatory markers in the circulation as well as age-related muscle atrophy and decreased physical activity (Misra et al., 2015). Blaum et al. assessed the association between obesity and frailty in older women and found that BMI and CRP levels correlated with frailty (Blaum et al., 2005). Since elevated CRP levels are known to occur in individuals living with OA (Spector et al., 1997), it is possible that CRP could provide a link between OA and frailty although this requires validation. Sarcopenia is another common denominator between frailty and OA (Milte and Crotty, 2014), but whether treating sarcopenia could improve both conditions is unknown. As far as can be discerned, there are no published articles assessing frailty in pre-clinical models of OA. With the growing body of clinical evidence linking the two conditions, further research is required to understand the underlying mechanisms and identify potential targets to prevent the development of frailty in OA patients.

While it is clear that OA can render an individual more frail, we hypothesise that frailty itself could precipitate OA-like joint degeneration. Frail individuals have greater muscle atrophy (Misra et al., 2015) which makes joints less stable and therefore more susceptible to biomechanical damage. Pro-inflammatory cytokines are known to be elevated in the systemic circulation of frail individuals (Giovannini et al., 2011) and accumulation of these mediators in synovial joints would likely lead to catabolism of joint structures and thence arthritis. Finally, a frail person is more prone to falls (Fried et al., 2001) which could result in the development of post-traumatic OA. Future studies are required to test this hypothesis which may reveal novel mechanisms and new therapies to treat OA.

9. Conclusion and future research

By exploring the relationship between ageing, frailty and OA, it is increasingly apparent that OA is not simply a result of 'wear and tear' of the joint. Changes in the ECM of cartilage, a decline in chondrocyte population and altered chondrocyte signalling with age indicate that aged cartilage is more likely to become damaged and less able to repair itself. Similarly, in subchondral bone, an age-related shift towards bone resorption without adequate bone replacement compromises the integrity of the joint and OA is a likely sequalae. Attempts are underway to improve the repair capacity of articular cartilage and bone by using stem-cell based therapeutic approaches. While pre-clinical models have shown promising results, clinical data are unconvincing largely due to a limitation in the long-term viability of the regenerated tissues (Jevotovsky et al., 2018).

The presence of SnCs in the joint of older individuals and those with OA has supported the study of senolytic agents. Preclinical studies using these drugs that target SnCs in OA and sarcopenia have provided promising results and a clinical trial of the senolytic UBX0101 is currently underway in OA patients (Cosgrove et al., 2014; Jeon et al., 2017; Sousa-Victor et al., 2014). While well-designed clinical trials are needed to ensure efficacy and safety, these drugs may be able to prevent age-related development of OA or act as disease modifying agents for people at risk of contracting OA.

Inflamm-ageing is thought to contribute to a variety of age-related conditions including OA. Elevated levels of pro-inflammatory cytokines have been measured in old and OA individuals and have become appealing targets for the treatment of OA. Surprisingly, however, when age-associated OA was examined in IL-6 knockout mice, these animals developed more severe OA than aged wild-type animals (de Hooge et al., 2005). This study suggests that targeting a single mediator of inflamm-ageing may not be sufficient to treat OA effectively. It is more likely that a cocktail of various anti-inflammatory and pro-resolution agents will be necessary to alleviate the symptoms and development of OA in frail, ageing populations.

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