Osteoarthritis and Cartilage 33 (2025) 921–932

Osteoarthritis and Cartilage

OARSI OSTEOARTHRITIS RESEARCH SOCIETY INTERNATIONAL

Review

How aging causes osteoarthritis: An evolutionary physiology perspective

David Gems *

Institute of Healthy Ageing, and Department of Genetics, Evolution and Environment, University College London, Gower Street, London, UK

ARTICLE INFO

Article history:
Received 20 January 2025
Accepted 5 May 2025

Keywords:
Antagonistic pleiotropy
Chondrocyte
Evolutionary medicine
Hyperfunction
Osteoarthritis
Programmatic theory

SUMMARY

Late-life diseases result from the poorly understood process of senescence (aging), which is largely genetically determined. According to a recently proposed evolutionary physiology-based account, the multifactorial model, senescence is largely caused by evolved but non-adaptive programmatic mechanisms specified by the wild-type (i.e. normal) genome. These act together with disruptions to wild-type function (due e.g. to infectious pathogens, mechanical injury and malnutrition) in a variety of combinations to generate diverse late-life diseases. Here, I explore the utility of this model by testing its capacity to provide an account of one complex, late-life disease, osteoarthritis (OA), and suggest a framework for understanding OA etiology. In this cartilage-focused framework, a core OA disease mechanism is a futile (non-adaptive) developmental program of endochondral ossification, in which hypertrophic articular cartilage chondrocytes alter joint architecture. Programmatic changes prime chondrocytes for futile program activation, which can be triggered by secondary causes of OA (e.g. joint mechanical injury). I suggest that an evolutionary cause of this priming, involving antagonistic pleiotropy, is selection to maximize early-life tissue repair benefits at the expense of late-life programmatic costs.

> "The physician is constantly referring to the biologist for a scientific basis for geriatrics, and finding that it is not there" Alex Comfort[1]

The biological process of senescence (aging) remains poorly defined and, consequently, our understanding of late-life disease etiologies remains far from complete. Arguably, the main purpose of biogerontology, the study of the biology of aging, is to provide an account of the mechanisms of senescence in terms of general principles that can guide research on late-life disease.[1] Thus far, such accounts have remained fragmentary, and with only limited capacity to do so. However, recent years have seen the emergence of programmatic theory, a promising evolutionary physiology-based conceptual framework that combines evolutionary and proximate mechanisms to explain the causes of aging. This framework includes the hyperfunction (or developmental) theory of aging,[2,3] among other programmatic mechanisms,[4] and a multifactorial model of the origins of late-life diseases[5] (see Box 1 for glossary of key terminology from evolutionary physiology).

In this article, I investigate the capacity of the multifactorial model to explain a test-case complex late-life disease, osteoarthritis (OA). To do this, I have used a conceptual research approach, wherein an existing theory is tested by examining and repurposing existing published findings.[6] The result is a proposed account of the multifactorial etiology of OA in terms of general biogerontological principles. This work endeavors to bridge the conceptual gap between biogerontology and rheumatology, in a manner in which the former more usefully informs the latter.

The multifactorial model

The foundation of the multifactorial model is the evolutionary theory of aging.[7,8] The maximum lifespan of different mammalian species ranges from ~3 years in small rodents to over 200 years in bowhead whales. From this, it is evident that the aging rate is largely a function of the normal genome, as shaped by evolution. Senescence is not an adaptation, but rather a non-adaptive by-product of the evolutionary process.[8] Here, a major determinant is the declining force of natural selection with increasing age,[9] sometimes referred to as the late-life selection shadow. Many genes are pleiotropic (affecting multiple characteristics), and a given new allele can result in phenotypic changes that, in different ways, both increase and reduce fitness - a property described as antagonistic pleiotropy (AP). Due to the selection shadow, where beneficial effects occur earlier in life

* Correspondence to: Institute of Healthy Ageing, and Department of Genetics, Evolution and Environment, University College London, Gower Street, London WC1E 6BT, UK.
E-mail address: david.gems@ucl.ac.uk.

https://doi.org/10.1016/j.joca.2025.05.001

Box 1
Glossary of evolutionary physiology terminology.

Antagonistic pleiotropy: A property of genes, where gene action is both beneficial and detrimental to function, health and/or evolutionary fitness. If detriments occurs later in life, when selection is weaker, such genes may be favored by natural selection due to their early benefits, and contribute to senescence (aging).
Biological constraint: A property of organisms and/or their ecology that prevents the evolution of traits that would increase fitness. An underlying cause of antagonistic pleiotropy.
Evolutionary medicine: The study of how evolutionary processes determine health and disease (including diseases of later life).
Evolutionary physiology: The study of how biological mechanisms underlie evolutionary processes, important for senescence (aging), where late-life deterioration (including diseases) is largely the consequence of evolutionary processes.
Hyperfunction: Where wild-type gene function and processes actively contribute to disease, particularly senescent pathology.
Quasi-program: A cause of pathology, particularly senescence, entailing a relatively ordered series of biological processes that do not promote fitness. Quasi-programs in aging may result from futile run-on of wild-type programs that are beneficial earlier in life, or be triggered later in life.
Maturo-developmental: This describes developmental processes, involving e.g. growth, differentiation and morphogenesis, that occur during adulthood, including those linked to reproduction, tissue repair and immunity.
Multifactorial model of ageing: Argues that two main types of cause act in combination to generate diseases of aging: disruptions (wholly deleterious factors such as infectious pathogens, injury, mutations) and programmatic changes arising from the normal genome (e.g. quasi-programs).
Programmatic theory: A category of interrelated theories that share a view of aging as evolved and genetically determined but non-adaptive, and primarily the consequence of wild-type gene action through non-adaptive, often development-like processes.

but deleterious ones much later, natural selection may favor the new allele, though it promotes pathology (senescence) as well as fitness[7] (Fig. 1A).

Though evolutionary theory largely explains why aging exists, it leaves undefined the proximate mechanisms of senescence, including the precise causes of late-life disease. Such an explanation in terms of evolutionary physiology[8] is what programmatic theory aims to provide. Here, senescent changes are specified by the genome, as earlier life traits are, but differ from them in being non-adaptive. One proposed form of programmatic aging involves developmental functions that in later life are executed in a futile and pathogenic fashion.[2] These are *quasi-programmed*, i.e. programmed in the mechanistic sense, but not the adaptive sense.[3]

According to this view, cells and tissues contributing to pathology often exhibit *hyperfunction*, i.e. a level of activity that is in excess of what is optimal to maintain health[3] (Fig. 1B) rather than, as is more traditionally assumed, passive breakdown of cellular function (due e.g. to molecular damage). Such quasi-programs may result from futile run-on of ontogenetic functions[2,3] or, perhaps more plausibly, from triggering in later-life of adult, maturo-developmental programs (e.g. of tissue homeostasis, wound-healing and reproduction).[10,11]

A previously influential theory of aging is that it is the result of molecular damage, particularly reactive oxygen species (ROS) generated as a by-product of mitochondrial respiration.[12] A proposition of programmatic theory is that the increased levels of oxidative damage observed in later life are more a consequence than a cause of senescent changes.[13] In line with this, treatment with antioxidants has little effect on senescence, including OA.[14]

Programmatic theory argues that genes frequently exhibit AP due to the ubiquity of biological constraint, arising in particular from the interconnected nature of biological functions.[4] Thus, selection for a change in one trait can result in a non-selected change in a coupled trait, which may promote pathology through hyperfunction or hypofunction (Fig. 1C).

Though programmatic theory goes some way towards an account of aging in terms of evolutionary physiology, it is insufficient to provide detailed explanations of late-life disease etiology. To overcome this, the multifactorial model was devised by integrating programmatic theory with Vladimir Dilman's earlier four models theory of late-life disease causation.[5,15] In outline, the recent model is as follows.

Late-life diseases are typically multifactorial in etiology. The multifactorial model identifies two broad categories of etiology that combine in diverse ways to generate late-life disease[5] (Fig. 1D). The first category, *disruptions*, includes the diverse insults that cause most diseases of earlier life - infectious pathogens, sub-optimal nutrition, mutation (somatic and inherited), mechanical injury, and so on. Here, in each case, normal biological function is disrupted by such factors, leading to disease. The second category includes programmatic changes, consequences of the normal genome.

As an example, consider sudden acute respiratory syndrome (SARS), a frequent cause of death during the recent COVID-19 pandemic. This largely afflicted the elderly, due to age-related hyperfunction of the innate immune system, of likely programmatic origin. SARS occurred when infection with the coronavirus SARS-CoV-2 triggered a lethal immunological quasi-program (cytokine storm). Thus, here SARS is a multifactorial disorder, due to the combined effects of programmatic changes (immunosenescence) and a disruption (a virus).

Osteoarthritis is a function of biological age

OA is a slow, progressive, degenerative, multifactorial disease of joints involving loss of articular cartilage, bone overgrowth and inflammation. It particularly afflicts the knee and hip joints, and those of the lower back and the neck. The affected joints can become stiff and painful, seriously affecting around 10% of men and 18% of women over 60.[16] Reflecting the numerous existing theories of aging, there are many theories about the causes of OA.[17] These include accumulated mechanical wear-and-tear to joint cartilage[18]; glycation of cartilage collagen[19]; chondrocyte apoptosis due to mitochondrial dysfunction[20] or deficiency in the unfolded protein response[21]; accumulation of senescent chondrocytes[22] caused by DNA damage[23]; epigenetic changes[24]; deficiency in autophagy[25]; inflammaging[26]; the microbiome[27]; and the hallmarks of aging.[28]

Comparing these theories with the multifactorial model, two particular and related shortcomings stand out: an overemphasis on disruption-type explanations, and a neglect of the question of why OA only emerges in later life. Disruption-type theories of aging sometimes explain the delayed onset of senescence in terms of slow, time-dependent cumulative processes, for example, as gradual accumulation of DNA damage. Yet OA onset is less a function of time than of the proportion of the overall life history that has been played out, as is evident from the comparative biology of this disease.

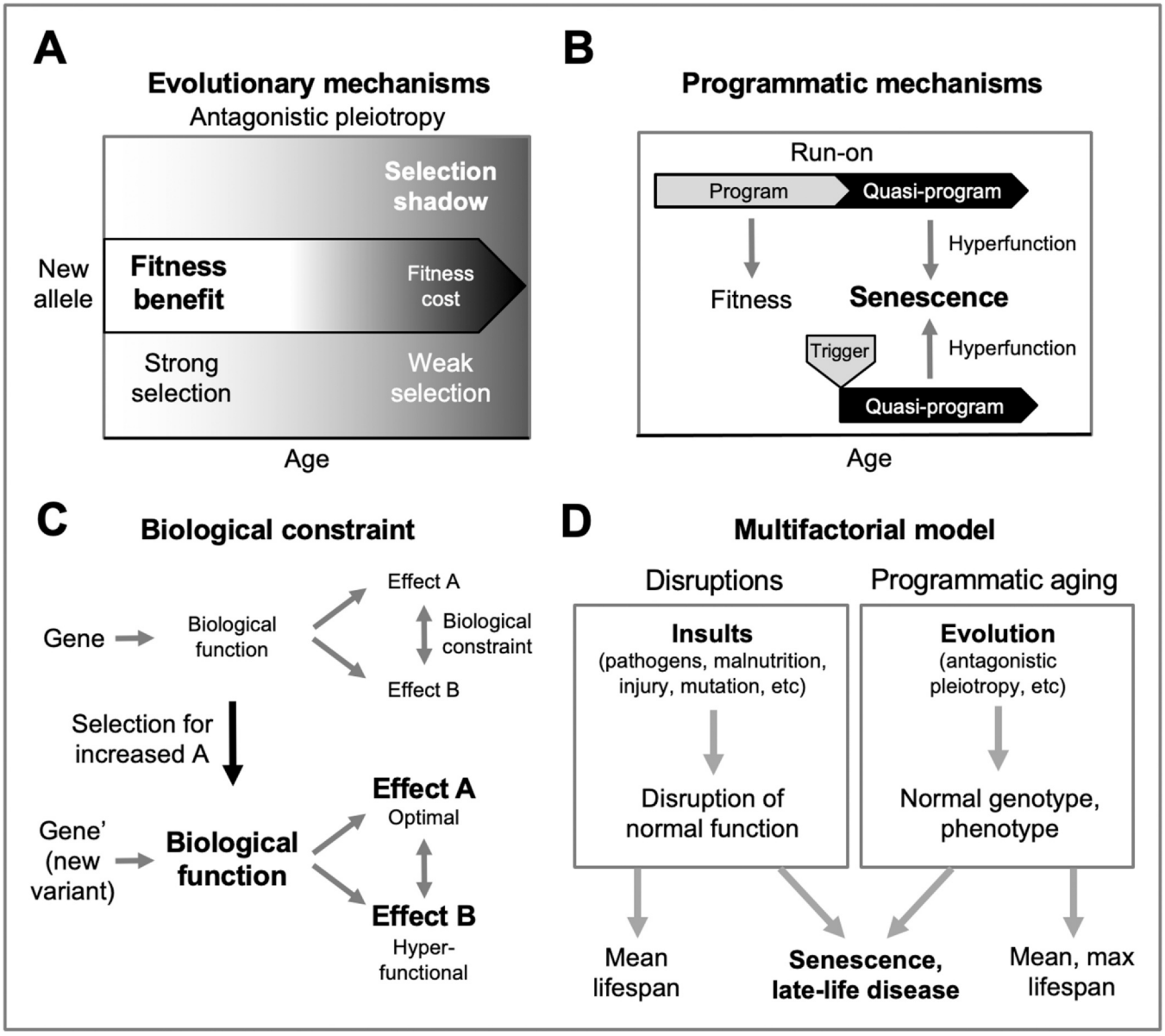

Fig. 1

Osteoarthritis and Cartilage

The multifactorial model and its constituent concepts. A general evolutionary medicine model for senescence (aging). A, Antagonistic pleiotropy. A new allele that confers a fitness benefit in early life but a fitness cost (e.g. increased pathology) in later life may cause a net benefit in overall fitness due to the selection shadow.[7] B, Examples of programmatic mechanisms of aging. Quasi-programs that contribute to senescence involve non-adaptive action of wild-type biological programs,[3] and may arise due to futile run-on of wild-type programs (as in presbyopia),[83] or they may be triggered by other events (as in rheumatoid arthritis).[10] C, Biological constraint as a cause of antagonistic pleiotropy. Where two traits, A and B, are coupled due to biological constraint, selection for an increase in A results in a non-adaptive increase in B, which in this case is hyperfunctional (i.e. pathogenic). Likewise, selection for reduced A can result in a non-adaptive reduction in B that is hypofunctional (also pathogenic).[4] D, Multifactorial model, simplified scheme.[5] This depicts the multifactorial etiology typical of late-life diseases as arising from two broad categories of cause: disruptions to normal function (e.g. infectious pathogens, mechanical injury, mutation) (left), and programmatic consequences of the normal genotype (right), whose pathogenicity originates in the evolutionary process. Variation in disruptions suffered contributes to inter-individual differences in lifespan and to mean lifespan. By contrast, programmatic aging sets maximum as well as mean lifespan; for example, the longer maximum lifespan of humans compared to chimpanzees is a function of the normal genome and programmatic mechanisms, not disruptions.

OA occurs widely among mammals, including lions, hyenas, bears, camels, elephants and dolphins, which in the latter particularly affects the humeral trochlea at the base of the flipper.[29,30] Longer-lived species develop OA later than shorter-lived species. Comparing approximate estimates for age of onset of OA and mean lifespan in selected species, one sees mouse (*Mus musculus*), onset: 9–12 months, lifespan: 12–18 months; rabbit (*Oryctolagus cuniculus*), onset: 6–9 years, lifespan: 8–12 years; rhesus monkey (*Macaca mulatta*), onset: 16–20 years, lifespan: 25–30 years; human (*Homo sapiens*), onset: 50–60 years, lifespan: 80–85 years. Thus, the timing of OA onset approximately scales to lifespan across mammalian species that exhibit the disease.

The timing of OA is therefore a function of biological age (i.e. relative age), not chronological age. Such scaling to lifespan of time of onset is typical of many diseases of aging, illustrating how late-life disease is rooted in an underlying aging process that occurs at very different rates. These differences are specified by the normal genome and, ultimately, by the evolutionary process. Thus, the primary causes of OA and main determinants of its timing of onset are almost certainly programmatic, rather than disruption-based. Ultimately, OA, like other afflictions of old age, is a disease of evolution, fully explicable only in terms of evolutionary medicine.[31] Yet having said this, one disruption theory of OA is particularly well supported.

Osteoarthritis as a triggered quasi-program

The wear-and-tear theory argues that in joints, as in moving parts of machinery, the physical stress of repeated use leads to eventual wearing out.[18] This views OA as a disease of mechanical senescence. Supporting this, OA risk is increased by injury to joints, and also by imperfections in joint structure due to developmental or genetic abnormalities.[16] Similarly, obesity, which increases stress on weight-bearing joints, increases the likelihood of developing OA, particularly of the knee, where risk is increased three-fold[32] (though it should be noted that the increased low-grade inflammation that accompanies obesity also contributes to OA). But again, where the wear-and-tear theory falls short is in explaining why OA develops only later in life. For example, intra-articular knee fracture is 3–4 times more likely to trigger OA development after the age of 50.[33]

Here, the multifactorial model provides a hypothesis: that OA is the result of a triggered quasi-program (Fig. 1B). In this form of etiology, programmatic changes in later life create conditions in which quasi-program triggering becomes possible. According to this hypothesis, mechanical stress to joints acts as a trigger to initiate OA only once programmatic changes have occurred.

The causal relationship between trigger and quasi-program resembles that in a gun: though pulling the trigger is the cause of the gun firing, the major cause of the gunshot is the cartridge. Thus, the process of aging effectively loads the OA gun, such that triggers can lead to it firing. In line with this, stress on joints in later life may trigger disease onset, or damage from injuries to joints incurred early in life can lie latent for many years before leading in later life to OA.[34] In the latter case, the trigger was, as it were, being pulled earlier in life without consequence prior to quasi-program loading (Fig. 2).

Accounts of OA distinguish two forms: primary and secondary. Primary OA is sometimes described as idiopathic (in other words, a

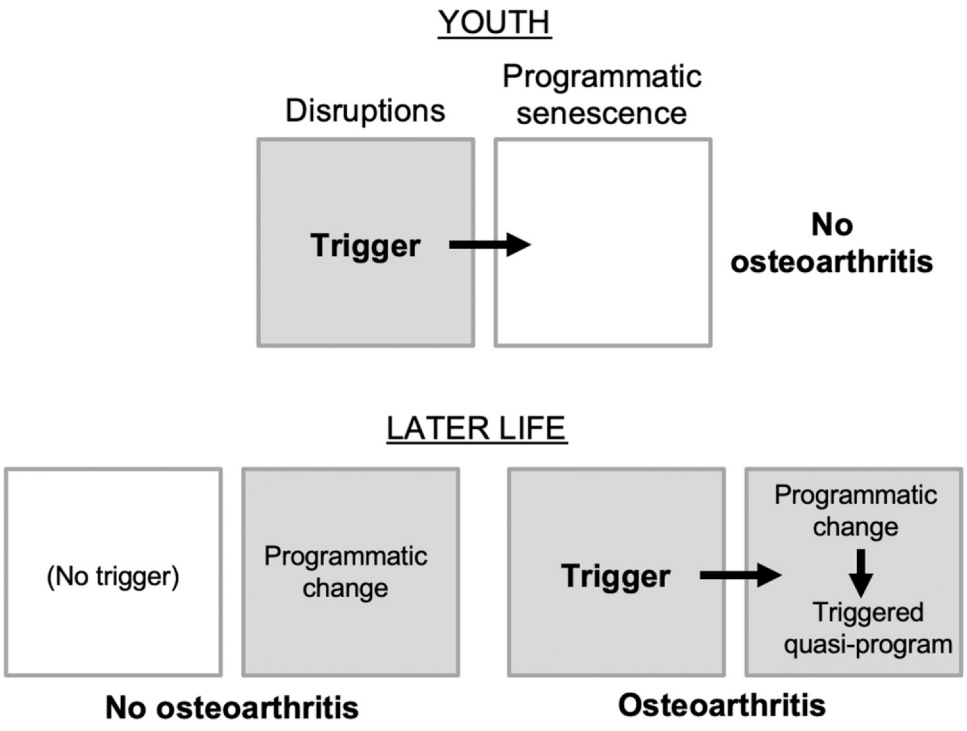

Fig. 2

Osteoarthritis and Cartilage

Osteoarthritis as a triggered quasi-program. Based on the multifactorial model (Fig. 1D); gray fill indicates active etiology. Top, in youth, disruptions (e.g. joint injury) do not trigger OA development (analogous to pulling the trigger of an unloaded gun). Bottom left, in later life, programmatic changes occur that predispose to OA (analogous to the loading of a gun), but may be insufficient to cause disease. Bottom right, disruptions trigger OA development, where programmatic changes create a predisposition. By the same principle, infection with coronavirus SARS-CoV-2 triggers fatal SARS far more frequently in the elderly than in the young (Fig. 1D).

disease of unknown cause). Secondary OA is a consequence of known causes, such as joint injury, gout, diabetes or obesity.[16] Arguably, primary OA is that arising from programmatic aging alone, while secondary arthritis involves additional accelerants of programmatic aging, particularly disease triggers, caused by disruptions or other quasi-programs.

Osteoarthritis as a programmatic disease

Next, let us consider the possible role of programmatic changes in OA. The programmatic theory predicts (i) that destructive programmatic mechanisms, linked in particular to tissue-level homeostasis, emerge in joints in later life; and (ii) that these will involve triggered programs, leading to destructive developmental and morphogenetic changes. Several features of OA are broadly consistent with this scenario. First, cell types that control tissue homeostasis in joints (particularly chondrocytes) show hyperfunctional and quasi-programmed changes in later life (described below). Second, OA does involve complex and concerted developmental and morphogenetic changes.

Consider first how overall joint structure changes during OA (Fig. 3). The surfaces of the two opposing bones are protected by a layer of smooth, tough hyaline cartilage, which is bathed in synovial fluid. The joint is surrounded by a joint capsule, lined by the synovial membrane (synovium), which secretes into the synovial fluid lubricants such as hyaluronan and lubricin. In OA, the articular cartilage shrinks, growing thinner, while the synovium and capsule become hypertrophied. In terms of pathophysiology, a critical site of disease development is the boundary between the articular cartilage and the underlying bone (the subchondral bone). Here, futile activation of a bone formation (endochondral ossification) program takes place,[35] leading to loss of cartilage and changes in subchondral bone, including development of bone marrow pockets, a blood supply, and fluid-filled subchondral cysts.[16] In addition, at the junction of the articular cartilage and the synovium (Fig. 3), chondrocytes derived from the periosteum (bone sheath) promote the formation of bone spurs (osteophytes), which can restrict joint movement.[36] Thus, OA is a disease involving complex developmental and morphogenetic changes in joints, starting in later life.

A prediction of programmatic theory is that tissue-level changes leading to OA will result from hyperfunctional changes to cells. Four main cell types contribute to tissue homeostasis within the joint: osteocytes in the bone, synoviocytes (fibroblast- and macrophage-like) in the synovium and, particularly, chondrocytes that generate and maintain cartilage. Thus, key to deciphering the causes of OA is understanding how and why chondrocyte function changes in later life. Consequently, much research on OA has focused on age changes in chondrocytes, and it is here, arguably, that disruption-based explanations are particularly insufficient.

The senescent chondrocyte hypothesis

An influential disruption-type account of aging is that it is caused by molecular damage accumulation. In line with this, it has been proposed that cellular stress and molecular damage cause pathogenic changes in chondrocytes. One scenario is that this causes cell death, promoting OA. Apoptotic and dead chondrocytes have been observed in degenerating cartilage in OA,[37] and autophagy has been proposed as a mechanism that protects against chondrocyte apoptosis that otherwise promotes OA.[25] An alternative view is that aging chondrocytes show aberrant behavior, destroying articular cartilage, due e.g. to disruption of cellular signaling by elevated ROS levels.[14] More recently, such changes have been interpreted as DNA damage-induced cellular senescence,[23] suggesting that the accumulation of senescent cells causes OA.[22] But what exactly is cellular senescence?

During cellular senescence, cells exit the cell cycle and undergo a major differentiative change, becoming hypertrophic and hypersecretory. Senescent cells accumulate during aging, and exert pathogenic effects due mainly to hypersecretion.[38] The senescence-associated secretory phenotype (SASP) includes a variety of factors that alter the local tissue microenvironment in diverse ways, including proteases, growth factors and inflammatory cytokines.[39] Particularly striking was the finding that in aging mice elimination of senescent cells delayed onset of many late-life diseases, including cancer, atherosclerosis and kidney disease, and also markedly extended lifespan.[40]

Drawing on these advances, a cellular senescence theory of OA emerged, with good evidential support. In later life, chondrocytes from human articular cartilage show increased levels of two markers of cellular senescence, lysosomal β-galactosidase (senescence-associated β-galactosidase, or SA-β–Gal), and $p16^{INK4a}$ (p16) mRNA.[41] In mouse cartilage, p16 mRNA also increases with age.[41] If senescent chondrocyte accumulation is a cause of OA, then their elimination from osteoarthritic joints using senolytic drugs might ameliorate the disease.[23] Supporting this, in a mouse model of injury-induced OA, clearance of p16-positive cells in the p16–3MR transgenic mouse, or intra-articular injections of the senolytic compound UBX0101, reduced senescent chondrocyte numbers and SASP levels, and slowed progression of OA.[42]

But why do senescent chondrocytes accumulate? More broadly, the causes of cellular senescence leading to senescent cell accumulation in vivo remain unclear. One suggestion is that chondrocyte senescence is a consequence of DNA damage and cellular stress.[23] An alternative possibility, discussed next, is that such late-life alterations in chondrocyte function are a consequence of maturo-developmental change.

Reinterpreting cellular senescence

In recent years, a new perspective on cellular senescence has emerged.[43–45] A long-standing puzzle was why senescent cells should behave in so actively pathogenic a manner, particularly though SASP production. This was solved by the discovery that senescent cells have a developmental function, particularly in tissue remodeling.[46] For example, senescent fibroblasts contribute to wound healing in skin,[47] senescent stellate cells to tissue repair in liver,[48] and senescent cells play a role in tissue remodeling during embryogenesis[49] and parturition.[50]

This provides an explanation for the cellular hypertrophy and hypersecretory properties of senescent cells. Working in a coordinated fashion with macrophages, they enact tissue remodeling functions in various contexts, including major and minor tissue trauma. This includes debriding damaged tissue (e.g. breaking down extracellular matrix), preventing fibrosis, promoting re-epithelialization and laying down new extracellular matrix.[51]

Given that such tissue-remodeling processes are not part of the aging process, the term “cellular senescence” has become something of a misnomer, that is both confusing and obsolete. One proposed solution is to update terminology, for example, replacing “cellular senescence” with *remodeling hypertrophy*, “senescent cells” with *remodeling cells* and “senescence-associated secretory phenotype (SASP)” with *remodeling-associated secretory phenotype* (*RASP*).[44]

These considerations raise questions about the nature of putative senescent chondrocytes observed in OA tissue. Fibroblasts, in which cellular senescence is best characterized, play a similar role in connective tissue to that of chondrocytes in articular cartilage, and fibroblast-like synoviocytes in the synovium: tissue formation and homeostasis, and repair after trauma (e.g. bone fracture repair).[52] Moreover, remodeling fibroblasts engaged in wound healing show both SA-β-Gal and p16 expression.[47] That SA-β-Gal and p16

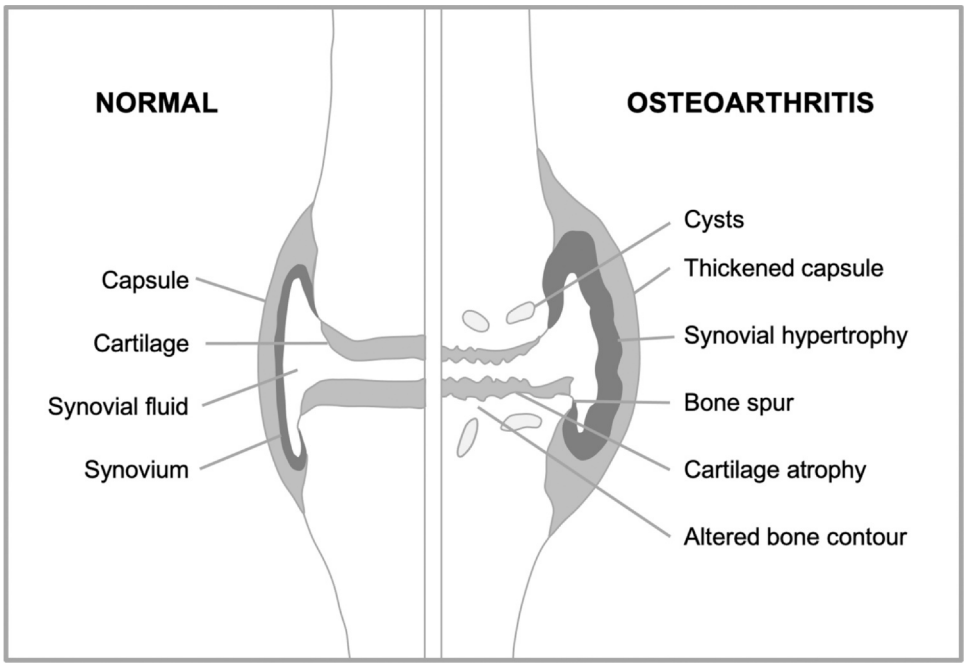

Fig. 3

Osteoarthritis and Cartilage

Developmental and morphogenetic changes occurring during osteoarthritis. Schematic representation of a knee joint that is normal (left), and with osteoarthritis (right). Major changes in the disease include a loss of the cartilage that allows smooth articulation of bones during joint movement, and overgrowth of new bone.

expression both occur during remodeling hypertrophy suggests that increases in these markers with increasing age in human chondrocytes[41] could reflect remodeling hypertrophy (i.e. chondrocyte hypertrophy). Similarities between (putative) chondrocyte senescence and chondrocyte hypertrophy have been previously noted.[53]

Developmental changes in chondrocytes in later life

An alternative view of the age-changes occurring in the cartilage chondrocytes is that they reflect quasi-programmed developmental change, as follows. Chondrocytes develop through a series of stages, first emerging from the differentiation of mesenchymal stem cells (chondroblasts), to perform the task of generating cartilage. They can then undergo hypertrophy, increasing 10–15-fold in volume[54] and becoming osteogenic, converting cartilage into bone in the process of endochondral ossification. Once their work is done, hypertrophic chondrocytes undergo apoptosis. The formation of articular cartilage requires, in a manner of speaking, that a program for osteogenesis be frozen in mid-stream. One interpretation of the development of OA is that this block fails, leading to run-on into futile osteogenesis.[35,55] Thus, plausibly, the age changes in chondrocytes that cause OA are better understood as remodeling hypertrophy that is part of an osteogenic quasi-program than as cellular senescence (Fig. 4).

Gene expression changes occurring during chondrocyte hypertrophy include a decrease in hyaline cartilage markers such as collagen type II, and SOX9, and high expression of runt-related transcription factor 2 (RUNX2), matrix metalloproteinase-13 (MMP-13), alkaline phosphatase, and collagen type X, a homotrimer-forming short chain collagen. Notably, articular chondrocytes in OA show features characteristic of hypertrophic differentiation, including expression of MMP-13, alkaline phosphatase, and collagen X.[56] Moreover, OA cartilage typically becomes mineralized,[35] with hypertrophic chondrocytes often co-localized with deposits of calcium pyrophosphate dihydrate crystals and hydroxyapatite.[57]

Taken together, this supports the view that a major driver of OA is an endochondral ossification quasi-program, previously described as "illegitimate hypertrophic differentiation",[35] involving chondrocyte hypertrophy. This appears to involve not so much an exact recapitulation of normal endochondral ossification, as a muddled attempt at one, with more emphasis on the earlier collagen breakdown stage than the later ossification stage; this is consistent with the axiom that quasi-programs are imprecise by nature.[58]

A critical question here is: what causes the late-life activation of this osteogenic quasi-program? Chondrocyte differentiation is subject to a complex system of autocrine, paracrine and endocrine regulatory control, including factors known to be involved in OA development.[35,59] Among these are BMP, Wnt and TGF-β signaling, the last which inhibits the progression from cartilage to bone, by acting on the ALK5 (activin-like kinase 5) TGF-β receptor.[60] Based on this, one suggested OA etiology is loss of inhibition by TGF-β (Transforming Growth Factor-β).[61]

A possible interpretation here is that loss of this critical off-switch contributes to the loading of the osteoarthritic gun (Fig. 2). Supporting this model, mice in which this TGF-β signal is blocked (by mutation of Smad3) show increased levels of collagen X-expressing cells (hypertrophic chondrocytes) in their articular cartilage, and OA-like joint degeneration, including formation of large osteophytes.[60]

Why might loss of the TGF-β off switch occur? This can be taken as a question about both evolutionary causes, which are the ultimate reason that aging occurs, and proximate mechanisms of aging. Here, it is helpful to consider a suggestion by evolutionary biologist George Williams for how AP might operate in terms of gene function, which used a hypothetical example involving a gene that promotes calcium deposition into bone. In his scenario, a new mutation in this gene enhances calcium deposition thereby accelerating bone

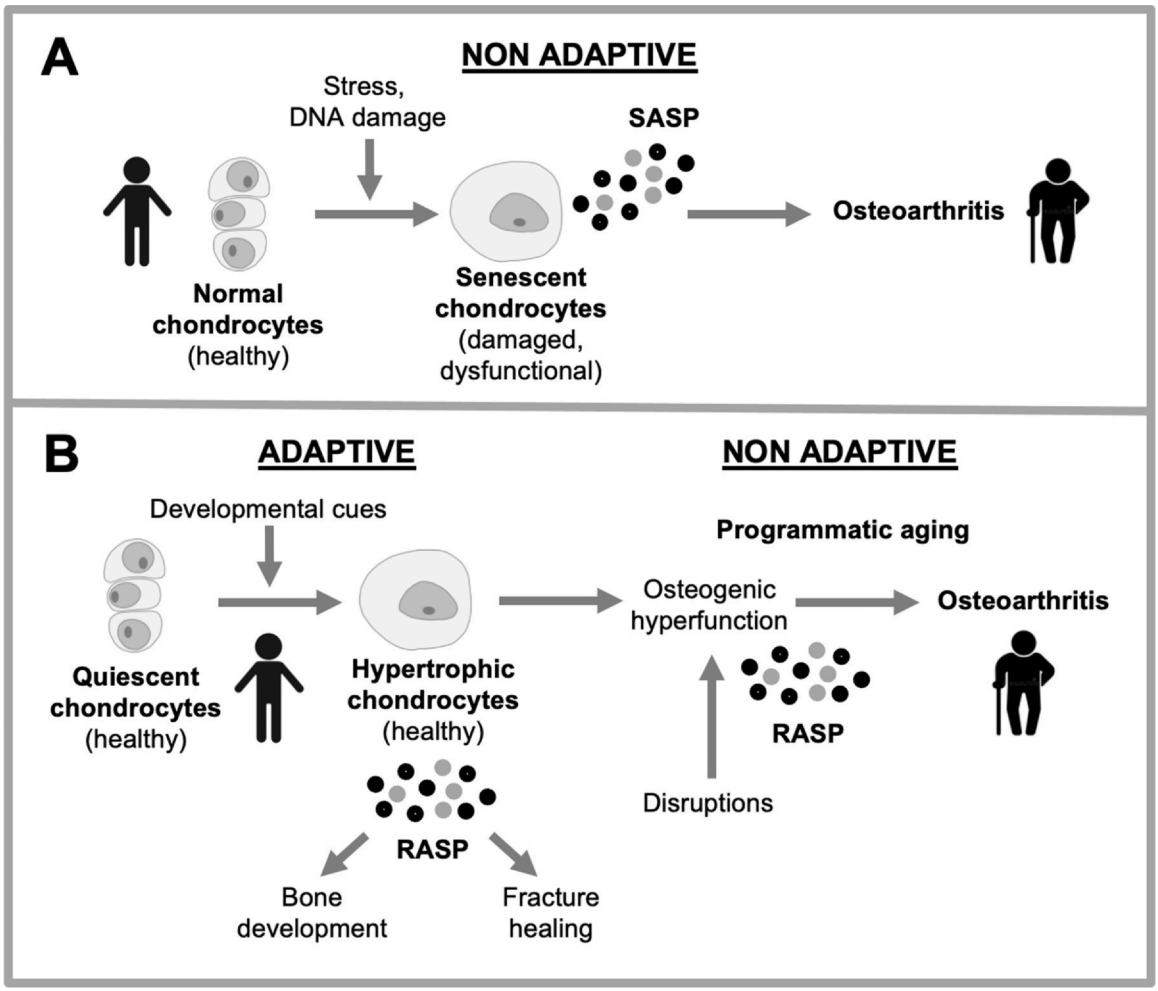

Fig. 4

Osteoarthritis and Cartilage

Two explanations for changes in chondrocyte behavior in osteoarthritis. A, Disruption-based explanation. Effects of stressors (e.g. DNA damage, ROS) cause chondrocytes to undergo cellular senescence. Consequent dysfunction leads to hypertrophy and hypersecretion, which damages articular cartilage. B, Programmatic explanation. As part of their normal function in bone development and bone fracture healing, chondrocytes become hypertrophic and hypersecretory. Their remodeling function is executed via the remodeling-associated secretory phenotype (RASP).[44] Programmatic changes during aging lead to futile activation of chondrocyte remodeling function, leading to transformation of hyaline cartilage into bone, leading to cartilage atrophy and bone hypertrophy.

mineralization during development, and promoting fitness; however in later life it increases vascular calcification, promoting pathology.[7] He argued that an off-switch for such calcium deposition could in principle evolve and reduce arteriosclerosis; but such a switch could be absent in later life due to the selection shadow (i.e. lack of selection for it).

Employing a similar evolutionary physiology argument, van der Kraan and van den Berg reasoned that the beneficial TGF-β off-switch is not retained in later life due to the selection shadow.[61] Wondering about trade-offs that might favor the evolutionary loss of the off switch, they suggested that maintenance of the switch might be costly in resource terms. This is in line with the disposable soma theory of aging, an influential, earlier alternative to programmatic theory.[62] However, it is not clear why maintenance of signaling should be costly in resource terms. More plausibly, some form of programmatic change, perhaps arising from signaling constraint[4] leads to loss of the TGF-β off switch.

Inhibiting the osteogenic quasi-program to prevent osteoarthritis

Hyperfunction of the growth-promoting mechanistic Target of Rapamycin (mTOR) pathway plays a prominent role in programmatic aging, and contributes to many late-life diseases.[3] Programmatic theory emerged in part from the discovery that inhibition of signaling pathways that promote growth and development can retard aging,[2,3] and the deduction that this particularly involves suppression of hyperfunction and quasi-program emergence. Notably, hypertrophy and hypersecretion during cellular senescence are promoted by mTOR, and inhibited by mTOR-inhibitory drugs such as rapamycin.[63] This suggests that mTOR-driven hyperfunction could contribute to OA pathogenesis, and provide a target for preventative intervention.

Human chondrocytes from OA cartilage show elevated mTOR expression, and the same is true for induced OA in mouse and dog models.[64] They also show reduced levels of autophagy, a process

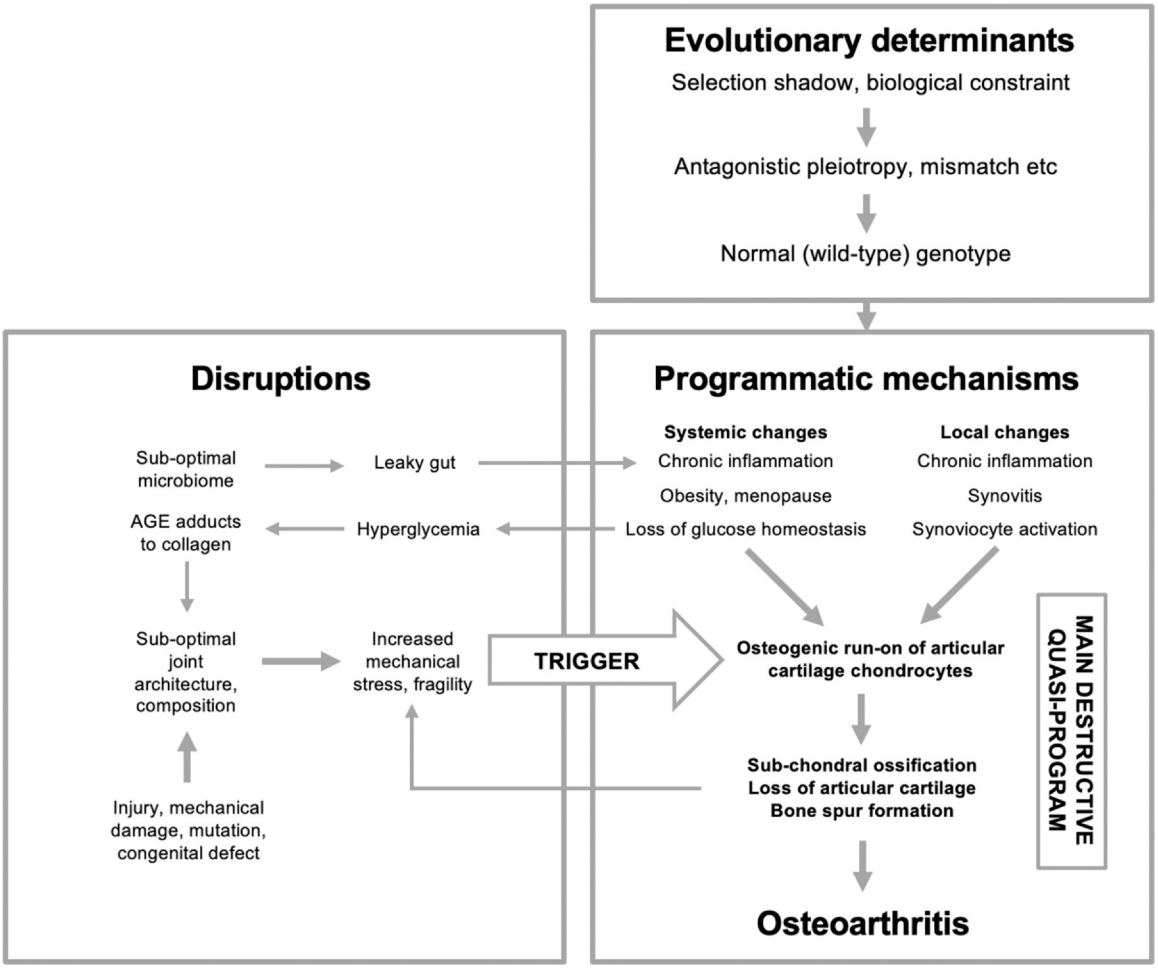

Fig. 5

Osteoarthritis and Cartilage

Osteoarthritis etiology viewed in terms of the multifactorial model. Here, OA is primarily an evolutionary disease: evolutionary determinants generate a normal (wild-type) genome that specifies programmatic determinants of OA. The main driver of disease is quasi-programs enacted by cells controlling development and tissue-level homeostasis within joints, particularly chondrocytes. Primary programmatic changes create predisposition to OA, creating susceptibility to OA-inducing triggers, caused by disruptions. Changes to joint architecture create further mechanical triggers in a positive feedback loop. AGE, advanced glycation end products. This is a highly simplified scheme; for example, obesity acts in multiple ways, including increasing load on joints, increasing inflammation, which may promote programmatic change in chondrocytes, and increasing type 2 diabetes, hyperglycemia and AGE adducts to cartilage collagens. Menopause is of programmatic origin, and contributes to OA by reducing estrogen levels.[84].

inhibited by mTOR. While this could in principle reflect cellular senescence, chondrocyte hypertrophy is also promoted by mTOR.[65] Notably, bone growth can be inhibited by rapamycin.[65] Moreover, in mouse models of OA, disease severity is reduced by both rapamycin and cartilage-specific deletion of mTOR.[64] Thus, pharmacological inhibition of mTOR might inhibit the endochondral ossification quasi-program.

About treatment timing: if, as proposed here, OA is a maturo-developmental disease, the effective way to treat it will be to pre-emptively block expression of the osteogenic quasi-program. By contrast, treatments that block chondrocyte hypertrophy or kill hypertrophic chondrocytes will have little effect on OA that has already developed. For example, it was recently reported that in marmosets rapamycin treatment from 9.2 ± 3.0 year of age until death (2.1 ± 1.5 years later) did not reduce OA burden; however, the authors noted that many of the test animals already had some degree of OA at the start of the treatment.[66] In line with this view, a study of late-stage OA, specifically in joints removed during knee replacement surgery, found markers of chondrocyte hypertrophy to be absent.[67]

A multifactorial model of osteoarthritis

If the multifactorial model (Fig. 1) has explanatory value with respect to general mechanisms of aging, then it should be possible to derive a specific version of it for each individual late-life disease. The process of fitting the multiple causes proposed for a given multifactorial disease into an integrated multifactorial model entails generation of diverse new hypotheses and questions about disease etiology.

Fig. 5 presents a prototype evolutionary medicine-based representation of OA seen through the lens of the multifactorial model.

According to this scheme, the core mechanisms of OA are specified by the wild-type genome, and expressed in late life in the form of pathogenic quasi-programs, in particular that involving articular chondrocytes as already described.

Guided by the standard view of disease as caused by disruptions (Fig. 1D), various types of insult have been listed as causes of OA, including mechanical damage,[18] modification of articular collagen by advanced glycation end products (AGEs),[19] and dysbiosis of the microbiome.[27] While these causes contribute to OA, arguably all are secondary factors that trigger the primary, programmatic disease mechanism; likewise poverty, cold and malnutrition can trigger the development of the active form of tuberculosis, where the primary cause is infection with the bacterium *Mycobacterium tuberculosis*.

In the case of the microbiome for example, leakage of bacterial antigens though the gut into the blood stream may contributes to the development of systemic inflammation,[68] which as inflammaging is itself, plausibly, a primarily programmatic process contributing to multiple diseases of aging, including OA.[26] The contributory role of systemic factors in OA is supported by the observation that parabiosis (linkage of circulation) of young and old mice can reduce it in the latter.[69] Similarly, synovitis (inflammation of the synovial membrane) increases levels of inflammatory mediators within the joint,[70] which may promote programmatic change in chondrocytes.

This account suggests that the primary, programmatic mechanism of OA, involving chondrocyte hypertrophy, may itself be a downstream element of a cascade of triggered quasi-programs.[10] If so, then the constraints and trade-offs generating primary pathogenic triggers may be those involved in the origins of chronic, late-life inflammation.

Positive feedback may also contribute to disease progression, as joint dysfunction promotes inflammation and increased tissue repair function, which in turn promote destructive quasi-programs, leading to a vicious cycle. Chondrocyte apoptosis is not a primary cause, but rather a final stage in the osteogenic quasi-program. Accumulation of AGEs in collagen is exacerbated by hyperglycemia resulting from type 2 diabetes, a largely programmatic disease, an example of programmatic molecular damage,[4] contributing to the triggering of the main disease-driving quasi-programs.

Regarding the genetics of OA, several hundred gene variants have been identified that increase disease risk, which in some cases affect Wnt, BMP and TGFβ pathway determinants of chondrocyte development.[71] In principle, these could affect disruption-type triggers of OA (e.g. by altering joint morphology) or the core programmatic mechanisms (e.g. by altering chondrocyte quasi-programs).

Programmatic theory, as applied here, predicts that a major, primary cause of OA is wild-type genes involved in chondrocyte developmental functions that exhibit AP. Thus, identifying such genes is of particular interest - but also difficult. AP genes are usually identifiable by virtue of allelic variation that alters the balance of benefit and cost; for example, a number genes affecting both immune function and late-life neurological disease risk have been identified in this way.[72] However, many (most?) AP genes will have evolved to fixation, i.e. lack such allelic variation.[4] Thus, genes whose AP is rendered visible by allelic variation may be the tip of an iceberg.

A likely example of AP is *GDF5* (growth differentiation factor 5), where a polymorphism linked to OA risk colocalizes with peaks of positive selection.[73] It has been suggested that changes to knee morphology linked to the evolution of bipedalism entailed selection for chondrocyte-expressed alleles that, due to biological constraint, exhibit AP and increase OA risk.[74]

How might biological constraint lead to osteoarthritis?

The proposed model (Fig. 5) portrays the primary causes of OA as programmatic and specified by the wild-type genome. According to recent theory, biological constraint, particularly of the interconnection type (Fig. 1C), leads to programmatic trade-offs that cause disease.[4] Thus, according to the model, to fully understand the programmatic causes of OA will require identification of its causative trade-offs and the constraints that give rise to them. While the nature of such constraints remains little explored, recent theory provides a few pointers for hypothesis generation, as follows.

An instructive example of how constraint can give rise to trade-offs, AP and programmatic age-related disease, relates to cardiovascular disease. The protein product of the AP gene *ORL1* (lectin-like low-density lipoprotein receptor 1) has been suggested to assist immunity by binding bacterial cell wall proteins, but also to promote atherosclerosis by binding oxidized low-density lipoprotein (LDL) in endothelial cells.[75] Here AP appears to result from biological constraint: the binding properties of the *ORL1* protein to one target (bacterial cell wall proteins) are inseparable from those to another (oxidized LDL).

The *ORL1* example illustrates how constraints that lead to AP in gene action, and to late-life disease, can particularly evolve where responses to life-threatening challenges earlier in life are concerned (here bacterial infection). Arguably, it is where trade-offs involve surviving life-threatening challenges or avoiding reproductive failure that particularly brutal compromises will be made, and the greatest collateral damage tolerated (in the form of late-life disease).[4] Given that articular joints are not reproductive organs, this suggests that constraints causing diseases of aging will often involve those operative in repair of life-threatening tissue injury, such as repair after infection (and immune defense itself) and wound healing, e.g. in skin and bone.

For OA, this suggests the hypothesis that constraints relating to bone fracture healing play a role in late-life priming for quasi-programmed endochondral ossification. The process of fracture healing to some extent recapitulates developmental endochondral bone formation, including chondrocyte hypertrophy.[76] According to this scenario, the quasi-program driving endochondral ossification in OA is less an ontogenetic one than a maturo-developmental, remodeling one.[11] Changes during chondrocyte hypertrophy in bone fracture healing are similar to those in osteogenesis.[76] In this context, the extent to which changes to chondrocyte function during OA show features normally restricted to bone fracture healing is of interest. In fact, periosteum-derived progenitor cells contributing to osteophyte growth do resemble those seen during bone repair.[36]

What, then, might be the programmatic mechanisms that cause late-life priming of articular cartilage for quasi-programmed endochondral ossification? One hypothetical possibility is that there exist constraints on the signaling systems regulating immune and tissue remodeling functions. Such constraints could lead to developmental costs, in the form of maladaptive developmental and morphogenetic changes to bone in articular joints. In other words, informational constraints where signaling factors that regulate endochondral ossification)[35,59] serve multiple function leads to pathogenic cross-talk, promoting harmful developmental quasi-programs. This may reflect signaling constraints within the joint itself, and/or systemic factors (Fig. 5).

The fact that OA is not only widespread among mammals,[29,77] but also present in birds, reptiles and amphibians suggests the presence of evolutionarily ancient, insuperable constraints in musculoskeletal development and tissue-level maintenance. In amphibians and fish, as in higher vertebrates, hypertrophic remodeling (“senescent”) fibroblasts and macrophages work together to effect tissue remodeling during development, and also limb regeneration.[46]

Evolutionary mismatch, programmatic mechanisms and OA

Other evolutionary explanations have linked OA etiology to the appearance of bipedalism,[78] the obstetrical dilemma[79] and to

mismatch between our physiology, as adapted to the conditions under which we evolved, and those typical of life in the developed world today. Of these hypotheses, evidence for the latter is the most compelling: OA frequency has increased greatly during the last century, probably as a result of increased obesity in particular, and also reduced physical activity.[80]

Pathogenic effects of evolutionary mismatch may be understood in programmatic terms. Like senescent pathologies, mismatch-generated pathologies are a consequence of failure of adaptation.[81] Both involve quasi-programs specified by the wild-type genome. In each case, useful biological programs become destructive due to their expression in the wrong context. In metabolic syndrome, for example, a useful program for storing energy in fat tissue turns into a destructive quasi-program for obesity and type 2 diabetes, due to evolutionary mismatch.

A priori there is no reason to expect that senescence- and mismatch-generated pathologies will involve the same quasi-programs. Notably, however, senescence and mismatch both contribute to OA, suggesting possible convergence on the same quasi-programs. This could imply that similar biological constraints are operative in optimizing traits across ages as across environmental conditions.

Concluding remarks

An adequate account of the general principles governing the development of late-life diseases should serve a similar role to that of the periodic table in chemistry, which can instruct understanding of the chemical composition of all matter. The multifactorial model-based account of OA presented here (Fig. 5) has strengths and weaknesses. To fully understand how senescence generates diseases requires an explanation in terms of evolutionary physiology.[8] This the programmatic theory component of the multifactorial model provides, which is broadly in line with the developmental model of OA.[35,55] Here OA is a hyperfunctional process, involving chondrocytes that are “activated”,[59] and an endochondral ossification quasi-program.

It is notable here how the multifactorial model offers an explicit account of disease etiology that would be difficult to achieve using the main, earlier evolutionary physiology model, the disposable soma theory.[62] More broadly, the multifactorial model offers a conceptual framework that can help the ambitions of evolutionary medicine to be more fully realized.[31] Another strength of the multifactorial model is that it offers a big picture understanding of OA that can incorporate and integrate many different existing theories about disease etiology.

It should be emphasized that the model presented is very much a prototype, and that it integrates some but not all features of OA etiology. In particular, the emphasis of the model is on cartilage and chondrocyte function, with relatively little focus on bone and synovium, though inflammation in the latter is the main cause of pain in OA.[82] Nevertheless, integrated overviews of the general sort presented here are necessary, possible and currently lacking, and it is hoped that the basic prototype proffered here might provide a starting point for the development of better general models. In particular, such overviews are critical for generating relevant hypotheses and questions, thereby fruitfully guiding experimental research. These include: how does AP determine OA, and which genes does this involve? How have constraints and the selection shadow led to trade-offs in wild-type function that underpin programmatic OA? And: how is the late-life timing of the programmatic emergence of OA specified? Such questions illustrate how, if the proposed model is realistic, it should at least enable investigators to orient themselves in terms of general principles in a way that allows facts to fall into place and leads to useful questions to ask.

Role of the funding source

This work was supported by a Wellcome Trust Investigator Award (215574/Z/19/Z) to D.G. The funder had no role in the writing of the manuscript or in the decision to submit the manuscript for publication.

Author contributions

The author was responsible for review conception and design, drafting the article, critical revision of the article for important intellectual content, and final approval of the article. David Gems (david.gems@ucl.ac.uk) takes responsibility for the integrity of the work as a whole, from inception to finished article.

Declaration of competing interests

The author states that he has no competing interests.

Acknowledgments

The author wishes to thank H. Chapman, B.O. Diekman, C.C. Kern, J. Labbadia, R.F. Loeser, I. Meulenbelt, D. Richard, G. Sessions and B. Zhang for useful discussion and/or comments on the manuscript. This work was supported by a Wellcome Trust Investigator Award (215574/Z/19/Z) to D.G.

References

1. Comfort A. The Biology of Senescence. Third edition New York: Elsevier; 1979.
2. de Magalhães JP, Church GM. Genomes optimize reproduction: aging as a consequence of the developmental program. Physiology 2005;20:252–9.
3. Blagosklonny MV. Aging and immortality: quasi-programmed senescence and its pharmacologic inhibition. Cell Cycle 2006;5:2087–102.
4. Gems D, Kern CC. Biological constraint, evolutionary spandrels and antagonistic pleiotropy. Ageing Res Rev 2024;101, 102527.
5. Gems D. Understanding hyperfunction: an emerging paradigm for the biology of aging. Ageing Res Rev 2022;74, 101557.
6. Blagosklonny MV, Pardee AB. Conceptual biology: unearthing the gems. Nature 2002;416:373.
7. Williams GC. Pleiotropy, natural selection and the evolution of senescence. Evolution 1957;11:398–411.
8. Arnold KR, Rose MR. Conceptual Breakthroughs in The Evolutionary Biology of Aging. Academic Press; 2023.
9. Medawar PB. An Unsolved Problem Of Biology. London: H.K. Lewis; 1952.
10. Kern C, Stebbing J. Uncovering the blueprint of aging: how aging causes late-life disease. *Preprintsorg*; 2023. doi:10.20944/preprints202310.201387.v202312.
11. Gems D, Singh Virk R, de Magalhães JP. Epigenetic clocks and programmatic aging. Ageing Res Rev 2024;101, 102546.
12. Beckman KB, Ames BN. The free radical theory of aging matures. Physiol Rev 1998;78:547–81.
13. Blagosklonny MV. Aging: ROS or TOR. Cell Cycle 2008;7:3344–54.
14. Loeser RF. The role of aging in the development of osteoarthritis. Trans Am Clin Climatol Assoc 2017;128:44–54.
15. Dilman VM. Development, Aging and Disease: A New Rationale for an Intervention Strategy. Harwood Academic Publishers; 1994.
16. Glyn-Jones S, Palmer AJ, Agricola R, *et al*. Osteoarthritis. Lancet 2015;386:376–87.

17. Aigner T, Rose J, Martin J, *et al*. Aging theories of primary osteoarthritis: from epidemiology to molecular biology. Rejuvenation Res 2004;7:134–45.
18. Radin EL, Burr DB, Caterson B, *et al*. Mechanical determinants of osteoarthrosis. Semin Arthritis Rheum 1991;21:12–21.
19. Liu HZ, Song XQ, Zhang H. Sugar-coated bullets: unveiling the enigmatic mystery 'sweet arsenal' in osteoarthritis. Heliyon 2024;10, e27624.
20. Loeser RF. Aging and osteoarthritis. Curr Opin Rheumatol 2011;23:492–6.
21. Huang R, Hui Z, Wei S, *et al*. IRE1 signaling regulates chondrocyte apoptosis and death fate in the osteoarthritis. J Cell Physiol 2022;237:118–27.
22. Jeon OH, David N, Campisi J, *et al*. Senescent cells and osteoarthritis: a painful connection. J Clin Invest 2018;128:1229–37.
23. Coryell PR, Diekman BO, Loeser RF. Mechanisms and therapeutic implications of cellular senescence in osteoarthritis. Nat Rev Rheumatol 2021;17:47–57.
24. Tangredi BP, Lawler DF. Osteoarthritis from evolutionary and mechanistic perspectives. Anat Rec (Hoboken) 2020;303:2967–76.
25. Luo P, Gao F, Niu D, *et al*. The role of autophagy in chondrocyte metabolism and osteoarthritis: a comprehensive research review. Biomed Res Int 2019;2019, 5171602.
26. Motta F, Barone E, Sica A, *et al*. Inflammaging and osteoarthritis. Clin Rev Allergy Immunol 2023;64:222–38.
27. Arora V, Singh G, O-Sullivan I, *et al*. Gut-microbiota modulation: the impact of the gut-microbiota on osteoarthritis. Gene 2021;785, 145619.
28. Mobasheri A, Matta C, Zákány R, *et al*. Chondrosenescence: definition, hallmarks and potential role in the pathogenesis of osteoarthritis. Maturitas 2015;80:237–44.
29. Föllmi J, Steiger A, Walzer C, *et al*. A scoring system to evaluate physical condition and quality of life in geriatric zoo mammals. Anim Welfare 2007;16:309–18.
30. Nganvongpanit K, Soponteerakul R, Kaewkumpai P, *et al*. Osteoarthritis in two marine mammals and 22 land mammals: learning from skeletal remains. J Anat 2017;231:140–55.
31. Nesse RM, Williams GC. Why We Get Sick: The New Science of Darwinian Medicine. Random House; 1994.
32. Blagojevic M, Jinks C, Jeffery A, *et al*. Risk factors for onset of osteoarthritis of the knee in older adults: a systematic review and meta-analysis. Osteoarthritis Cartilage 2010;18:24–33.
33. Stevens DG, Beharry R, McKee MD, *et al*. The long- term functional outcome of operatively treated tibial plateau fractures. J Orthop Trauma 2001;15:312–20.
34. Toivanen A, Heliövaara M, Impivaara O, *et al*. Obesity, physically demanding work and traumatic knee injury are major risk factors for knee osteoarthritis—a population-based study with a follow-up of 22 years. Rheumatology (Oxford) 2010;49:308–14.
35. Dreier R. Hypertrophic differentiation of chondrocytes in osteoarthritis: the developmental aspect of degenerative joint disorders. Arthritis Res Ther 2010;12:216.
36. Roelofs AJ, Kania K, Rafipay AJ, *et al*. Identification of the skeletal progenitor cells forming osteophytes in osteoarthritis. Ann Rheum Dis 2020;79:1625–34.
37. Blanco FJ, Guttian R, Vázquez-Martul E, *et al*. Osteoarthritis chondrocytes die by apoptosis. A possible pathway for osteoarthritis pathology. Arthritis Rheum 1998;41:284–9.
38. Birch J, Gil J. Senescence and the SASP: many therapeutic avenues. Genes Dev 2020;34:1565–76.
39. Basisty N, Kale A, Jeon O, *et al*. A proteomic atlas of senescence-associated secretomes for aging biomarker development. PLoS Biol 2020;18, e3000599.
40. Baker DJ, Childs BG, Durik M, *et al*. Naturally occurring p16(Ink4a)-positive cells shorten healthy lifespan. Nature 2016;530:184–9.
41. Diekman BO, Sessions GA, Collins JA, *et al*. Expression of p16 INK 4a is a biomarker of chondrocyte aging but does not cause osteoarthritis. Aging Cell 2018;17, e12771.
42. Jeon OH, Kim C, Laberge R-M, *et al*. Local clearance of senescent cells attenuates the development of post-traumatic osteoarthritis and creates a pro-regenerative environment. Nat Med 2017;23:775–81.
43. Davan-Wetton CSA, Pessolano E, Perretti M, *et al*. Senescence under appraisal: hopes and challenges revisited. Cell Mol Life Sci 2021;78:3333–54.
44. Gems D, Kern CC. Is "cellular senescence" a misnomer? Geroscience 2022;44:2461–9.
45. de Magalhães JP. Cellular senescence in normal physiology. Science 2024;384:1300–1.
46. Yun MH. Cellular senescence in tissue repair: every cloud has a silver lining. Int J Dev Biol 2018;62:591–604.
47. Demaria M, Ohtani N, Youssef SA, *et al*. An essential role for senescent cells in optimal wound healing through secretion of PDGF-AA. Dev Cell 2014;31:722–33.
48. Krizhanovsky V, Yon M, Dickins RA, *et al*. Senescence of activated stellate cells limits liver fibrosis. Cell 2008;134:657–67.
49. Storer M, Mas A, Robert-Moreno A, *et al*. Senescence is a developmental mechanism that contributes to embryonic growth and patterning. Cell 2013;155:1119–30.
50. Menon R, Richardson LS, Lappas M. Fetal membrane architecture, aging and inflammation in pregnancy and parturition. Placenta 2019;79:40–5.
51. Plikus MV, Wang X, Sinha S, *et al*. Fibroblasts: origins, definitions, and functions in health and disease. Cell 2021;184:3852–72.
52. Marsell R, Einhorn TA. The biology of fracture healing. Injury 2011;42:551–5.
53. Rim YA, Nam Y, Ju JH. The role of chondrocyte hypertrophy and senescence in osteoarthritis initiation and progression. Int J Mol Sci 2020;21:2358.
54. Farnum CE, Lee R, O'Hara K, *et al*. Volume increase in growth plate chondrocytes during hypertrophy: the contribution of organic osmolytes. Bone 2002;30:574–81.
55. van der Kraan PM, van den Berg WB. Chondrocyte hypertrophy and osteoarthritis: role in initiation and progression of cartilage degeneration? Osteoarthritis Cartilage 2012;20:223–32.
56. von der Mark MK, Kirsch T, Nerlich A, *et al*. Type X collagen synthesis in human osteoarthritic cartilage. Indication of chondrocyte hypertrophy. Arthritis Rheum 1992;35:806–11.
57. Ishikawa K, Masuda I, Ohira T, *et al*. A histological study of calcium pyrophosphate dihydrate crystal-deposition disease. J Bone Joint Surg Am 1989;71:875–86.
58. Blagosklonny MV. Paradoxes of aging. Cell Cycle 2007;6:2997–3003.
59. Goldring MB. Chondrogenesis, chondrocyte differentiation, and articular cartilage metabolism in health and osteoarthritis. Ther Adv Musculoskelet Dis 2012;4:269–85.
60. Yang X, Chen L, Xu X, *et al*. TGF-beta/Smad3 signals repress chondrocyte hypertrophic differentiation and are required for maintaining articular cartilage. J Cell Biol 2001;153:35–46.
61. van der Kraan PM, van den Berg WB. Osteoarthritis in the context of ageing and evolution. Loss of chondrocyte differentiation block during ageing. Ageing Res Rev 2008;7:106–13.
62. Kirkwood TBL, Rose MR. Evolution of senescence: late survival sacrificed for reproduction. Phil Trans R Soc London 1991;332:15–24.
63. Demidenko Z, Zubova S, Bukreeva E, *et al*. Rapamycin decelerates cellular senescence. Cell Cycle 2009;8:1888–95.

64. Zhang Y, Vasheghani F, Li Y-H, *et al*. Cartilage-specific deletion of mTOR upregulates autophagy and protects mice from osteoarthritis. Ann Rheum Dis 2015;74:1432–40.
65. Chen J, Long F. mTORC1 signaling controls mammalian skeletal growth through stimulation of protein synthesis. Development 2014;141:2848–54.
66. Minton DM, Ailiani AR, Focht MDK, *et al*. Impact of long-term rapamycin treatment on age-related osteoarthritis in common marmoset. bioRxiv 2024. https://doi.org/10.1101/2024.05.14.594256
67. Brew CJ, Clegg PD, Boot-Handford RP, *et al*. Gene expression in human chondrocytes in late osteoarthritis is changed in both fibrillated and intact cartilage without evidence of generalised chondrocyte hypertrophy. Ann Rheum Dis 2010;69:234–40.
68. Biver E, Berenbaum F, Valdes AM, *et al*. Gut microbiota and osteoarthritis management: an expert consensus of the European society for clinical and economic aspects of osteoporosis, osteoarthritis and musculoskeletal diseases (ESCEO). Ageing Res Rev 2019;55, 100946.
69. Li L, Wei X, Wang D, *et al*. Positive effects of a young systemic environment and high Growth Differentiation Factor 11 levels on chondrocyte proliferation and cartilage matrix synthesis in old mice. Arthritis Rheumatol 2020;72:1123–33.
70. Sellam J, Berenbaum F. The role of synovitis in pathophysiology and clinical symptoms of osteoarthritis. Nat Rev Rheumatol 2010;6:625–35.
71. Zhai G, Huang J. Genetics of osteoarthritis. Best Pract Res Clin Rheumatol 2024;38, 101972.
72. Provenzano F, Deleidi M. Reassessing neurodegenerative disease: immune protection pathways and antagonistic pleiotropy. Trends Neurosci 2021;44:771–80.
73. Capellini TD, Chen H, Cao J, *et al*. Ancient selection for derived alleles at a GDF5 enhancer influencing human growth and osteoarthritis risk. Nat Genet 2017;49:1202–10.
74. Richard D, Capellini TD. Shifting epigenetic contexts influence regulatory variation and disease risk. Aging (Albany NY) 2021;13:15699–749.
75. Predazzi IM, Rokas A, Deinard A, *et al*. Putting pleiotropy and selection into context defines a new paradigm for interpreting genetic data. Circ Cardiovasc Genet 2013;6:299–307.
76. Bahney CS, Zondervan RL, Allison P, *et al*. Cellular biology of fracture healing. J Orthop Res 2019;37:35–50.
77. Greer M, Greer JK, Gillingham J. Osteoarthritis in selected wild mammals. Proc Okla Acad Sci 1977;57:39–43.
78. Haüsler M, Bender N, Aldakak L, *et al*. Musculoskeletal system. In: Brüne M, Schiefenhövel W, editors. The Oxford Handbook of Evolutionary Medicine. Oxford: Oxford University Press; 2019. p. 269–99.
79. Xu L, Kun E, Pandey D, *et al*. The genetic architecture of and evolutionary constraints on the human pelvic form. Science 2025;388, eadq1521.
80. Berenbaum F, Wallace IJ, Lieberman DE, *et al*. Modern-day environmental factors in the pathogenesis of osteoarthritis. Nat Rev Rheumatol 2018;14:674–81.
81. Arnold KR, Rose MR. 1985: Genotype-by-environment interaction shown for aging. Conceptual Breakthroughs in The Evolutionary Biology of Aging. Academic Press; 2023. p. 117–21.
82. Wood MJ, Miller RE, Malfait AM. The genesis of pain in osteoarthritis: inflammation as a mediator of osteoarthritis pain. Clin Geriatr Med 2022;38:221–38.
83. Strenk SA, Strenk LM, Koretz JF. The mechanism of presbyopia. Prog Retin Eye Res 2005;24:379–93.
84. Mei Y, Williams JS, Webb EK, *et al*. Roles of hormone replacement therapy and menopause on osteoarthritis and cardiovascular disease outcomes: a narrative review. Front Rehabil Sci 2022;3, 825147.