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Life history evolution, reproduction, and the origins of sex-dependent aging and longevity

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Males and females in many species differ in how they age and how long they live. These differences have motivated much research, concerning both their evolution and the underlying mechanisms that cause them. We review how differences in male and female life histories have evolved to shape patterns of aging and some of the mechanisms and pathways involved. We pay particular attention to three areas where considerable potential for synergy between mechanistic and evolutionary research exists: (1) the role of estrogens, androgens, the growth hormone/insulin-like growth factor 1 pathway, and the mechanistic target of rapamycin signaling pathway in sex-dependent growth and reproduction; (2) sexual conflict over mating rate and fertility, and how mate presence or mating can become an avenue for males and females to directly affect each other's life span; and (3) the link between dietary restriction and aging, and the emerging understanding that only the restriction of certain nutrients is involved and that this is linked to reproduction. We suggest that ideas about life histories, sex-dependent selection, and sexual conflict can inform and be informed by the ever more refined and complex understanding of the mechanisms that cause aging.

Keywords: aging; senescence; sexual selection; life span; adaptation; sexual conflict

Introduction

Aging, the progressive, generalized decline of biological function with advancing age, increases susceptibility to disease and death and often reduces fertility.[1] Aging varies dramatically in timing and expression among species, populations, individuals, and the sexes. Males and females can age in quite different ways, resulting in substantial average differences in life span, reproductive timing, and causes of death. In humans, for example, the diseases of late adulthood, including cancers, cardiovascular disease, and dementia, afflict women and men at dramatically different rates.[2]

The study of aging follows two largely parallel but increasingly overlapping trajectories, roughly corresponding to the proximate/ultimate or how/why distinction that pertains in much of biology.[3,4] Mechanistic "how" studies investigate physiologic, genetic, epigenetic, and other proximate processes that influence the onset of age-dependent diseases, quality of life, and longevity. Mechanistic studies still explore evolutionary aspects of aging, but with a focus on pathways and processes that may play conserved roles in regulating life span across diverse taxa.

Links to costs of energy production have propelled mechanistic aging research over much of the last 50 years. Early hypotheses for the mechanistic, conserved causes of aging revolved around the potential damaging effects of free radicals,[5] produced mainly as a consequence of mitochondrial respiration.[6] Free radicals, it has been variously argued, can cause oxidative damage to a variety of different macromolecules,[7] impair mitochondrial function (generating the production of further free radicals),[6] hasten the erosion of telomeres,[8] and impair redox homeostasis[9]—each potentially accelerating the onset or course of aging.

Genetic impairments of antioxidant defenses in both invertebrate and vertebrate model organisms

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have demonstrated that, at least in laboratory conditions, animals can cope with high levels of oxidative stress without major reductions in life span.[10,11] Owing to this, and the realization that mutational disruption of genes involved in cell signaling can have more profound effects on aging,[12] mechanistic theories for aging have expanded to acknowledge the presence of specific signals that can regulate aging while also influencing other aspects of life history. Signals hypothesized to be central to aging and largely conserved across species include insulin/insulin-like growth factor 1 (IGF-1), the mechanistic target of rapamycin (mTOR), and sirtuins.[13] At the same time, additional aspects of damage and dysregulation that might contribute to aging, some of which are influenced by the downstream activity of these signals, have come to light. These include epigenetic dysregulation, loss of protein homeostasis, inflammation, and declines in stem cell function.[14,15]

While there has been substantial discussion of whether specific mechanisms of aging have shared roles across several different species, experimental studies within species have tended to focus on only one sex, eliminating the extraneous variation arising from sex differences (e.g., Refs. 16 and 17). Where mechanistic studies acknowledge the existence of such sex differences, it is often in the course of identifying physiological or mechanistic pathways that might explain sex differences in human life span (e.g., telomere length[18]), and thus point to important mechanisms underpinning human aging or aging in general. Nonetheless, both sex-dependent genetic inheritance and sex hormones have been implicated in aging, and it is increasingly clear that responses to many antiaging interventions are sex specific.[19–22] The need for an understanding of how and why males and females age in often quite dramatically different ways has never been so strong.

Evolutionary perspectives, steeped in the importance of sex and reproduction, have much to offer the study of aging. Recent evolutionary studies have made considerable progress toward understanding the evolution of sex differences in aging and the resulting effects on male and female longevity (comparative studies;[23–25] reviews[2,26,27]). Much of that progress grows from an understanding of how the sex-dependent selection that leads to the evolution of sex differences in size, behavior, and physiology also influences the evolution of life histories. This review will first consider how aging and sex differences evolve, and then consider how sex-dependent evolution might shape some of the mechanisms and pathways implicated in aging.

Aging evolves

The evolutionary study of aging seeks to understand why animals age; why there is variation in aging between species, populations, sexes, and individuals; and how this is influenced by environmental conditions. In general, natural selection eliminates genetic variants that cause disease and mortality and favors variants that support somatic and genetic repair. But the strength of this selection declines with advancing age. Since the canonical early ideas of Medawar,[28] Williams,[29] and Hamilton,[30] this was thought to be because extrinsic mortality, like predation, infection, and accidents, progressively thins a cohort, shielding late-acting variants from the full force of selection. And yet higher extrinsic mortality does not always lead to accelerated senescence.[31,32] Instead, selection against aging declines because older individuals have less of their total lifetime reproductive success ahead of them than younger individuals do.[30,33] As a result of this decline, however it arises, late-acting variants that cause aging can persist.[28–30,32]

Those deleterious alleles may accumulate via mutation–selection balance because, owing to their late-life expression, they are selectively near neutral in the wild[28] or because they enhance early-life fitness (i.e., they have deleterious pleiotropic effects at advanced ages[29]). A large body of genetic evidence suggests that both types of genetic variant segregate in animal populations and cause aging.[3,34] Where genetic associations between early- and late-life fitness exist, however, they are often positive.[35,36] Theoretical work has shown that alleles that have generally deleterious pleiotropic effects on both early and late fitness can also persist in populations, generating both positive genetic correlations between early and late fitness, and, when those deleterious effects grow stronger with age, still result in aging.[37–39]

One way in which pleiotropic genetic effects can influence aging is via life history trade-offs. According to the disposable soma theory of aging,[3,40–42] the soma, unlike the germ line, cannot persist indefinitely because of mortality, and thus the fitness payoffs of somatic maintenance dwindle with age.

Reproductive investment ensures propagation of the germ line, but it can inflict cellular damage or use up resources that would otherwise be used for somatic maintenance, thus resulting in earlier onset and more extreme aging and shorter life span. Evolutionary theories of aging, and the disposable soma theory in particular, view the timing and rate of senescence as life history traits influenced by the optimization of these trade-offs. Evidence, including from wild free-living populations,[43–47] supports the idea that resource allocation to reproduction in early adulthood trades off with somatic maintenance and late-life performance. But the notion of direct allocation of resources to survival at the expense of reproduction, or vice versa,[42] is being challenged by the complexities emerging from detailed laboratory studies of mechanistic pathways involved in aging.[48]

Evolution of sex differences in aging

A remarkable number of hypotheses have been proposed to explain the observed sex differences in aging and life span, particularly in humans. One form that these hypotheses take involves identifying a mechanism thought to be involved in aging, which shows some sex differences, and inferring that the mechanism in question is the cause of the sex differences. One but by no means the only example involves telomeres, which shorten each time the DNA is replicated in cell division and may incur damage from reactive oxygen species. Evolved mechanisms, including the action of the enzyme telomerase, restore and repair telomeres, but the action of these mechanisms is often downregulated in older mammals, and telomere shortening inevitably limits the number of times normal cells may divide.[49] Telomere dynamics are, therefore, thought to be linked to both cellular senescence and organismal aging (but see Ref. 50).

Differences between women and men in telomere shortening rates have been suggested as one mechanism underpinning sex differences in human aging. Stindl[18] argued that, because men are larger than women, normal growth requires more cell divisions for men, and so they approach the limit in the number of possible divisions and thus begin cellular senescence at a younger age than women do. This formulation appears overly simplistic. For a start, in many species, males' telomeres shorten faster than those of females, but females age more rapidly or live shorter lives than males.[51] Sexual dimorphism in size is only loosely associated with differences in telomere shortening and aging. Not only do sex differences in telomere shortening and/or repair not provide a general explanation for sex differences in aging,[51] but the evidence that telomeres are causally involved in aging at all remains unconvincing.[50]

Like so many single-cause explanations for sex-dependent aging, the telomere argument begs the question. To properly answer whether sex-dependent aging is caused by the association with a given mechanism requires demonstrating how that mechanism comes to be associated with sex-dependent aging in the way that it is, and that necessitates integrating our mechanistic understanding of aging and longevity within the evolutionary framework by which we understand how sex differences arise.

Costly reproductive allocation

Sex differences in a wide variety of traits have arisen as a result of sex-dependent selection, together with differences in the social and ecological microenvironments experienced by females and males. Sex-dependent selection results largely from differences in the demands that reproduction imposes on males and females. Differences in the metabolic requirements for and costs of gestation and lactation, as opposed to sperm production and territory defense, have, for example, driven the evolution of differences in body size, aggression, sociability, and even metabolic traits in many mammals.[52]

Sex-dependent selection goes well beyond static differences in how males and females produce gametes and care for offspring. Each sex competes for access to mates, and the resulting sexual selection represents a potent force driving the evolution of sexual dimorphism.[53,54] Competition for mates, as well as the traits that result from this process, is an important and often costly component of reproduction, usually differing in its intensity between the sexes.

Sex differences in relative allocation to these different components of reproduction can generate sex differences in aging and longevity[25,26] by altering the mortality risks faced by males and females or as a consequence of life history trade-offs. Among large mammals, for example, sexual selection on male territoriality, aggression, and sexual signaling is far more intense in polygynous than socially

monogamous species, and adult males from polygynous species consistently live shorter lives than females as a consequence of higher mortality and the life history costs of allocation to weaponry, sexual display, and competitive behavior. Reduced male life spans in such polygynous species have been associated with both an earlier male onset of senescence[55] and more rapid declines in male survival.[25]

Among birds, too, higher intensities of male–male competition push mortality rates from the avian-typical female bias toward male bias.[24] However, sex-biased mortality also depends on the relative amount of parental care, with the sex that invests more in care suffering greater mortality costs.[24,56]

The intensity of sexual selection in several insect species is also associated with sex differences in aging and life span. Manipulations of the opportunity for sexual selection by allowing insect lines to evolve under either monogamy or polygamy/polygyny have yielded important insights into sex-dependent selection on life span and aging. The consequences of within-line sexual selection for the evolution of life span and age-dependent mortality can vary considerably among species, and even within species depending on the aspects of sexual selection manipulated (e.g., Refs. 57 and 58 and discussion in Ref. 59). Responses to the experimental manipulation of sexual selection may entail correlated responses to selection on genetically correlated traits, such as attractiveness, condition, and longevity. They might equally be due to disrupted antagonistic coevolution between females and males.

The effects of sexual selection on sex-dependent mortality and aging also depend on the age-dependent patterns of reproductive effort within each sex. For example, male and female decorated crickets (*Gryllodes sigillatus*) show a genetic correlation between high early-adulthood reproductive effort and aging rate, but the relationship is stronger in females.[60] Male decorated crickets live longer and age more slowly than females, possibly because of differences in the timing of reproductive effort; males increase calling effort, the main determinant of reproductive success, with age, whereas female egg laying decreases with age.

The costs of reproduction are far from fixed, varying, within each sex, with individual condition, environmental circumstances, and the local density of competitors and potential mates. As a result, both female and male life histories, including aging and longevity, can vary in complex, plastic ways that are somewhat independent of one another. For example, the sexes can show strong differences in their ability to withstand different environmental conditions. In red deer, juvenile male mortality is higher than that of females when overwinter food shortages during early life are severe.[61] Several more recent studies have also noted that poor early-life environments can generate sex differences in adult survival and aging, with adult male survival in great tits and roe deer showing greater dependence on early-life environments than that of females.[62,63] The presence of sex differences in aging may therefore vary across time and environments, and our picture of sex differences in aging in laboratory conditions may differ from the true extent that is observed in the wild.

Humans provide an instructive example of social and environmental context altering sex differences in longevity and, potentially, aging. In most 21st century societies, women live longer, on average, than men, so much so that reviews of human sex differences in life span treat the difference as a general feature of human society.[2,20,64,65] But the size of the sex difference varies dramatically among societies and, in several, men live longer than women.[66] Countries with low fertility rates tend to be those in which women outlive men the most dramatically,[67] suggesting a link between the costs of reproduction paid by women and longevity gaps. A recent analysis of the full reproductive lives of more than 140,000 adult men and women born in Utah between 1820 and 1919, a time period during which women went from having 8.5 to having 4.2 children, on average, as the demographic transition unfolded, substantiates this interpretation.[68] Women who bore large numbers of children lived shorter lives, but the same was not true for men. As fertility dwindled, female life span increased, but male life span did not, and so adult life span shifted from male biased to female biased.

Sexual conflict

Beyond sex differences in reproductive investment, competition, and associated hazards, there exists in evolutionary biology a growing appreciation that the interests of mates are not identical and that the harm that individuals inflict on their mates generates sex-dependent selection.[69,70] This sexual conflict pits the interests of mates, or potential mates, against one another. It is sometimes referred to

by the rather clunky "interlocus sexual conflict" to distinguish it from intralocus sexual conflict, the constraint on sex-specific optimization of the phenotype imposed by developing from a shared genome.[71]

For example, males of many species overcome female reluctance to mate by harassing, coercing,[72] and even blackmailing[73] them to mate. When they do mate, males can inflict damage[74,75] or ejaculate chemicals[76,77] that harm the female but benefit the male—either giving his sperm an advantage over that of the female's other mates or inducing the female to lay more eggs than she otherwise would. And even the seemingly cooperative business of biparental care entails conflicts, with bird,[78] fish,[79] and even human[80] parents tussling over how much work each does caring for the young.

We have already seen how sex differences in parental care can alter relative male and female life spans.[24,56] Likewise, sexual conflict over mating and fertility provides manifold examples of males and females altering one another's life span and patterns of aging.[77,81–85] Below, we consider in detail some of the fine-scale mechanistic work that has been done dissecting the links between mating interactions, sexual conflict, and aging.

Sexual conflict and sexually antagonistic genes

The implications of intralocus sexual conflict for aging have been thoroughly reviewed elsewhere,[26,86] and we only touch on them in brief here. Some alleles can have sexually antagonistic effects on fitness,[87] imposing considerable genetic load on one or both sexes. Such sexually antagonistic genes tend to accumulate on the sex chromosomes.[88,89] It has been suggested that sexually antagonistic genes on the sex chromosomes may play a prominent role in sex-specific aging.[90] Likewise, the maternal inheritance of mitochondria, together with the importance of mitochondria in oxidative stress and apoptosis, implicates mitochondrial genes in sex-dependent aging.[90–92] Some of the most exciting recent work at the interface of evolutionary and mechanistic aging concerns these mitochondrial effects.

Sexually antagonistic genes, particularly when inherited in more typically Mendelian fashion, rather than promoting sexual dimorphism in aging and life span, may instead constrain the sexes from evolving toward different life history optima.[26] Evidence from the seed beetle *Callosobruchus maculatus*[93,94] and the nematode *Caenorhabditis remanei*[95] shows that their antagonistic effects can maintain some of the genetic variance in aging and longevity. Only a handful of empirical studies have explored the possibilities in any depth (e.g., Refs. 93–97), and it looks like the possibility of sexually antagonistic constraint on aging and life histories remains a likely important factor for studies to consider.

Sex hormones, growth, reproduction, and trade-offs

Estrogens

One potential cause for longer female life spans, when present, is that estrogens may delay aging or otherwise protect against early death.[64] Female ovariectomy can lead to a reduction in survival in mice,[98] and transplanting young ovaries into old mice can extend life span.[99] Estrogens can act as antioxidants[100] and have beneficial effects on glucose and lipid metabolism, which protect against dysregulation of glucose homeostasis and metabolic diseases in laboratory conditions.[101–103]

The beneficial effects of estrogens on female survival, at first sight, appear at odds with evolutionary theories for aging and the trade-off between reproductive allocation and survival. These are hormones that facilitate female reproduction, and without them females are infertile. Indeed, some evolutionary theories suggest that human menopause may have evolved to prolong female survival while caring for grandchildren.[104] One possibility is that the relationship between estrogen levels and survival is nonlinear: completely losing ovarian hormone production (e.g., ovariectomy) or lacking ovarian hormones throughout life (e.g., males) might have negative effects on survival, while in normal females the presence of estrogens during certain life periods facilitates survival. But relative estrogen exposure, in terms of duration or concentration, particularly if associated with greater childbearing, might still be negatively correlated with survival among females.

Another possibility is that estrogens provide survival benefits in laboratory environments and in humans living in contemporary conditions where food abounds, but may not have such beneficial effects in more challenging environments where trade-offs are more stringent. While both male castration and testosterone administration have been

shown to alter male survival in wild environments (see below), we are unaware of studies that have assessed the survival effects of female hormone manipulation in similar conditions. Such data will be important in understanding how female-specific hormone production contributes to the frequent presence of sex differences in aging in wild animals.

Testosterone

Since testosterone is the initial signal that triggers the development of many costly male secondary sexual traits, it has long been assumed that testosterone may be the cause for sex differences in life span.[105] Castration, and thus removal of testosterone production, has been associated with improved male survival in many mammals, including humans,[105,106] primates,[107] sheep,[108] cats,[109] dogs,[110] rats,[111] and mice.[112] In birds, supplementation with additional testosterone has generally reduced the survival of males.[113,114] Male gonads and their associated hormones, therefore, seem to constrain male survival, while facilitating the development of male-specific traits that provide an advantage in competition for males.

To begin with, and even in some cases today, the effects of testosterone seemed to be treated as something of a *fait accompli*, an invariant property of androgen levels. As with telomeres (above) and many other mechanistic explanations, the evolutionary question—why testosterone reduces male survival and accelerates male aging—went begging, and it still does, attracting scant attention from scientists exploring the cell and molecular biology of aging. This is surprising, given the comparative consistency with which testosterone reduces life span. Since testosterone increases allocation to male-specific weapons, ornaments, aggressive behaviors, and risk taking, part of testosterone's effect on average life span may be simply a consequence of increased energetic and predation costs or behavioral changes that increase mortality. Castration of male Soay sheep living on the island of Hirta, St. Kilda, for example, led to an increase in life span such that these males lived longer than either intact rams or ewes. Jewell *et al.*[108] suggested that their subsequent lack of engagement in the autumn rut might facilitate such improved survival, noting that during the rut period "Castrates continued lying, cudding, or grazing despite agonistic encounters between rams, or mating activity, nearby."

The suppressive effects of testosterone on the immune system have frequently been suggested to be a cost of production of androgen-dependent sex signals, one that might limit the ability of males in poor condition from maintaining the development of these traits.[115–117] It is conceivable, therefore, that this suppression of the immune system might reduce male survival relative to that of females because it increases male susceptibility to parasites and pathogens. While testosterone can suppress the immune system, these effects appear variable,[118] as is the relationship between testosterone levels and the degree of parasite burden in wild animals.[119] Notably, castration can also increase survival of male rodents in laboratory conditions, [98,120] where exposure to parasites and pathogens is lower, and infection-related mortality is low or nonexistent, suggesting effects of testosterone on aging outside of the relationship with parasitic infection.

Testosterone has been suggested to have other negative effects on various functions and pathologies involved in aging, including oxidative stress, autophagy, and proteosomal activity.[121] Most data exploring these effects focus on alterations in specific tissues, and we have little understanding of how these changes influence the physiology of the whole organism, or, ultimately, how they might reduce male survival. Testosterone's effects on various aspects of physiology, at least in laboratory conditions, also differ in relation to age, with the loss of circulating testosterone levels during aging also having negative effects on some aspects of metabolic function and age-associated health.[122]

The question remains, why do testosterone's suppressive effects on beneficial traits, such as immune responses, antioxidant defense, and autophagy, persist? How might androgen signaling elevate male reproductive success despite the costs to these protective pathways? Immune responses are considered to be energetically costly,[123] and therefore suppression of these systems might free up resources for allocation to male-specific growth and reproduction. Alternatively, oxidative stress and inflammation might be an avoidable consequence of greater anabolic synthesis and energy metabolism,[6] the benefits of which to reproductive success may outweigh their negative effects, particularly if these negative effects manifest later in life.

Over the past decade, research in cell lines and model organisms has highlighted molecular signals

and hormones that can facilitate growth and often reproduction but at the same time reduce stress resistance and survival.[124] Genetically decreasing the activity of particular signals, sometimes just in specific tissues, can reduce adult size and reproductive traits, like brood size and testicular function, but at the same time increase life span.[125] Intriguingly, various manipulations of these pathways produce sexually dimorphic effects on survival—at least in mice.[20] There has been little investigation into why these sex differences occur, but they hint that sex-specific traits, such as male-specific testosterone production, might feed into these pathways, adjusting trade-offs toward sex-specific optima for growth and survival.

Growth, nutrient sensing, and life span–extension pathways

Growth hormone (GH) and IGF1 signaling provide much of the hormonal stimuli for mammalian growth from puberty and continuing through to adulthood. Across mammals, plasma levels of IGF1 correlate with the pace of life, with high plasma IGF1 found in small, short-lived species that grow and reproduce fast.[126] While larger mammals tend to live longer than smaller species, the opposite pattern pertains to variation within some species (but see counterexamples in roe deer and bighorn sheep[127]), probably as a consequence of within- and between-species differences in the relative pace of growth.[128,129] Among breeds of dogs, large breeds grow fast but age more rapidly.[130] Much of the variation in breed size appears to be due to *IGF1* allelic variation[131] and circulating GH,[130] supporting a link between selection—in this case, artificial selection by breeders—and growth and aging rates.

The direct links between the growth-promoting GH/IGF1 pathway and aging and life span are already well characterized in laboratory mice. Reducing either the production or detection of GH in mice produces animals that are approximately 50% smaller than normal. Surprisingly, these animals can also live up to 50% longer than their wild-type counterparts.[132–134] Detection of GH in the liver stimulates the production of most of the circulating IGF1, which in turn stimulates growth promotion in multiple tissues. Reducing the production or reception of IGF1 also reduces body size and can extend life span.[135,136]

Heterozygous deletion of the gene encoding the IGF1 receptor appears to extend life span to a greater extent in females than males.[135,137,138] Females also show an increased resistance to oxidative stress with this manipulation, while males do not.[135,137] Sexual dimorphism in life span extension with reduced activity of growth-promoting pathways is not limited to IGF1. At a cellular level, growth-promoting signals like GH and IGF1, in addition to modifying energy and nutrient levels, induce activation of mTORC1 signaling.[139] Activation of this signaling complex increases many different cell functions, particularly protein translation, which influence cell growth and proliferation, but at the same time this complex reduces functions that facilitate cell survival.[140] Reducing the activity of mTOR, either genetically or with the drug rapamycin, also increases life span to a greater extent in female than male mice,[22] further highlighting sexual dimorphism in life span extension when specific signals that promote growth are reduced. Sex specificity in manipulations that alter life span is not confined to life extension: several manipulations that reduce aspects of insulin signaling can reduce life span, but do so to a much greater extent in males than females.[141,142]

Can this tell us anything about the mechanistic and evolutionary causes for sex differences in aging? The levels of both IGF1 and mTOR signaling vary in relation to sex, albeit in a tissue- and age-dependent manner.[143,144] These signaling pathways are also important in sexually dimorphic growth. Reducing mTOR signaling with rapamycin from weaning to the normal age of adulthood can abolish sexual dimorphism in body size, with males requiring a higher drug concentration to produce a proportionally similar reduction in body size to females.[145] Similarly, reducing aspects of GH signaling can also abolish sexual dimorphism in body size.[146,147] Thus, the greater baseline activity of these signaling pathways in males facilitates male growth but might have pleiotropic effects that ultimately reduce life span. This may be why greater concentrations of rapamycin are required to produce equivalent increases in male life span.[148]

In insects, insulin-like signals and alterations in mTOR signaling can also regulate body size and life span, with various different mutant strains of *Caenorhabditis* nematodes and *Drosophila* vinegar flies showing slower development and/or smaller

body size but a substantial extension in life span.[149] Where two sexes are present, life span extension in response to different interventions is also sexually dimorphic, but the pattern of dimorphism differs considerably from that observed in mice. In *Drosophila*, reduced mTOR signaling through rapamycin treatment has been qualitatively described as providing greater life span extension in females,[150] although a meta-analysis of life extension with reduced mTOR signaling showed no overall bias in the sex response in this species, whereas the effect in mice is consistently biased toward females.[22] A recent study of dioecious nematodes demonstrated greater life extension in males than females at equivalent levels of rapamycin concentration.[151] Both the physiological control of sexual dimorphism and total dimorphism in body size differ considerably in these species when compared with mice, likely contributing to this disparity. In these invertebrates, females are much larger than males, and the authors suggested that rapamycin preferentially extends the life span of the smaller sex (presumably with the lowest levels of mTOR signaling), which would be consistent with observations in mice and the roles of mTOR signaling in sex-dependent growth and aging.

The effects of IGF1 and related insulin signaling in different species on sexual dimorphism are not limited to growth. IGF1 signaling is critical for the development of exaggerated weaponry in beetles and antlers in some mammals.[152] Similarly, insulin signals in *Drosophila* more broadly influence individual attractiveness to the opposite sex, at least partly through effects on cuticular hydrocarbon profiles.[153] We therefore envisage that the sexual selection also acts on these signaling pathways, facilitating the development of traits and behaviors involved in competition for mates. Sex-specific selection for weapon or ornament elaboration may further contribute to sexual dimorphism in aging beyond the more generalized effects on sexually dimorphic growth.

Mating interactions affect life span and aging

Mating interactions with members of the opposite sex create the possibility of mates influencing each other's relative reproductive allocation, and, ultimately, patterns of survival across life. Interlocus sexual conflict over whether and how often to mate, how many offspring to have, and how much to invest in those offspring, as well as incidental harm imposed by one mate on the other, can generate sex differences in life span, alter reproductive scheduling, and potentially alter aging trajectories.[26] Here, we consider some ways in which the molecular and physiological pathways involved in such conflict-riddled mating interactions are revealing new insights into the evolution of sex-dependent aging and longevity.

Sensory perception of mates

Traditional life history theory expects individuals to pay costs for the allocation of resources to reproductive traits, such as parental care, particularly in females, and the production of traits used for competing for males, such as weapons and sexual signals, particularly in males. Allocating resources to these traits directly increases mating opportunities or offspring survival, but doing so can reduce survival. Recently, it was highlighted that simply perceiving a potential mate's presence can have major effects on life span in model organisms[83,85] and, importantly, that these effects can even be reduced when direct access to mates is provided. This hints that a direct resource-allocation paradigm, when considered in its simplistic form, does not capture the complexity of reproduction's negative link with life span.

Perhaps the most striking example of the effects of mate perception on life span was the approximately 30–40% reduction in male *Drosophila* life span when exposed to female pheromones.[85] Female life span is also reduced when exposed to male pheromones, but the effect was much more modest, an approximate 5% reduction in life span. Interestingly, when males exposed to female pheromones are also provided with the ability to mate with females, with females provided in excess to males, the negative effects of female pheromone exposure are reduced. This highlights that responses to cues of mating might sometimes be more costly than the mating event itself. The reduction in life span with perception of mates in *Drosophila* is still linked, in some respects, to resource allocation. Males exposed to female pheromones show a strong reduction in triglyceride levels and reduced survival with starvation. This highlights that resource-allocation trade-offs underlying reproduction–life span trade-offs in males might be generated in anticipation of and preparation for mating, rather than by mating itself.

While the effects of male pheromones on female life span are weaker in *Drosophila*, mating instead has major effects on survival, and thus the mating event is expected to be costly in this sex. However, at least part of this effect of mating on female aging occurs without the requirement of egg production and the transfer of sperm.

Seminal fluid proteins

Females with experimentally elevated mating rates have shorter life spans than controls, an effect that is observed across a variety of insect species.[154] Some of this reduction in life span occurs simply as a consequence of the transfer of seminal fluid proteins (SFPs), since females mated with males that produce seminal fluid but no sperm also show a reduction in life span.[76] Genetic inhibition of specific SFPs in males has been shown to be sufficient to alter the life span of mated females,[77,155] and ectopic expression of SFPs directly in females can also reduce their life span.[156]

The shortening of female life span in response to SFPs has been hypothesized to be either a side effect of some function that SFPs have in males or an evolutionarily selected toxic trait in males that increases female current investment in reproduction and/or reduces female remating.[157,158] While reducing female life span, SFPs have a range of additional effects on female behavior and physiology, in particular inducing female egg laying and reducing female future mating receptivity,[159] as well as altering sperm storage, food intake, activity levels, and immune activation (for a review of these effects, see Ref. 155). However, the reduction in female survival does not seem to be purely a side effect of increased female egg laying, since SFPs also decrease life span in sterile mutant *Drosophila* females.[160] Thus, direct resource allocation trade-offs between offspring production and life span, as traditionally expected to generate female aging, do not appear to be the major generator of this reduction in female life span. Recent work in *Caenorhabditis elegans* has also documented the deleterious effects of mating with males on hermaphrodite survival.[84] Reduced life span also seems to result from the effects of male transfer of both sperm and seminal fluid, and, similarly to *Drosophila*, this reduction in life span also occurs in females with no germ line that do not produce progeny.

The proximate causes for seminal fluid–induced female reproductive changes and increased aging are still poorly understood. In *C. elegans*, aspects of steroid and insulin signaling seem to partly underlie the female aging response to seminal fluid, as reductions in female survival with mating are diminished in animals with mutations in aspects of these signaling systems.[84] Hormonal signaling may also underlie some of the life history effects of SFPs in *Drosophila*, since juvenile hormone levels are elevated by SFPs[159] and are associated with the aging process in some insects.[161,162] Thus, hormone effects of mating may feed into those pathways that contribute to sex differences in life span extension.

Diet, reproduction, and aging

Some of the most prominent and promising research on aging concerns the role of diet. Over 80 years ago, McCay and collaborators[163] recognized that rats fed a restricted amount of food grew more slowly and lived longer than rats fed *ad libitum*. Since then, considerable support has amassed for the view that restricted diets delay aging and prolong life in a variety of taxa from yeast to mammals.[90,164–167] The effects of diet on aging and life span have inspired fascinating research within both the mechanistic and evolutionary traditions. Mechanistic research into nutrient-sensing and metabolism pathways, including sirtuin, mTOR, fibroblast growth factor 21, and the insulin, IGF1, and GH pathways, has driven considerable progress in the cellular and metabolic study of aging and identified targets for antiaging drug discovery.[168]

Dietary restriction (DR) effects that prolong life span and delay aging have long been interpreted as consequences of restricted energy intakes (i.e., caloric restriction), but over the last decade, more directed manipulations of diets, most following an approach developed by Simpson and Raubenheimer[169,170] within evolutionary and physiological ecology, have instead implicated restrictions in certain macronutrients, notably low protein to carbohydrate (P:C) ratios (e.g., Refs. 171–173; see review in Ref. 174).

Within evolutionary life history theory, it is the acquisition of resources and their allocation to current reproduction, somatic maintenance, or storage that determines the shape and strength of life history trade-offs,[175,176] including those involved in aging.[3,43,44] One reason that low P:C ratios

prolong life span may be that when animals are faced with insufficient protein for reproduction, they might allocate those resources they do have to somatic maintenance and survival until such time as they have sufficient protein for reproduction.[174] Reproductive performances of female *Drosophila melanogaster* flies,[171,177] Queensland fruit fly, *Bactocera tryoni*,[178] *Teleogryllus commodus* crickets,[172] and house mice (*Mus musculus*)[179] were all maximized on higher P:C ratios (between 1:3 and 1:1) than the high-carbohydrate, low-protein diets that maximized life span. Animals are expected to and consistently choose diets higher in protein than those that maximize longevity, due to the importance of protein in reproduction.

Diet choice, then, can entail dynamic optimization of the reproduction–aging trade-off via the intake of protein, carbohydrates, and, potentially, other nutrients. Adding further complexity, macronutrients can have different effects on female and male fitness, creating sex-specific dietary optima, leading to sex differences in diet, and, potentially, sex differences in life span and aging. In mice, measures of male reproductive allocation (testes mass and epididymal mass) were maximized on 1:1 P:C ratios, somewhat lower than the 3:1 P:C ratio that maximized female uterine mass and ovarian follicle number,[179] but still requiring a far higher protein intake than the 1:13 and 1:11 P:C ratios maximizing, respectively, male and female life span.

In those insect studies that measured male reproductive performance, both male *T. commodus*[172] and *D. melanogaster* [177] performed best on very low P:C ratios, similar to those that maximized life span. Differences in dietary fitness optima should lead to sex-specific diet choice. Female field crickets, given free choice, eat slightly more protein than males, but the diets of both sexes converged on the sex-specific optimum diets for lifetime fitness.[172] This raises the possibility that constraints on the evolution or expression of sex-specific dietary optimization may generate intralocus sexual conflict over diet choice,[172] potentially accelerating aging or otherwise lowering fitness in one or both sexes.

The study of diet-mediated, sex-dependent aging and longevity has only just commenced, but the evidence that has been published suggests that complex interactions are likely to be widespread. In *D. melanogaster*, for example, late-life mortality rates are influenced by an interaction between sex and diet.[180] Adding even greater complexity, in one experiment, adult life span was influenced by interactions between sex, social environment (being kept in same-sex or mixed-sex cages), dietary yeast concentration, and the addition of methionine to the diet.[181] The emerging picture suggests that the complex links between sex, reproduction, and diet influencing aging and life span will need considerable further study, but resolving those links might prove a fertile source of ideas concerning the mechanisms that influence aging, potentially turning up new interventions or exposing antiaging interventions tailored to particular contexts, and perhaps only to one sex.

The importance of methionine sparks a cautionary word about evolutionary trade-offs and aging. Although the evidence that reproductive effort trades off against aging and life span is generally robust, nutrients and potentially drugs or other interventions can affect one without altering the other. Adding essential amino acids to restricted diets in *D. melanogaster* restores fecundity and reduced life span to levels comparable to unrestricted diets.[182] Adding only methionine, however, restored fecundity but left the life span–extending effects of DR intact (but see Refs. 181 and 182). This evidence implies that the life span–extending effects of DR are far more complex than a reallocation of resources from reproduction to somatic maintenance, a complexity likely only to be resolved by understanding the metabolic pathways involved (Ref. 182 identifies changes to the activity of the insulin/ IGF pathways).

While most research has focused on diet choice and trade-offs associated with differences in the ratios of proteins, carbohydrates, and fats, there may be more specific nutrition requirements, such as specific amino acids, which each sex requires to allocate to a particular component of reproduction. Similarly, it may be specific amino acids or other specific nutrients that generate dietary-mediated aging. For example, mTORC1 signaling can be activated by specific amino acids, including lysine and arginine,[183] while reduced dietary intake of certain amino acids, including methionine and tryptophan, can slow aspects of aging in rodents.[184,185] Understanding whether diet choices and the resulting effects on longevity are driven by more specific dietary preferences will be a complex undertaking, but might ultimately help to refine our

understanding of sex-dependent dietary choice and help to resolve why certain diets alter rates of aging in some contexts.

In an intriguing essay, Adler and Bonduriansky[186] argue that dietary restriction prolongs life span not because nutrients have been diverted from reproduction to somatic maintenance, but rather because full-fed animals inhibit the crucial aging-inhibiting processes of autophagy and apoptosis in order to maximize growth, whereas animals on restricted diets disinhibit autophagy and apoptosis to increase nutrient-recycling efficiency. Those recycled nutrients can then be used to eke out some reproductive effort. This idea reconciles the importance of nutrient-sensing pathways, including the TOR and insulin/IGF1 pathways in the life span–extending effects of dietary restriction[186] and, in particular, the evidence that the life span–extending effects are not present when autophagy is inhibited.[187–189] The extent to which this idea is an improvement on more established ideas about reproductive trade-offs remains to be directly tested, but it does appear to be fertile ground for the cultivation of alternative hypotheses concerning the relationships among nutrients, reproduction, molecular pathways, and aging.

Conclusions

Ample evidence suggests that reproduction and the physiological pathways enabling reproduction provide the key to understanding the evolution of sex differences in longevity and aging. Nonetheless, the simple model according to which resources are allocated either to reproduction or to somatic maintenance at the expense of the other, giving rise to relatively tractable trade-offs, has been confronted with several challenging lines of evidence and argument. As ideas about life histories, sex-dependent selection, and sexual conflict become further integrated with the increasingly complex and contingent mechanisms that are being revealed as the proximate causes of aging, our understanding of both aging and trade-offs and life history evolution will deepen. Only with such an understanding will we be able to resolve the general principles that underpin aging from the many private mechanisms that make it so species, sex, and environment specific.

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Conflicts of interest

The authors declare no conflicts of interest.

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