Gender, immunity and the regulation of longevity

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Summary

For humans and many other animals, gender is a fact of life. Most individuals are born either male or female and their sex will have an enormous influence on their behaviour, physiology and life history. In this review, I consider the effect gender has on lifespan. In particular, I discuss the role played by behaviour, immunity and oxidative damage in determining sex-dependent differences in longevity. I consider existing explanations for the effect of gender on lifespan and how these explanations fit together. Finally, I expand on the recent suggestion of a key role for the insulin/IGF-1 signalling pathway in regulating sex-dependent differences in lifespan[1] and I highlight a number of areas for future investigation. ***BioEssays*** **29:1–8, 2007.**

Introduction

We are all aware that men and women differ not only in their anatomy and physiology, but also in more complex biological traits such as lifespan. For example, a male baby born in the United Kingdom in 2005 had a life expectancy of 77 years, whilst girls born at the same time would be expected to live, on average, more than four years longer.[2] This effect is not human specific, since sex differences in longevity occur in a huge range of animals, regardless of the absolute mean lifespan of individual species. This is true not only for mammals[3] but also for other vertebrates (such as birds[4] and fish[5]) and for many invertebrate species.[6–9]

How longevity evolves is an issue that has vexed evolutionary biologists for many years. The conundrum of 'old-age' survival has been a particular puzzle, since factors that influence only post-reproductive lifespan cannot, by definition, be selected for directly. This issue was famously addressed by Hamilton in his landmark 1966 paper on the evolution of ageing, in which he demonstrated that senescence is an inevitable consequence of selection for maximal reproductive success.[10] This paper provided a mathematical framework for the concept of 'antagonistic pleiotropy', proposed by Medawar, Williams and others (for a recent review, see Charlesworth[11]), in which factors that incur a survival cost late in life can still be selected for if they confer a reproductive advantage in youth.

The existence of sex differences in lifespan would suggest that the two sexes experience different selective 'optima' early in life and therefore show a corresponding difference in median lifespan. In this review, I discuss a range of factors that may underlie sex differences in longevity, with a particular emphasis on recent data concerning the molecular determinants of lifespan. I propose that sex-dependent mortality can be evolutionarily selected for by both antagonistic pleiotropy (e.g. if 'risky' behaviour results in higher mortality but also higher reproductive success) and synergistic pleiotropy (e.g. if improved immunity protects against fatal infections before reproductive maturity and then remains effective against infections in old age). Finally, I suggest that the insulin/IGF-1 signalling pathway may be one example of a synergistically pleiotropic pathway that exerts strong effects on sex-dependent longevity.

'Risky' behaviour as a lifespan determinant

Many theorists have sought an explanation for sex-dependent longevity differences by looking at the most-obvious difference between males and females, that of behaviour. In many species, particularly mammals, male animals engage in complex courtship rituals, displays of dominance, male–male conflict and other sex-specific activities. If such behaviour leads to an increased risk of death (as would clearly be the case with displays of aggression), then males would, on average, be expected to die earlier.

Sex-specific behaviours certainly appear to contribute to male mortality,[12,13] especially in humans, where males are far more likely to die as a result of 'risky' or violent behaviour at all ages.[14,15] However, a number of studies have indicated that this level of increased risk is insufficient to fully explain the higher rate of male mortality in most species,[3] nor can this model account for species in which the 'risk-averse' sex is nonetheless shorter lived.[4,16]

Parental investment theory

Evolutionarily speaking, sons and daughters are not of equal value to a parent because of the different reproductive rates of the two sexes. In general, females are a 'safe' bet: the majority of females mate successfully, but total reproductive output

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over their lives is low. In contrast, sons represent the 'high risk, high gain' approach: many males never succeed in mating (thereby representing a genetic dead-end), whilst a minority are very successful and produce far more offspring than a daughter would have.[17,18] This disparity predicts that parents ought to invest in sons when resources are abundant but to favour daughters when resources are limited. Such a bias would be expected to be more pronounced in the many vertebrate species that show significant sexual size dimorphism, since male offspring are larger and hence more costly to raise. Given this, one might expect average male lifespan in most species to be shorter, since parents would neglect male offspring during resource-poor seasons leading to higher mortality in male infants.[19]

A number of studies support this prediction of higher male infant mortality in both mammals and birds.[20,21] However, these observations have more recently been attributed to the greater susceptibility of males to starvation, presumably as a result of their larger bodies imposing a higher energy demand.[22] In this context, increased male mortality when resources are limited can be seen as a direct consequence of sexual size dimorphism—the larger sex is more vulnerable to energy deprivation at all ages, not only during infancy. This alternative interpretation would also explain the observation of higher male mortality in many invertebrate species,[23,24] which typically show little parental investment in their young and are thus difficult to reconcile with the 'biased investment' theory of Trivers and Willard.[19]

Sex differences in the burden of disease

More recently, differences in the burden of parasitism (or, more generally, infectious disease) have been proposed as an explanation for sex-biased mortality in many animal species. It is very clear that many species show sex-specific variation in parasitism, with parasite infection rates and overall parasite burdens being higher in males in both mammals[3,25] and birds.[26] Similar sex-dependent differences are observed for bacterial and viral infections,[27] suggesting that males may in general show lowered disease resistance.

More than twenty years ago, Hamilton and Zuk suggested that infectious disease may be the selective agent that drives the evolution of superficially maladaptive secondary sex characters such as bright plumage and elaborate ornamentation.[28] This theory of 'parasite-mediated sexual selection' suggests that animals select mates with higher disease resistance (an 'invisible', but highly desirable, trait) by assessing 'honest signals' of health, such as colouration. Ten years later, Folstad and Karter combined the Hamilton-Zuk hypothesis with the wealth of data showing higher disease burdens in males relative to females, thereby developing the influential 'immunocompetence handicap' hypothesis.[29] This hypothesis proposes a trade off between secondary sex characters and immunity. The trade off results from the dual role of the sex hormone testosterone, which positively regulates secondary sexual characters (e.g. bill colouration in birds[30,31]) but simultaneously suppresses immunity.[32–35]

However, since male-biased parasitism also occurs in species that lack testosterone, such as insects, the immunocompetence handicap theory in its current form cannot explain the ubiquity of this phenomenon.[9] In addition, it is hard to understand why some mammals show a reversal in sex-dependent parasitism (i.e. with females being more heavily parasitised than males[3]) whilst testosterone levels are always higher in males than in females.

Moore and Wilson have instead proposed that body size, rather than testosterone level, may account for sex-biased parasitism in mammals.[3] In this model, the larger sex presents a larger 'target' for parasitic infection and a larger 'resource' to support heavier infestations. A powerful argument in favour of this hypothesis is the finding that species with reversed sexual dimorphism (i.e. females larger than males[16]) also show a reversal in parasitism (i.e. females are more heavily parasitised),[3] thus arguing against a role for testosterone. In this context, it is interesting to note that two of the model organisms most widely used for longevity research, the nematode Caenorhabditis elegans and the fruitfly Drosophila melanogaster, both show a reversed sexual size dimorphism (i.e. females are the larger sex) and a similar reversal in longevity (i.e. males are the longer-lived sex).

An important aspect of the 'sexual size dimorphism' argument is that sex-dependent differences in disease burden may not result from differences in size per se, but also from the consequences of size differences. For example, for many large parasites (particularly ectoparasites such as ticks) host body size is likely to directly affect parasitic burden—large bodies provide large 'targets' for parasite attachment. For smaller pathogens, however, the benefit of a larger host may lie not in an increased body size itself, but rather a related aspect of the host's biology such as increased dietary intake (for example, larger animals eat more than smaller individuals and may therefore be at higher risk of food-borne disease) or increased host range (larger animals have larger territories,[36,37] although the link with parasitism has been disputed by Wilson et al.[38]). In this context, sexual size dimorphism may lead to a shortened lifespan in the larger sex due to both reduced parental investment during infancy and, subsequently, a combination of increased mortality during resource limitation (such as starvation) and an increased burden of disease during adulthood.

Infectious disease as a cause of mortality

In wild populations of most species, parasitism and infectious disease are likely to be major causes of mortality, both directly and indirectly (e.g. by increasing morbidity and thus leading to higher levels of predation of infected individuals).[39–41] Thus if

one sex bears a heavier burden of disease than the other, lifespan in this sex may be directly reduced as a result.

This effect has been empirically demonstrated for at least one mammal species, the Soay sheep (**Ovis aries**). In comparison with female sheep, male Soays are larger, more heavily infected with intestinal parasites[42] and are shorter lived.[43] Importantly, when parasite burdens were experimentally reduced in both male and female sheep, the sex difference in mortality was lost.[44] Interestingly, it appears that the higher levels of parasitism experienced by males do not in themselves trigger increased mortality, but rather they reduce the host's ability to survive periods of malnutrition.[42,44] Thus sexual size dimorphism inflicts a 'double whammy' on the larger sex during starvation: not only do large animals require a higher dietary intake in order to support a larger body, but, in addition, a higher proportion of their diet is appropriated by parasites.

Lifespan differences in the absence of infection

For many animal species, it is possible that a combination of increased risk and increased parasitism may account entirely for the higher rate of male mortality. However, for humans this appears not to be the case. The last century has seen an unprecedented improvement in medical treatment and living conditions for those fortunate enough to live in developed countries. The result of this enormous change is that infectious diseases are no longer a major cause of death for people in Europe or the USA[45] and yet there is a still a sex difference in longevity.[46] This trend remains even when deaths due to obvious behavioural differences (deaths due to road traffic accidents or firearms, for example) are accounted for.[15,47] Indeed, Kruger and Nesse have calculated that only 35% of the excess male mortality seen in American populations can be directly attributed to risky behaviour.[46] Of the residual excess male mortality, only 1% was directly attributable to infectious disease (pneumonia and influenza). Clearly, then, reduced male lifespan (at least in humans) cannot be explained solely in terms of behaviour or infectious disease. Rather, sex-dependent mortality results from a combination of factors, some of which are yet to be determined.

For obvious reasons, performing a similar analysis on most animal species is exceptionally difficult—in wild animal populations, the vast majority of individuals die either from disease or predation. However, limited data from animals kept in relatively disease-free conditions in laboratories or zoos indicate that sex differences in longevity persist in these circumstances.[48–52] Thus, although infection may be a major contributor to sex-dependent longevity differences in many animal populations, there remains an underlying sex difference in lifespan even in the absence of disease.

Oxidative damage and lifespan

Research into the biology of ageing has exploded over the last three decades, with a combination of interventional and non-interventional studies in humans and experimental investigation in vertebrates[53] and invertebrates.[54–56] A major finding from these studies has been the role played by oxidative damage in reducing lifespan.[57] Levels of damaging reactive oxygen species (ROS) are regulated by a complex interplay of factors, including daily calorie intake,[58] dietary levels of antioxidants such as vitamin E[59] and resveratrol,[60–62] as well as by endogenous levels of antioxidant enzymes such as superoxide dismutase.[63–65] Experimental modification of many of these factors directly alters longevity[63,66–68] (although note contradicatory evidence from mice[69] and *Drosophila*[70]) suggesting that oxidative damage may directly shorten lifespan.

If males and females suffer differing levels of oxidative insult, the resultant damage may therefore be sufficient to explain the residual sex-specific lifespan difference observed in the absence of infection. Indeed there is mounting evidence to suggest that both male humans and male mice express lower levels of protective enzymes such as superoxide dismutase and catalase than females and consequently suffer higher levels of oxidative damage.[71–73] It is thus tempting to speculate that higher levels of oxidative damage in men may lead indirectly to shortened lifespan, particularly since such damage is known to trigger cardiovascular disease,[62] which is the main cause of increased male mortality in the USA.[46]

Towards a comprehensive model

The wealth of data available on sex differences in lifespan highlights a number of recurrent themes. Firstly, sex differences in longevity are seen in a wide range of species from different phyla, regardless of whether their absolute lifespan is measured in days or decades. Secondly, either sex can be the longer-lived sex although, in most species, females outlive males. Thirdly, there is considerable evidence suggesting that at least three factors contribute to this difference in lifespan between the sexes: differential behaviour, differential infection rates and differential levels of oxidative damage (Fig. 1).

Much of this inter-sex variability may be accounted for by sexual size dimorphism. Larger animals suffer heavier burdens of infection[3] and, in many species, larger animals are more dominant and therefore more vulnerable to mortality associated with 'risky' behaviour (such as aggression).[74] However, sex-dependent differences in lifespan remain even in the absence of infection and 'risky' behaviour, primarily because of sex-dependent differences in 'cellular ageing' processes (such as the accumulation of oxidative damage). In the final part of this review, I propose that insulin/IGF-1 mediated stress responses may underlie this 'third facet' of sex-dependent ageing, thereby linking gender and longevity at the molecular level.

Stress responses and longevity

The use of small invertebrates as model organisms has revolutionised much of biology, not least the study of ageing. Genetic studies in the nematode, *Caenorhabditis elegans* and

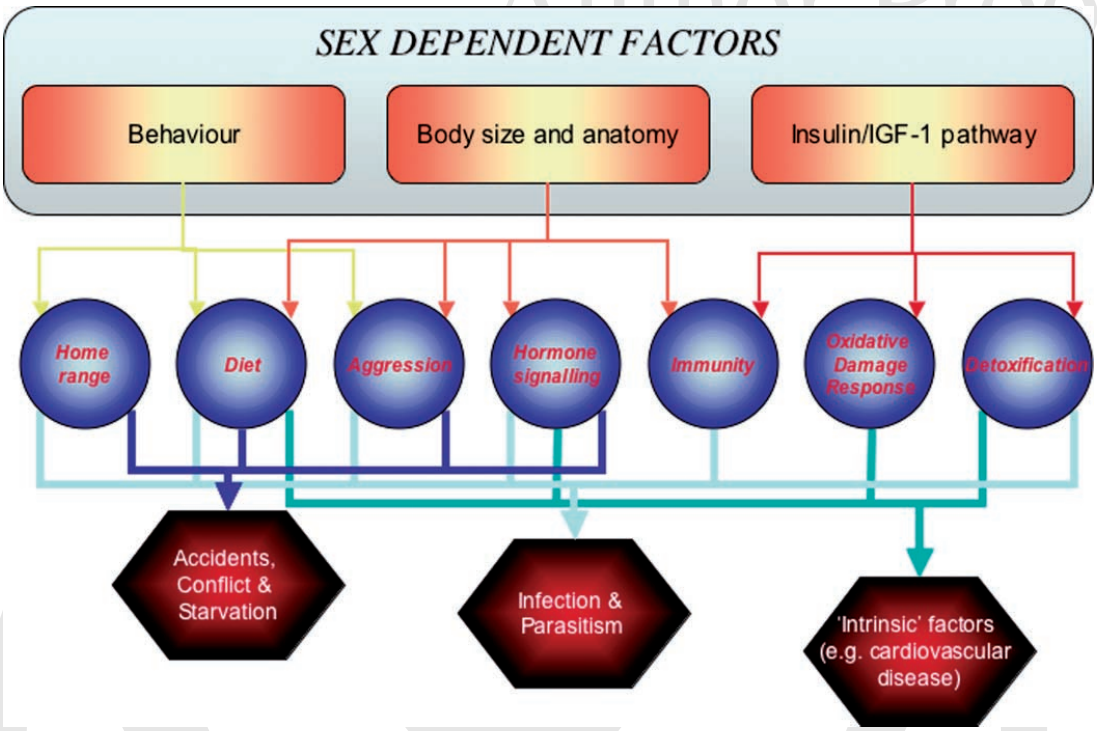

Figure 1. Lifespan is influenced by several 'macro' factors, including behaviour, body size and the insulin/IGF-1 signalling pathway, all of which are affected by the sex of the individual. These modulate numerous biological traits (in blue), such as diet and immunity. The end result of these changes is to alter the probability of death due to extrinsic factors (such as injury), intrinsic factors (such as organ failure) and infectious disease.

the fruitfly, *Drosophila melanogaster*, have identified a number of so-called 'gerontogenes'—genes whose activity directly regulates longevity. In 1993, Cynthia Kenyon and colleagues demonstrated that mutations in the gene *daf-2*, an insulin-like growth factor receptor, could double the lifespan of *C. elegans*.[75] Extraordinarily, *daf-2* homologues and their downstream effectors have subsequently been shown to regulate lifespan in both *Drosophila*[76,77] and mice.[78]

The DAF-2 protein and its homologues influence longevity by controlling the activity of a signalling pathway that culminates in a FOXO (FOrkhead class, boX O) transcription factor, such as *daf-16* in *C. elegans*[79] and dFOXO in *Drosophila*.[80] These proteins typically control the expression of hundreds of genes, including many that are involved in detoxification, control of oxidative damage and immunity.[81–83] In line with these findings, several studies have shown a critical role for the DAF-2/DAF-16 signalling cascade in regulating antimicrobial defence[84–87] and oxidative stress tolerance[66,88–90] in *C. elegans*.

DAF-2 and its downstream effectors may therefore provide a molecular link between longevity, oxidative stress and immunity in both invertebrates and vertebrates[86] (Fig. 1). If the relative activity of this pathway is different in the two sexes, this could explain much of the sex difference in longevity. In support of this hypothesis, there is growing evidence in favour of sex-dependent activity of this pathway. In *C. elegans*, males are both the longer-lived[50,51] and more-pathogen-resistant[91] sex. Importantly, however, both effects are completely lost in *daf-16* knockout males,[50,91] suggesting that the enhanced lifespan of male *C. elegans* may result from constitutive activation of DAF-16. Indeed there is evidence that this may also occur in other animals. In both flies and mice, activation of the insulin/IGF-1 receptor pathway (homologous to the DAF-2/DAF-16 pathway in worms) increases female lifespan dramatically, but male lifespan only marginally, perhaps suggesting that this pathway may be constitutively 'on' in wild-type males.[1,76–78,92] Intriguingly, recent work has demonstrated that reduction-of-function polymorphisms in the human IGF-1 receptor (the equivalent of *daf-2* mutations in *C. elegans*) correlate with reduced body size and improved old age survival in women,[93] suggesting that the link between insulin/IGF-1 signalling, body size and lifespan may also exist in humans.

The evolution of sex-dependent differences in longevity

Given that sex differences in longevity occur in most species, why might such differences have evolved? Bateman[94]

highlighted an intrinsic difference between the sexes, in that the most-efficient way for males to increase their fitness is by mating with more partners, whereas female fitness is most efficiently enhanced by living longer, a theory that has become known as Bateman's Principle. More recently, Rolff has invoked this principle[9] as an explanation for differential immunity between the sexes—females invest more in immunity in order to maximise lifespan, whereas males sacrifice immunity in order to maximise mating (the ''mate fast, die young'' strategy).

This model has two important implications. Firstly, differences in lifespan are not linked directly to gender, but rather to behavioural and ecological factors. Under conditions in which the difference in reproductive strategy between the sexes is lost (e.g. in monogamous species with substantial parental investment in the young from both parents), differences in lifespan between the sexes would not be advantageous.

Secondly, the relative advantage or disadvantage of longevity in the two sexes could potentially change on a rapid evolutionary timescale as changes in climate, habitat, predation and myriad other factors disperse or concentrate animal populations.

Regulation of lifespan by the stress–response pathway provides a molecular mechanism to satisfy both of these prerequisites. Since the insulin/IGF-1 pathway is not directly linked to sex determination mechanisms, constitutive activation of this pathway (and consequent lifespan extension) can therefore occur in either sex.

Similarly, regulating multiple determinants of longevity (immunity, oxidative stress responses, etc) via a single, master pathway such as the insulin/IGF-1 pathway means that longevity can evolve very rapidly in response to selective pressure (Fig. 1). For example, single mutations (e.g. in the DNA-binding domain of DAF-16 or its homologues) might raise the basal activity of this molecule, resulting in coordinated increases in immunity, detoxification and oxidative stress tolerance and thus a commensurate increase in lifespan. In contrast, if these responses were 'decoupled', the evolution of increased longevity would require multiple, coordinated genetic changes—a much rarer event. In this regard, it will be of great interest to learn more about how the insulin/IGF-1 pathway regulates longevity and stress responses both together[78,82,95] and independently.[76,96,97]

Outstanding questions and future directions

Notwithstanding the enormous interest in ageing and its consequences, our understanding of the molecular mechanisms that regulate this process, and how they are modulated by selective pressure, is in its infancy. Despite widespread predictions that longevity would be a hugely complex biological trait, it is becoming clear that a small number of regulatory genes have a profound impact on lifespan. It is therefore logical to assume that these 'master regulators' may also control differences in lifespan between the sexes. Importantly, the biological simplicity of this mechanism implies that lifespan can evolve rapidly in response to selective pressure, thereby explaining the observation of huge differences in lifespan that arise between closely related species[51] and on very rapid evolutionary timescales.[98]

An important and outstanding question in the field is to determine the cost of extended lifespan. It is clear that many longevity assurance mechanisms (enhanced immunity, heightened detoxification responses) are biologically costly, but there is a dearth of data on whether these 'costs' can fully balance the advantage of extended lifespan. In this regard, it is interesting to note that the 'classic' *C. elegans* ageing mutant, *daf-2*, is long-lived and pathogen resistant under laboratory conditions, but is rapidly outcompeted by wild-type strains in a more-natural, soil-based, environment.[99] It will therefore be of considerable interest to investigate the effect of lifespan-changing mutations on individual fitness under 'semi-natural' conditions for a range of different species.

In addition, there is much to be gained in adopting a more 'realistic' approach to the investigation of immunity mechanisms and their role in longevity. Most laboratory studies investigate the interaction between a single pathogen and its host in an otherwise sterile environment. Yet, in reality, most animals are perpetually infected with an astounding range of pathogens and parasites. Clearly, evolving an improved response to one infectious agent may have a dramatic effect on immunity (and thus longevity) under laboratory conditions, but may be of no consequence in a wild population.

Finally, the importance of ecological factors in immunity and longevity has long been overlooked. In order to understand the full complexity of phenotypes such as sex-dependent longevity, it is essential to first understand the selective forces that influence these phenotypes. This is of particular importance for organisms, such as *C. elegans* and *Drosophila melanogaster*, that are exceptionally well understood in the laboratory but for which field data is scarce.

Conclusion

Differences in lifespan between the sexes occur in most animal species and yet there is still no comprehensive explanation for why. A number of theories exist, but none can fully account for the observed differences. Instead, I propose that a combination of factors may, together, determine sex-dependent differences in longevity. Firstly, differences in behaviour and anatomy combine to increase mortality in one sex (usually males) due to accidents and aggression. Secondly, differences in size, hormonal signalling and pathogen exposure contribute to lifelong differences in infectious burden between the sexes. Finally, sex-dependent differences in the basal level of the insulin/IGF-1-like signalling pathway result in differences in innate immunity, detoxification mechanisms and oxidative damage tolerance, which together result in increased lifespan in one of the sexes.

These differences are the result of the two sexes experiencing different selective pressures for reproduction. The value of longevity rises with the increasing difficulty of successful mating (e.g. in widely dispersed species) but falls when it is more advantageous to divert resources away from 'expensive' traits, such as immunity, in favour of traits such as brood size or parental care. Retaining diverse phenotypes (immunity, stress responses, etc) under the control of a single 'master' regulator (such as DAF-16) can therefore be seen as an evolutionary stable strategy. Individuals that 'decouple' these effects may gain a short-term advantage (in being able to alter immunity independently of lifespan, for example) but will be unable to respond rapidly to the changing lifespan optima that result from variation in the population structure or other ecological changes.

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