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Guest Editorial

Sex and Aging

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Women have longer lifespans than men in all populations (1) and this has been attributed to various factors such as lifestyle, hormones, or asymmetry in the inheritance of mitochondrial DNA and chromosomes (2). Despite their longer lifespans, women tend to have longer periods of frailty and disability, the so-called "male-female health-survival paradox" (3) which suggests that sex influences the relationship between the deleterious effects of aging and lifespan in humans. In animal experiments, sex influences the rate of aging and the responses to many antiaging interventions including dietary restriction, genetic manipulation and pharmaceutical agents (2,4). Yet as pointed out by Pomatto *et al*. in this issue (5), only 22–42% of all aging studies report the sex of the animals used, and even less report the sex of cell lines. Regardless of the profound effects of sex on aging, it seems that biogerontologists have yet to fully embrace research into the effects of sex on the aging process. Therefore in this special issue of the Journal of Gerontology Biological Sciences, we have published a series of review and research articles that explore the relationship between sex and aging in animals and humans.

One of the key questions is whether sex differences in aging are unique to humans or occur across species. Amongst free-living mammals there is a general pattern that females outlive males while the effects of sex on aging on laboratory models of aging such as *Caenorhabditis elegans*, Drosophila, and mice are more difficult to discern due to variability in animal husbandry and experimental design among the various aging studies (2). The effect of sex on lifespan of companion dogs is particularly interesting and important because dogs are a model for studies of antiaging drugs such as rapamycin (6) and caloric restriction (7), and because many dogs are neutered so that the effects of sex hormones on lifespan can be evaluated. Hoffman *et al*. (8) studied two very large veterinary databases and found few sex differences in lifespan or causes of death and concluded that any sex differences in lifespan are secondary to neutering. Neutering increased lifespan consistent with the concept that sex hormones are detrimental to aging and that there maybe be a trade-off between longevity and reproduction.

Gibbs *et al*. (9) provide insight into the effects of sex on the response of mice to acarbose, a pharmaceutical agent that delays aging. On average across multiple studies, male and female mice have similar lifespans, although this varies substantially probably secondary to differences in animal husbandry and genetics. In the Interventions Testing Program (ITP), the median lifespan of female mice was about 13% longer than male mice (2), which is probably the most robust indicator that we have of sex differences in lifespan of mice. Perhaps more important is the variability in the lifespan responses of mice to genetic, pharmacological, and dietary interventions (2), including acarbose. Acarbose is a medication that is approved for the treatment and prevention of type II diabetes mellitus in humans. It inhibits intestinal alpha glucosidase, thereby reducing the breakdown of complex carbohydrates so that less glucose is absorbed. Acarbose increased median lifespan in male mice by 22% but only 5% in female mice, while the effects on maximum lifespan were 11% and 9%, respectively (10). To further explore mechanisms for these sex differences, Gibbs *et al*. (9) fed mice either control diet *ad libitum*, with 40% caloric restriction or with 0.1% acarbose until 12 months of age when liver and cecal contents were analysed for metabolomics. There were large differences by sex in the response of liver metabolome to both acarbose and caloric restriction with over 50% of metabolites dissimilar between males and females. However, there were no sex differences in the gut metabolome which is perhaps not surprising since the microbiome is separate to (if not independent from) its host. Acarbose only recapitulated some of the characteristic changes in both cecal and liver metabolome generated by caloric restriction. It is interesting that caloric restriction was associated with increased cecal metabolites while acarbose, which tends to increase food consumption, reduced cecal metabolites. This might reflect bacterial population-type differences in the gut microbiome's response to nitrogen sources, where previous independent studies found that one guild utilized dietary nitrogen, while the other guild used host mucus as its nitrogen source (11). The study by Gibbs *et al*. provides an excellent example of the value in evaluating sex differences in the response to interventions that influence aging.

Fischer and Riddle (12) reviewed sex differences in genomic instability with aging across a range of species including humans. The

Hallmarks of Aging include many genetic mechanisms, specifically genomic instability, as well as other genetic changes to the epigenome, telomeres, and mitochondria (13), all of which are covered in this extensive review. Fischer and Riddle find that somatic mutation rate and load are higher in men which may account for earlier onset of cancers in men. This does not seem to be secondary to sex differences in the efficiency of DNA repair. On the other hand, sex differences in laboratory animals such as mice and *Drosophila* occur but are complex and not as well described as in humans. The effects of sex on age-related mitochondrial mutations are largely unexplored because the vast majority (88%) of published studies failed to indicate the sex of the animals used in the study. Women may have longer telomeres regardless of age or cell type while the effects of sex on epigenetics and nuclear architecture are not clear. Given the established importance of genetic mechanisms of aging, the authors conclude that are an "urgent need and terrific opportunities" for studies that specifically evaluate the effects of sex on the molecular drivers of aging.

Pomatto *et al.* (5) also provide an in depth review across species, including humans, on the effects of sex on adaptive homeostasis. Adaptive homeostasis refers to the transient changes in homeostatic range that occur in response to mild stresses such as non-damaging doses of oxidative stress (14). There are some overlaps with the concept of "hormesis" where mild stresses are not just tolerated, but generate beneficial outcomes (15). However, adaptive homeostasis refers to plasticity in the homeostatic target induced by mild stress, focusing on the response specifically rather than on evidence of damage or the implicit protective responses seen with hormesis. They conclude that there are marked differences in adaptive homeostasis between males and females at younger ages but that this difference disappears as homeostasis deteriorates with aging. This may be secondary to differential effects of sex hormones, or expression of X-linked genes involved with stress resistance. Pomatto *et al.* (5) note that despite the marked effects of aging on adaptive homeostasis, the effects of sex on this aging response has largely been overlooked.

This issue also contains a research study on the effects of sex on human aging. Cohen *et al.* (16) explore the "male-female health-survival paradox" whereby women live longer but at higher risk of frailty. This group has previously put forward the concept that physiological dysregulation with aging can be quantified using the Mahalanobis distance (D_M) which is a metric that measures how different a set of markers is from the norms for that population. Using data from two longitudinal studies, BLSA and InCHIANTI, and one cross-sectional study, NHANES, they found higher physiological dysregulation measured using the D_M in a number of systems in men. Although there was an association between dysregulation, frailty, and mortality, the authors were unable to show that greater dysregulation in women predisposes them to frailty. In fact they suggested the possibility of a "male–female dysregulation–frailty paradox" whereby men have greater dysregulation but show less susceptibility to frailty.

All these important publications show the value of studying the effects of sex on aging, and several have drawn attention to the fact that many aging studies have not reported either the sex of their aging models, or the effect of sex on the outcomes. In 2001 the Institute of Medicine released a book entitled "Exploring the Biological Contributions to Human Health. Does Sex Matter?" (17) that emphasised the striking effects of sex on biology and susceptibility to disease, and concluded that "sex should be considered when designing and analysing studies in all areas and at all levels of biomedical and health-related research." One of their key recommendations was the "encouragement of studies at different stages of the lifespan to determine how sex differences influence health, illness and longevity." Acknowledging the bias towards using male cell lines and animals, the NIH has mandated reporting the sex of animal and cell lines and requires the use of both sexes across research domains (18). The Journals of Gerontology encourages all authors and reviewers to take into account the need to report the sex of all experimental models including cell lines (19) and to report whether there are any sex differences in outcomes.

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