REVIEW

Widespread sex dimorphism in aging and age-related diseases

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Abstract

Although aging is a conserved phenomenon across evolutionary distant species, aspects of the aging process have been found to differ between males and females of the same species. Indeed, observations across mammalian studies have revealed the existence of longevity and health disparities between sexes, including in humans (i.e. with a female or male advantage). However, the underlying mechanisms for these sex differences in health and lifespan remain poorly understood, and it is unclear which aspects of this dimorphism stem from hormonal differences (i.e. predominance of estrogens vs. androgens) or from karyotypic differences (i.e. XX vs. XY sex chromosome complement). In this review, we discuss the state of the knowledge in terms of sex dimorphism in various aspects of aging and in human age-related diseases. Where the interplay between sex differences and age-related differences has not been explored fully, we present the state of the field to highlight important future research directions. We also discuss various dietary, drug or genetic interventions that were shown to improve longevity in a sex-dimorphic fashion. Finally, emerging tools and models that can be leveraged to decipher the mechanisms underlying sex differences in aging are also briefly discussed.

Introduction

A large number of metazoans species have evolved with sexual reproduction. In most cases, these species have two sexes, which often differ in many biological aspects. At the most fundamental biological level, both genetic and hormonal mechanisms can underlie phenotypic sex differences (Regitz-Zagrosek et al. 2015). To note, the term "gender" is primarily used to refer to the social aspects of male to females differences, whereas the term "sex" refers to the genetic/biological determination level (Haig 2004). Thus, biological sex, which we will focus on in this review, is primarily determined by sex chromosome karyotype (i.e. XY vs. XX in mammals), and secondarily by gonadal identity (i.e. testes vs. ovaries, leading to a predominance of estrogens or androgens) (Schurz et al. 2019). Although aging is thought to be very stereotypical, accumulating evidence has revealed strong sex dimorphism in aging and longevity phenotypes. For instance, female life expectancy always exceeds that of males in an analysis of 54 countries (Rochelle et al. 2015). However, remarkably little is known about the biological pathways which underlie these robust differences.

Phenotypic sex differences can result from the fundamental differences in sex chromosome complement between females and males (Schurz et al. 2019). The mammalian X and Y chromosomes started their evolution from ordinary autosomes ~ 180 million years ago (Schurz et al. 2019). Because mammalian females usually carry two X chromosomes, dosage compensation mechanisms evolved, leading to one of Xs to become repressed early in development

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through a mechanism called random X-chromosome inactivation (XCI) (Brown et al. 1992; Cordaux and Batzer 2009). Though rare, sex chromosome aneuploidies exist and can lead to various human diseases, including Turner syndrome (i.e. X monosomy) or Klinefelter syndrome (i.e. XXY) (Skuse et al. 2018). The mechanisms by which these aneuploidies lead to diseases are thought to stem both from dosage imbalance arising from the small number of genes that can escape XCI, and from the downstream endocrine impact of sex chromosomes (Skuse et al. 2018). Conversely, the fact that X aneuploidies lead to disease supports the notion that both X chromosomes are required for mammalian female health and may contribute to sex-dimorphic phenotypes.

The other driver of phenotypic sex differences can be sex-steroid signaling (Schurz et al. 2019). The most common estrogen species is 17-β-estradiol (commonly referred to as E2), and it can bind to classical estrogen receptors (ERs) ERα and ERβ. E2-bound ERs translocate to the nucleus, where these receptors are recruited to estrogen response elements (EREs), or indirectly bind to DNA via interaction with other transcription factors to regulate gene transcription (Menazza and Murphy 2016). Alternatively, E2 can bind to the membrane-bound forms of ERα and ERβ, or to the more recently discovered G protein-coupled estrogen receptor 1 (GPER1), activating intracellular signaling cascades leading to altered gene expression (Medzikovic et al. 2019; Menazza and Murphy 2016). Accumulating evidence supports the complexity of E2/ER signaling, for instance because ERα and ERβ control gene expression in different ways (Menazza and Murphy 2016). Importantly, relative expression levels for ERα and ERβ differ among cell types, sex, and disease status (Medzikovic et al. 2019). In males, testosterone is synthesized at high levels by Leydig cells in the testes (Hammes and Levin 2019) and performs most of its cellular effects through binding to the androgen receptor (AR). Similar to estrogen, androgens can signal through both nuclear and extranuclear compartments of different cell types and tissues (Hammes and Levin 2019). Estrogens are thought to be protective against a wide variety of diseases, whereas testosterone seems to enhance the risk of disease progression (Clocchiatti et al. 2016; Ostan et al. 2016). Consistently, the risks of hypertension and developing Alzheimer's disease (AD), two major causes of death in females, are remarkably inversely correlated with estrogen production (Ostan et al. 2016; Pike 2017). Despite the overwhelming evidence of sex differences in health and aging, underlying mechanisms for this phenomenon remain a major knowledge gaps of modern aging research (Austad and Fischer 2016; Clocchiatti et al. 2016; Ostan et al. 2016).

Here, we discuss the current knowledge of sex disparities in health, longevity, and longevity interventions, which will provide an important basis to frame new studies. Where the interplay between sex- and age-related differences has not yet been explored, we also present the current knowledge of each effect separately to delineate important gaps in knowledge in the field. Finally, we also discuss emerging tools which are available to effectively address these questions experimentally in the laboratory.

Sex-dimorphic outcomes in aging and longevity

Although numerous longevity and health-promoting interventions (e.g., genetic, dietary, drug) have been identified, much of the preclinical research supporting these interventions have not systematically and thoroughly explored sex-dimorphic effects (Miller et al. 2017). Indeed, most existing studies in the field have overwhelmingly favored the use of male samples. To address this fundamental gap, NIH guidelines now mandate the inclusion of sex as a biological variable in experimental design. However, except in rare cases, sex is still often treated by the field as a confounding factor rather a variable of interest in its own rights.

Sex dimorphism in mammalian health and longevity

The cohort of human supercentenarians (i.e. individuals aged over 110) reveals a surprising predictor for achieving such exceptional longevity: being female. Indeed, out of recorded 34 currently living supercentenarians, 33 are women (Adams 2019). Moreover, despite overall life expectancy increases for both women and men over the last few decades, human longevity has remained highly sex dimorphic, with the life expectancy of women systematically and robustly exceeding that of men (Austad and Fischer 2016). The increased life expectancy of women is likely to stem from the fact that they are less likely to succumb to most of the significant age-related causes of death: women die at a lower age-adjusted rate for 13 out of the 15 leading causes of death in the USA (Xu et al. 2016). In addition to humans, sex differences in lifespan have been observed across animal taxa, with mammalian females being generally longer lived than males (Austad and Fischer 2016; Bronikowski et al. 2011; Clutton-Brock and Isvaran 2007; Finch 1990).

In most reported cases, female laboratory rats live longer than their male counterparts (Berg and Simms 1960; Carlson and Hoelzel 1946; McCay et al. 1935; Nolen 1972). The existence of a similar female advantage for lifespan in laboratory mice is still hotly debated, especially for inbred strains (Austad 2011; Austad and Fischer 2016). However, in standardized husbandry conditions developed for the NIA Interventions Testing Program (ITP), female individuals consistently outlive males at three independent sites (Harrison et al. 2014; Miller et al. 2011; Strong et al. 2008), suggesting that the human female advantage may be recapitulated in

laboratory mice, at least in controlled conditions. Intriguingly, a recent report using an elegant genetic model showed that both the presence of two chromosome X and, to a lesser extent, the presence of ovaries led to increased survival in mice (see below) (Davis et al. 2018).

Hormonal inputs in mammalian health and longevity

A key difference in male and female milieu is the presence and endocrine fluctuations of sex-steroid hormones (e.g., 17-β-estradiol). Although these factors decline with age in both sexes, the rate of decline differs greatly between the sexes (Gubbels Bupp 2015). In addition, regular physiological fluctuations in sex-steroid hormone levels are seen throughout the menstrual cycle in women of child-bearing age, with increased estrogen production during the follicular phase, and increased progesterone production in the luteal phase. Similar cyclic fluctuations of sex-steroid hormones are observed throughout mammals and are known as the 'estrus cycle' in rodents (Hong and Choi 2018). Hormonal differences between sexes and natural fluctuations of hormonal levels are likely to broadly impact gene regulation, even in somatic cells, with both short and long-term effects. Indeed, as previously mentioned, estrogens and androgens can act through both (1) nuclear receptors (i.e. ER-α, ER-β, AR), which function like transcription factors, and (2) membrane-associated receptors (i.e. mER-α, mER-β, GPER) (Buskiewicz et al. 2016). The complex cross-talk between signaling from different receptors to the same hormone is still poorly understood (Buskiewicz et al. 2016) and may underlie the existence of context-dependent beneficial vs. pathogenic effects of the same hormone.

In addition to their role in sex determination and fertility, accumulating evidence suggests that sex steroids differentially contribute to health and lifespan in females vs. males (Austad and Fischer 2016; Dulken and Brunet 2015). Indeed, supporting a key role for sex-steroid hormones in female aging, later age-at-menopause is a strong predictor of increased woman longevity (Hong et al. 2007; Ossewaarde et al. 2005; Shadyab et al. 2017), and post-menopausal women are more at risk for many age-related afflictions (e.g., osteoporosis, immune decline, neurodegeneration) (Gubbels Bupp 2015). Consistently, many health parameters differ between male and female mice with aging (Fischer et al. 2016). In addition, several reports indicate that key adult stem cell populations (i.e. hematopoietic, neural and muscle stem cells) display higher self-renewal, and regenerative capacity in female vs. males (Deasy et al. 2007; Nakada et al. 2014; Pawluski et al. 2009). Moreover, females generally exhibit increased wound healing ability (Deasy et al. 2007; Gilliver et al. 2008; Yao et al. 2016) and liver regeneration (Tsukamoto and Kojo 1990).

Sex dimorphism in longevity phenotypes upon dietary or drug-based interventions

Dietary restriction (DR), the limitation of total caloric intake or specific nutrients (i.e. amino-acids) without malnutrition, has been generally shown to improve health and longevity outcomes across species (Fontana and Partridge 2015). However, when treating sex as a biological variable, clear differences emerge in the efficacy of DR as a health and longevity-extending intervention (Table 1). For instance, Honjoh and colleagues demonstrated sex-dimorphic responses to DR between hermaphrodites and males in the nematode *C. elegans*, with hermaphrodites displaying greater lifespan extension than males (Honjoh et al. 2017). The mechanism behind this DR response variation was proposed to involve the sex determination pathway and the worm steroid hormone receptor DAF-12 (Honjoh et al. 2017). Similarly, in *Drosophila melanogaster*, two studies reported a greater extension of lifespan in females vs. males upon DR, which could result from sex differences in insulin/insulin-like pathway signaling, nutrient-sensing pathways, and intestinal stem cell activity (Magwere et al. 2004; Regan et al. 2016). Although sex dimorphism has been observed in the mammalian response to DR, the better-responding sex is not always the same across studies of laboratory mice (selected examples in Table 1). This may be partly due to slight genetic background differences between studies (Liao et al. 2010), which could interact with genetic sex or reflect more complex interactions. Alternatively, these discrepancies in sex-biases responses to DR may result from cryptic differences (e.g., exact nature of the diet, hormonal status of mice, stress levels). Thus, systematic and well-controlled studies will be needed to establish whether the direction of sex-dimorphic effects of DR is a broadly conserved phenomenon.

In addition to DR, drug-based pro-longevity interventions have also been reported to display sex-dimorphic responses (see Table 2). Rapamycin is one of the best documented examples of such a response (Fischer et al. 2015; Miller et al. 2014). Rapamycin works as a DR mimetic by inhibiting mTOR, a kinase that regulates cell growth through cellular nutrient sensing (Wilkinson et al. 2012). Studies of rapamycin supplementation have reported sex-dimorphic differences in both longevity and health parameters (Table 2). To note, these effects have been suggested to partially stem from sex-dependent rapamycin bioavailability (Fischer et al. 2015; Miller et al. 2014). Another DR mimetic, metformin, is a common anti-hyperglycemic drug that primarily functions by uncoupling the electron transport chain, thereby mimicking a low-energy state (El-Mir et al. 2000). Sex-dimorphic differences in the response to neonatal exposure to metformin have been reported, with a greater lifespan extension observed in males compared to females (Anisimov et al. 2015). Acarbose, a glucosidase inhibitor, was also proposed

Table 1 Selected sex-dimorphic effects in dietary restriction as a health- and longevity-extending intervention in different laboratory models

Species	Strain	Type of DR	Sex-dimorphic effect	References
Caenorhabditis elegans	N2	CR	Greater lifespan in hermaphrodites than males	Honjoh et al. (2017)
Drosophila melanogaster	–	CR	Greater lifespan in females than males	Magwere et al. (2004)
		CR	Greater lifespan in females than males. Reduced gut pathology in aged females vs. males	Regan et al. (2016)
Mus musculus	C57BL/6	CR	Differences in liver but not caecal metabolites between sexes	Gibbs et al. (2018)
	C57BL/6J	Methionine deprivation	Greater expression of fibroblast growth factor-21 and UCP1 in males vs. females. Greater energy expenditure in females vs. males. Greater alteration in lipid metabolism in females vs. males	Yu et al. (2018)
	Growth hormone-releasing hormone KO (mixed C57BL/6 and 129Sv)	CR	Greater lifespan in females than males	Sun et al. (2013)
	Growth hormone receptor KO	CR	Greater maximal lifespan in females than males	Bonkowski et al. (2006)
	C57BL/6	CR (20% and 40%)	C57BL/6 mice with 40% CR—no difference and with 20% CR females lived longer than males	Mitchell et al. (2016)
	DBA/2J	CR (20% and 40%)	DBA/2J mice with 40% and 20% CR did not show any sex-differences	Mitchell et al. (2016)
	ILSXISS recombinant inbred strains	CR	Generally better outcomes in females, though strain specific	Liao et al. (2010)
Rattus norvegicus	Wistar	CR	Liver mitochondrial oxidative capacity is unaffected by CR	Valle et al. (2007)

Table 2 Summary of sex-dimorphic effects in drug-based health- and longevity-extending interventions studies on *Mus musculus*

Drug	Mouse strain	Sex-dimorphic effect	References
Rapamycin	UM-HET3	Greater lifespan in females than males	Miller et al. (2014)
	C57BL/6J	Greater total body mass in young females than males. Greater percent fat in young females than in males. Greater resting metabolic rate in young females than in males	Fischer et al. (2015)
Metformin	129/Sv	Greater lifespan in males than females	Anisimov et al. (2015)
Acarbose	UM-HET3	Greater lifespan in males than females. Improved metabolism (better glucose tolerance, mTOR signaling) in males than females. Reduced microglial activation in males than females	Garratt et al. (2017), Harrison et al. (2014, 2019) and Sadagurski et al. (2017)
17-α estradiol	UM-HET3	Improved metabolism (better glucose tolerance, mTOR signaling) in males than females. Reduced microglial activation in males than females	Garratt et al. (2017), Harrison et al. (2014) and Sadagurski et al. (2017)

to act as a DR mimetic to promote health and longevity (Harrison et al. 2014, 2019). Studies have shown that with age, postprandial glycemia becomes less tightly regulated (Frantz et al. 2005; Miyamura et al. 2010), and acarbose is thought to prevent this age-related defect by slowing carbohydrate digestion, thereby reducing postprandial glucose

spikes (Harrison et al. 2014). As part of the NIA ITP, acarbose has been well studied in male and female genetically heterogeneous UM-HET3 mice (Garratt et al. 2017; Harrison et al. 2014, 2019). In the context of this strain, male mice displayed substantially greater longevity and health compared to females (Garratt et al. 2017; Harrison et al. 2019). These effects included improved metabolism (i.e. glucose tolerance, mTOR signaling) and reduced microglial activation (Garratt et al. 2017; Sadagurski et al. 2017).

Supplementation with 17-α estradiol was another ITP success with sex-dimorphic impact on aging (Garratt et al. 2017; Harrison et al. 2014). This molecule was selected as a non-feminizing form of estrogen, which was thought to potentially engage estrogen-associated health insurance mechanisms without altering innate sexual characteristics (Garratt et al. 2017; Harrison et al. 2014). Intriguingly, despite not influencing sex characteristics, the longevity- and health-promoting effects of 17-α estradiol are sex dimorphic (Garratt et al. 2017; Harrison et al. 2014). Indeed, 17-α estradiol has been shown to lead to elevated mTORC2 activity in males, but not in females (Garratt et al. 2017). Similar to acarbose, 17-α estradiol also preferentially improved glucose clearance in males compared to females (Garratt et al. 2017).

Genetic longevity models with sex-dimorphic health of longevity phenotypes

More surprisingly than in response to drug supplementation, genetic manipulations have also been shown to exert sex-dimorphic impact on lifespan, leading to either greater lifespan extension in females vs. males (e.g., *Igf1r* haploinsufficiency), or lifespan extension exclusively in males (e.g., *Sirt6* overexpression) (Bokov et al. 2011; Enns et al. 2009; Holzenberger et al. 2003; Kanfi et al. 2012; Selman et al. 2008, 2009; Xu et al. 2014; Yao et al. 2016).

The insulin signaling pathway has been extensively studied in the context of aging and longevity, and mouse knockout (KO) models have been generated for many genes in the pathway. Interestingly, most of the insulin pathway KO mice display some measure of sex dimorphism. For example, *Igf1r* haploinsufficiency is thought to work by decreasing the biological activity of insulin growth factor-1 (IGF-1), which promotes anabolism and growth. Intriguingly, the scale of lifespan extension in this model differs significantly between males and females (Holzenberger et al. 2003). Indeed, $Igf1r^{+/-}$ mice from the 129Sv strain were found to display a larger increased in lifespan in females compared to males (Holzenberger et al. 2003). Although the same sex dimorphism in lifespan extension was also observed on the C57BL/6J background (Bokov et al. 2011; Xu et al. 2014), the extent of the sex dimorphism on the 129Sv background is substantially higher on the C57BL/6J background (Xu

et al. 2014). This discrepancy was suggested to stem from strain-specific differences in circulating IGF-1 (Xu et al. 2014) and shows that sex-dimorphic phenotypes may be modified by autosomal genetic variation. Conversely, insulin receptor heterozygous knock-out models have been shown to lead to increased lifespan of male mice only (Nelson et al. 2012). Downstream of the receptors, invalidation of the insulin receptor substrate 1 null in mice ($Irs1^{-/-}$) was found to lead to increased lifespan of female mice only (Selman et al. 2008).

Sirtuins are highly conserved NAD-dependent deacetylases that have been shown to regulate lifespan across taxa. In mammals, overexpression of *Sirt6* in mice was found to significantly increase lifespan in males only (Kanfi et al. 2012). Analysis of the *Sirt6* overexpression model revealed that the major components of insulin signaling were affected (Kanfi et al. 2012). Other genetic models that may mimic effective pro-longevity drug targets or dietary interventions are KO models of genes encoding protein kinase A RIIβ, and a subunit of the ribosomal S6 kinase (S6K) (Enns et al. 2009; Lamming et al. 2012; Selman et al. 2009). Protein kinase A (PKA) has been shown to be important in yeast longevity (Longo 2003). Intriguingly, mice without the PKA regulatory isoform RIIβ displayed increased lifespan in males but not in females (Enns et al. 2009), and were protected from age-related fatty liver, insulin resistance, and cardiac dysfunction (Enns et al. 2009). Independent studies have shown that null and heterozygous S6K subunit gene KO lead to increased lifespan in female mice but not males (Lamming et al. 2012; Selman et al. 2009). The S6 Kinase is part of the mTOR signaling cascade, and the female advantage on these genetic models is reminiscent of that observed upon rapamycin supplementation (Fischer et al. 2015; Miller et al. 2014).

Although most of the work in Ames dwarf mice has utilized exclusively male mice, a small study revealed that female Ames dwarf mice may live significantly longer than their male counterparts (Brown-Borg et al. 1996). Interestingly, long-lived mice lacking growth hormone (GH) and growth hormone receptor KO (GHRKO) may have a larger effect on females than males (Gesing et al. 2013). Intriguingly, only females GHRKO benefit from DR-induced lifespan extension (Bonkowski et al. 2006), whereas rapamycin treatment of GH mutant mice leads to a larger decrease in lifespan of male vs. females (12.5% vs. 6%) (Fang et al. 2018). Because of their role in GH signaling, a recent study of mice carrying both the Ames dwarf and GHRKO alleles suggested that females may also display a longevity advantage compared to males in this context (Gesing et al. 2017).

Thus, although differences in the bioavailability or metabolism of longevity-promoting compounds may be responsible for sex-dimorphic longevity effects of drug treatments, the existence of sex-dimorphic longevity effects

upon genetic manipulation suggests the existence of complex mechanisms regulating sex-dimorphic phenotypes throughout life.

Widespread sex differences are observed in age-related chronic diseases

Sex-steroid hormones, both androgens, and estrogens have been shown to exert a significant impact on energy metabolism, body composition, vascular function, inflammatory responses, and neurogenesis (Gambineri and Pelusi 2019). While aging is associated with progressive metabolic decline and increased prevalence of chronic diseases in both sexes, the presentation and prevalence of these diseases are highly influenced by sex. Indeed, sex difference/dimorphism is increasingly evident in age-related metabolic disease [obesity, type 2 diabetes mellitus (T2DM), and cardiovascular diseases (CVD)]. Understanding how sex differences in age-related diseases are established will be crucial to leverage these differences for the improvement of health in both sexes.

Sex dimorphism in age-related metabolic dysfunction

Obesity and adiposity

Obesity is a growing public health concern and a key risk factor for many age-related diseases, such as T2DM and CVD. In recent years, the prevalence of elderly obesity has steadily increased (Jura and Kozak 2016). In addition to life-style changes with retirement, a shift in sex hormone levels in the elderly may also lead to a chronic positive energy balance state (Masternak et al. 2012), leading to excess fat tissue accumulation. In turn, this increase in adiposity then potentiates the development of age-related diseases (Tchkonia and Morbeck 2010). In addition to increased adiposity, aging is also associated with fat redistribution from subcutaneous to abdominal areas (Kok et al. 2009). While aging is associated with increased adiposity across sexes, men and women exhibit different patterns of adipose storage throughout life. Women typically present with ~ 10% higher total body fat than men throughout life and are generally more prone to obesity. Women tend to store more adipose tissue in the hips and thighs, while men have a more central fat distribution pattern. The pear-shaped female fat distribution may confer protection against metabolic diseases, such as T2DM and atherosclerosis (Manolopoulos et al. 2010) (see below). In women, visceral adiposity rises during the peri-menopausal transition, and adipose tissue redistributes toward abdominal area after menopause (Toth et al.

2000; Kozakowski et al. 2017). Similarly, visceral adiposity increases in men with age as testosterone levels decline (Allan et al. 2008).

Type 2 diabetes mellitus (T2DM)

In contrast to type 1 diabetes, an early onset insulin-dependent autoimmune disorder, T2DM is non-insulin-dependent and becomes more common with increasing age (Arum et al. 2014). Independent of sex differences in obesity and adiposity, the risks of T2DM in men and women are directly affected by sex hormones. Indeed, testosterone can influence T2DM pathogenesis. Based on cross-sectional studies, lower levels of testosterone in men and higher levels of testosterone in women are associated with increased T2DM risks (Gambineri and Pelusi 2019). Polycystic ovary syndrome (PCOS) is the most common hyperandrogenic disorder in women (Conway et al. 2014). Intriguingly, the odds of T2DM are four times as high for women with PCOS compared to healthy women, even when matched for body mass index (BMI) (Gambineri and Pelusi 2019; Moran et al. 2010, Morgan et al. 2012). Thus, imbalance in sex hormones (e.g., PCOS) can directly impact the risk of developing T2DM. Conversely, low baseline testosterone levels in men are associated with a dramatically higher risk of developing T2DM in men (Dhindsa et al. 2010). Thus, in addition to sex differences in body composition and fat deposition, sex hormones directly contribute to sex-dimorphic risk for diabetes.

Metabolic syndrome

Although metabolic syndrome affects men more often than women overall, women only seem to be protected before menopause (Regitz-Zagrosek et al. 2007). Indeed, the female risk of metabolic syndrome becomes roughly equivalent to that of male counterparts after the onset of menopause. Consistent with human data, female mice showed fewer markers for Western diet-induced obesity despite having the same amount of energy intake than matched males (Kaliannan et al. 2018). Males appeared more obese than their female counterparts and had higher fat distribution, more evidence of glucose intolerance, non-alcoholic fatty liver disease, and dyslipidemia (Kaliannan et al. 2018). Thus, sex may also act as a modifier for the impact of metabolic imbalance.

Sex dimorphism in cardiovascular disease

Traditionally viewed as a man's disease, cardiovascular disease (CVD) is substantially more common in men than women, even with age-standardized statistics. The major areas of age-related CVD include ischemic heart disease, heart failure, and hypertension.

Ischemic heart disease, also known as coronary artery disease, occurs when plaque builds up inside blood vessels, leading to an inadequate blood supply to the heart (Regitz-Zagrosek and Kararigas 2017). Men and women are prone to develop different types: occlusive coronary artery disease is more frequent in male patients, while non-obstructive coronary artery disease or microvascular dysfunction is more common in women (Regitz-Zagrosek et al. 2015). In addition, men develop coronary artery disease earlier and usually present with more severe atherosclerosis in their coronary arteries than women. Indeed, myocardial infarction, which is a manifestation of coronary artery disease, occurs ~ 10 years earlier in men than women (Regitz-Zagrosek and Kararigas 2017). The reason for the relative protection of women may be due to the beneficial lipid profile and the role of estrogen signaling (Jiang and Tian 2017; Sudhir et al. 1997). Women with PCOS and men with a disruptive estrogen receptor mutation have been shown to develop early coronary artery disease (Legro 2003; Sudhir et al. 1997). Heart failure is a typical clinical syndrome arising from different pathophysiological conditions, affecting more than 10% of people aged > 70 years in western societies (Regitz-Zagrosek and Kararigas 2017). Though heart failure affects more women than men in terms of raw case numbers (Ambrosy et al. 2014), women have better odds of survival than men, and heart failure in women usually occurs at a later age (Regitz-Zagrosek and Kararigas 2017). In contrast to ischemic heart disease and heart failure, hypertension tends to affect more women in the elderly population (Vigen et al. 2012). Indeed, the percentage of women with hypertension is about twice that of men, and premenopausal women have lower rates of hypertension and lower lipid levels than age-matched men (Regitz-Zagrosek et al. 2015). Possible reasons for the shift in hypertension risk after the onset of menopause may be due to increased production of testosterone by the post-menopausal ovary (Maki and Henderson 2012). Consistently, women with PCOS have higher hypertension risk, indicating that higher testosterone levels are a risk factor for hypertension in women (Dworatzek et al. 2016).

Taken together, CVD shows a clear sex-dimorphic presentation during aging. In addition to the role of hormone-specific mechanism in men and women, sex-dimorphic CVD may also be explained by other mechanisms, such as sex-specific ion handling and rhythmicity in cardiovascular cells—women, in general, have faster resting heart rates and longer rate-corrected Q, T intervals, leading to higher susceptibility to drug-induced QT prolongation (Regitz-Zagrosek et al. 2015). Understanding these sex differences and their underlying mechanisms will be crucial to tailor therapeutic strategies that target sex-specific cardiovascular disease mechanisms.

Sex dimorphism in age-related eye disorders

Glaucoma

Glaucoma is a common age-related eye condition in which the optic nerve is damaged and can potentially lead to irreversible blindness. The maintenance of intraocular pressure is crucial to maintain clear vision (Pattabiraman and Toris 2016). Indeed, glaucoma is the leading cause of blindness in people aged > 60 years old, and is more common in women than men, suggesting sex dimorphism in glaucoma pathogenesis (Quigley and Broman 2006). Although the exact cause of this disparity remains poorly understood, anatomical differences, hormonal differences, lifestyle, and family history are thought to contribute to a significant amount (Brandt et al. 2001; Gordon et al. 2002; Høvding and Aasved 1986; Sommer and Tielsch 1996; Wilson et al. 1987). Several forms of glaucoma exist, the most common subtypes being angle-closure glaucoma (ACG) and open-angle glaucoma (OAG) (Lee et al. 2003; Pattabiraman and Toris 2016; Vajaranant and Pasquale 2012). The higher prevalence of glaucoma in women has been suggested to stem from the use of oral contraceptives (Lee et al. 2003; Pasquale and Kang 2011; Vajaranant and Pasquale 2012). Indeed, the use of oral contraceptives for more than 5 years is associated with a 25% increased risk of OAG (Pasquale and Kang 2011; Wang et al. 2016). Glaucoma incidence is also influenced by menopausal status (Hulsman et al. 2001; Newman-Casey et al. 2014), and post-menopausal hormonal replacement therapy (HRT) in women aged > 50 was associated with reduced prevalence of OAG (Newman-Casey et al. 2014). Conversely, pregnancy decreases intraocular pressure, which may reduce the chances of eventually developing glaucoma (Efe et al. 2012; Phillips and Gore 1985). In the case of OAG, sex is not considered a risk factor per se, although females often have more significant progression (Drange et al. 2001).

Age-related macular degeneration

The human eye has a *macula lutea* situated near the center of the retina. The macula region can be damaged as we age, which leads to a clinical condition called age-related macular degeneration (AMD) (Ambati et al. 2003; Elbay et al. 2019). AMD pathogenesis is multifactorial, with risk factors including heredity, obesity, hypertension, hypermetropia, ethnicity, and smoking. However, late menopause may be associated with a reduced risk of AMD (Snow et al. 2002). Additionally, increased risk in women is reported (Chakravarthy et al. 2010).

Cataract

Cataract is characterized by clouding or opacification of the lens in the eye, which dull the vision and is often age-related (Kahn et al. 1977). Studies have shown a higher prevalence of cataract in women vs. men of age group 65–75 years (~25% vs. ~15%) (Klein et al. 1992; Lundström et al. 1999, 2002; Mitchell et al. 1997). However, pre-menopausal women and age-matched men show the same risk of developing cataract (Klein et al. 1992; Mitchell et al. 1997). Higher rates of cataract surgery were reported in women (Lundström et al. 1999, 2002), which may result from declining estrogens after menopause. Interestingly, post-menopausal hormone replacement therapy may reduce the incidence of lens opacification (Freeman et al. 2001; Klein et al. 1992; Younan et al. 2002). The protective effects of estrogens may result from anti-oxidant properties since oxidative stress is a major pathway in the pathophysiology of cataract (Beebe et al. 2010). Moreover, in vitro treatment of lens epithelial cells with E2 was found to be protective against oxidative stress (Celojevic et al. 2011; Wang et al. 2003).

Sex dimorphism in age-related neurodegeneration

Neurodegenerative age-related diseases have a particularly staggering sex-dimorphic prevalence pattern. For instance, Alzheimer's disease tends to occur more commonly in females, while Parkinson's disease is biased toward presentation in males. All these major neurodegenerative diseases have associated genetic aspects and are incapable of being cured by treatment—current standard treatment practices can only hope to ameliorate symptoms. Thus, understanding sex differences may provide new research avenues for effective therapeutics.

Alzheimer's disease

Alzheimer's disease (AD), the most common form of dementia, is characterized by senile plaque and neurofibrillary tangle buildup in the brain and central and peripheral nervous system that leads to profound degeneration of large portions of the brain. This form of dementia accounts for more than 50% of dementia cases worldwide (Bekris et al. 2010). The degradation associated with AD appears to have a progression through the brain, beginning in medial temporal lobe structures before following temporal projections and causing degeneration in connected regions (e.g., subcortical structures, prefrontal structures, corpus callosum, and expansive cortex regions) (Smith 2002; Teipel et al. 2002). AD symptoms include hallmark progressive memory deficits, as well as language disturbance, visuospatial impairment, and higher executive function impairment (Schachter and Davis 2000). Additionally, many patients experience

personality changes, judgment impairments, psychosis, mood disturbances, and sleep disturbances (Schachter and Davis 2000). Due to the extent of degeneration experienced by AD patients in specific regions, most patients develop a similar cluster of symptoms.

There is a distinctive pattern of AD presentation in males and females. AD is a disease that is most commonly present in females, with higher AD occurrence levels in all age groups > 60 except for 65–69. Males face a ~6% risk of developing AD in their lifetime after age 65, while women face a ~12% chance of developing AD in the same timeframe (Podcasy and Epperson 2016; Viña and Lloret 2010). Clinical presentation of AD also tends to be sex dimorphic, with symptoms and degeneration occurring more rapidly in women than in men (Laws et al. 2016; Lin et al. 2015), and men having a shorter lifespan after diagnosis (Kua et al. 2014). The skewed proportions of female to male AD patients may be linked to sex hormone effects. Indeed, estradiol has been illustrated to have neuroprotective effects (Maki and Henderson 2012), and women who experience menopause later in life tend to have a later age of AD onset (Lin et al. 2015). The significant decline in circulating estradiol after menopause can no longer fully exert neuroprotective effects in the brain, while age-matched males are still capable of aromatizing testosterone into estradiol and, therefore, still experience these neuroprotective effects (Podcasy and Epperson 2016). Along the same lines, although HRT in women has not been reported to have strong protective effects, long-term hormone self-administration is associated with reduced AD risk (Imtiaz et al. 2017).

Interestingly, the genotype of *APOE*, the most impactful genetic risk factor, is located on chromosome 19 and has been associated with increased risk of late-onset AD, particularly for the e4 genotype (Bekris et al. 2010; Corder et al. 1993). The *APOE* gene may not directly be involved in the pathology of AD, although > 40% of individuals with AD have the e4 genotype, and ~40% of e4 carriers have senile plaques (Farrer et al. 1995; Kok et al. 2009). Interestingly, the *APOE* e4 allele risk factor appears to interact with sex, with males of *APOE* e3/e4 and *APOE* e3/e3 genotypes experiencing AD risk level markedly less than the risk for APOE e4/e4 genotype, while females of APOE e3/e4 genotype are nearly twice as likely to develop AD than those of APOE e3/e3 genotype (Poirier et al. 1993; Tsai et al. 1994).

Parkinson's disease

Parkinson's disease (PD) is characterized by a loss of dopamine neurons in the *substantia nigra pars compacta*, a region of the basal ganglia (Deumens et al. 2002; Kalia and Lang 2015). The basal ganglia are a collection of neural structures responsible for the control of movement (Mink 1996). Two pathways work together to allow movement by

enabling activity in a subgroup of neurons while preventing excessive movement (Calabresi et al. 2014). It is the substantia nigra pars compacta exerting a dopaminergic connection upon the striatum that both excite the direct (i.e. movement-initiating) pathway and inhibit the indirect (i.e. movement-inhibiting) pathway (Freeze et al. 2013). PD symptoms include tremor at rest, involuntary movement, and rigidity, which are classified as positive motor symptoms, and poverty of movement (i.e. bradykinesia) and posture disruption, which are classified as negative motor symptoms (Deumens et al. 2002). Cognitive impairments, including pain, fatigue, psychiatric disorders, olfactory dysfunction (Kalia and Lang 2015), and other general cognitive impairments are experienced by up to 50% of PD patients within 3 years of diagnosis (Geurtsen et al. 2014). Dementia is also frequently experienced by PD patients (Kalia and Lang 2015). Commonly, cognitive-motor impairments are seen in addition and include a severely impaired ability to make coarse and fine movement adjustments, as well as the transition between walking surfaces. The pathogenic mechanism for PD remains mostly unknown. While it is clear that PD involves dopamine neuron degeneration, there is no single underlying genetic indicator. Autosomal dominant forms of PD have been discovered [e.g., alpha-synuclein, parkin, leucine-rich repeat kinase 2 (LRRK2)] (Klein and Westenberger 2012; Wood-Kaczmar et al. 2006). Other genetic loci have been less conclusively associated with the disease (Klein and Westenberger 2012).

PD is a disease that is most commonly present in men, with reported proportions of disease occurrence that mostly range at 2:1 (Elbaz et al. 2002; Gillies et al. 2014). In addition, the clinical presentation of symptoms can have highly sex-dimorphic patterns, with females experiencing a later age-of-onset and milder PD phenotype than males (Alves et al. 2009; Haaxma et al. 2007; Miller and Cronin-Golomb 2010; Shulman and Bhat 2006). Women are more likely to experience tremor, dyskinesia, nervousness, and depression in their PD pathology (Haaxma et al. 2007; Martinez-Martin et al. 2012), while men are more likely to experience rigidity, rapid eye movement, and reduction in verbal fluency and facial expression recognition (Martinez-Martin et al. 2012). The sex-dimorphic pattern in both disease frequency and pathology cannot be entirely explained, but pre-existing sex-dimorphic patterns of structure, function, and hormone regulation are almost certainly involved (Gillies et al. 2014).

Sex dimorphism in the microbiome throughout life

Over the past decade, there has been increasing interest in the microbiome and its potential role in modulating overall human health and disease. From the ramifications of vaginal delivery vs. cesarean birth in the colonization of the newborn gastrointestinal tract and its effect on later health (Tanaka and Nakayama 2017), to cardiovascular disease and obesity, the human microbiome has now been shown to have a more significant role in maintaining health and homeostasis than previously imagined. Although many different microenvironments have been gaining interest, we will focus here on the gut microbiome, the influence of host sex on the microbiota, and the impact of the aging microbiome on overall health. To note, very little is known about sex-dimorphic features of the aging microbiome, so we will highlight the current knowledge in the fields of (1) sex differences and hormonal interactions to the microbiome in young animals, and (2) age-related effects on the microbiome. Future work integrating both these aspects will be a crucial step in the field.

The gut microbiome and age-related dysbiosis

The human gut microbiome is estimated to be composed of an estimated 10^{13} to 10^{14} micro-organisms (Bianconi et al. 2013; Savage 1977; Sender et al. 2016a, b). The microbial community consists of bacteria, viruses, and fungi. Bacteria represent the largest proportion of the microbial community with an estimated 500–1000 different bacterial species (Sender et al. 2016a). Relevant to aging, Elie Metchnikoff proposed in 1907 that age-related dysfunction was driven by chronic systemic inflammation, which occurred as a result of increased colon permeability (Metchnikoff 1907). The inflammation-driven hypothesis of aging is indeed now a leading hypothesis in the field, known as "inflamm-aging" (Franceschi and Campisi 2014). Although much remains to be studied, pioneering studies have started to map out the effect of aging on the gut microbiome (reviewed in (Nagpal et al. 2018)).

Interestingly, studies in *D. melanogaster* have revealed that age-related changes in the microbiome lead to increased intestinal permeability (Clark et al. 2015), which in turn promotes increased inflammation and mortality (Rera et al. 2012). The impact of the gut microbiome on systemic inflammation in mammals is supported by the fact that the composition of gut microbiome is correlated with inflammatory circulating cytokines in the human elderly (Claesson et al. 2012) and in aged mice (Conley et al. 2016; Thevaranjan et al. 2017). Interestingly, a recent study showed that intestinal barrier function fails with aging in mice, with increased levels of bacteria products in the blood of aged mice (Thevaranjan et al. 2017). Leveraging comparisons between specific pathogen-free and germ-free mice, the authors further demonstrated that intestinal barrier failure is driven by remodeling of gut microbial communities and alters macrophage function, reducing bacteria killing ability and increasing production of pro-inflammatory cytokines

(Thevaranjan et al. 2017). Thus, age-related changes in the composition of the gut microbiome may represent a form of "microbial dysbiosis" (Thevaranjan et al. 2017). Although these studies did not explore how sex may interplay with age-related microbial dysbiosis, gut microbiota composition is tightly associated with diet in the elderly (Claesson et al. 2012), suggesting that the effects of pro-longevity interventions may partially act through microbial community remodeling.

Dietary effects on the gut microbiome

Interestingly, high fat diet (HFD) has been shown to lead to reduced diversity in the gut microbes (Xiao et al. 2017), which itself is a form of "gut dysbiosis" (Turnbaugh et al. 2006). This lack of diversity is thought to leave fewer community members available to process toxic metabolites, which leads to an inflammatory response. This inflammatory response weakens cell–cell junctions and, therefore, increases permeability of the gastrointestinal tract and allows for bacterial translocation (Schwabe and Jobin 2013). Bacterial lipopolysaccharide (LPS), one of the main components of Gram-negative bacterial cell walls (Moreira et al. 2012), has been identified as a triggering inflammatory factor which can cause the onset of insulin insensitivity, obesity and diabetes (Cani et al. 2007; Moreira et al. 2012). Indeed, an HFD increases the proportion of LPS-containing microbiota in the gut (Cani et al. 2007), thus promoting systemic inflammation and metabolic endotoxemia. Interestingly, HFD-fed male mice over a 4-week period experienced similar weight gain and insulin resistance as mice that received a steady subcutaneous infusion of LPS (Cani et al. 2008). Since each microenvironment is affected by the diet and geographical environment the host organism is in (Yatsunenko et al. 2012), it would stand to reason that the sex of the animal could also influence the composition of the microbiome as well.

Sex differences in the microbiota: what do we know?

Although this has not been systematically studied in humans, studies in mouse models show that the composition of gut microbiota is very similar between females and males before puberty (Markle et al. 2013; Steegenga et al. 2014). Indeed, the colonic microbial community of 2-week-old C57BL/6 pups consists predominantly of bacteroidetes and firmicutes, with small amounts of actinobacteria and proteobacteria in both sexes (Steegenga et al. 2014). However, puberty may lead to shifts in the microbiome leading to the establishment of sex-dimorphic microbial communities. Indeed, although there were no differences in the gut microbiota before sexual maturation in the non-obese diabetic (NOD) mouse model for type 1 diabetes (Markle et al. 2013), sequencing of the

16S ribosomal RNA repertoire from the gut microbiota of males and females at weaning (3 weeks), puberty (6 weeks), and adulthood (14 weeks) before diabetes onset revealed that differences in the gut microbiome emerged at puberty (6 weeks) and were strengthened in adults (Markle et al. 2013). Thus, it seems that sex hormones may help shape the composition and function of the gut microbiota, thus potentially influencing disease pathogenesis in a sex-specific fashion.

Bidirectional dialog between gut microbiota and sex hormones

In 1978, Lombardi and colleagues showed that the gut microbiome may impact the concentration of circulating estrogens and androgens (Lombardi et al. 1978). Indeed, the human microbiota can hydrolyze estrogen sulfate and glucuronide conjugates, and rat intestinal flora can hydrolyze androgens and glucuronides (Lombardi et al. 1978). The rate of these hydrolytic reactions was proportional to the concentration of feces in the growth medium (Lombardi et al. 1978). The authors showed that with high fecal load, a reduction of the carbonyl group to a hydroxy group at positions 3 and 17 of androgens, and position 17 of estrogens could take place (Lombardi et al. 1978). These redox reactions, mediated by the intestinal microbiota, were capable of producing a shift in local relative amounts of estrone, estradiol, testosterone, and androstenedione (Lombardi et al. 1978). Importantly, subsequent reabsorption of these steroids into the animal can result in effective changes in the circulating concentration of estrogens and androgens.

In addition to its role on the organism's own cells, accumulating evidence shows that estrogens can directly impact gut microbiome composition and have a role in maintaining gut homeostasis. The terms "microgenderome" and "estrobolome" have been coined to describe this phenomenon, defined as "the gene repertoire of the microbiota of the gut capable of metabolizing estrogens" (Plottel Claudia and Blaser Martin 2011; Vemuri et al. 2019). In pre-menopausal females, estrogens are predominately secreted into the plasma by the ovaries and are immediately bound to sex hormone-binding globulin (SHBG), which is produced by the liver (Anderson 1974). More than 90% of systemic estrogen is bound to SHBG and thus biologically unavailable (Anderson 1974). Recent work has shown that the amount of biologically available estrogen is partially regulated by the gut microbiome in females (Vemuri et al. 2019). The gut microbiota in pre-menopausal women secretes beta-glucuronidase, which deconjugates SHBG from circulating estrogen, thereby making it biologically available and active (Baker et al. 2017; Kwa et al. 2016; Laurent et al. 2016). This microbially mediated increase in circulating estrogens may confer a protective effect on the host. However, when

perturbations of the estrobolome arise, either via pathology (e.g., PCOS, metabolic syndrome) or aging (e.g., menopause), many of these benefits can be lost (Vemuri et al. 2019).

Beyond a mere correlation, hormonal inputs may directly shape the composition of microbial communities. Indeed, oral supplementation of 17-β estradiol suppressed the development of Western diet-induced obesity in both males and in ovariectomized (OVX) females, and that there were no significant differences in metabolic syndrome parameters between intact females and E2 supplemented males (Kaliannan et al. 2018). Importantly, the microbiota of each experimental group clustered as a function of hormonal profiles: the OVX female and untreated male microbiota clustered together apart from that of male E2-treated and intact females (Kaliannan et al. 2018). Once the influence of estrogen on the gut microbiome was lost, the protective benefit was lost. This loss of protection was also demonstrated in intact mice, given antibiotics to deplete the microbiome (Kaliannan et al. 2018). Their serum estrogen levels decreased, and their metabolic syndrome markers resembled those of their male counterparts.

Although clear impact of age and sex have been independently observed in the gut microbiome, the interplay between these inputs is till mostly unexplored and will deserve future study in the field. Thus, the microbiome may be an important component to integrate in studies of sex dimorphism in mammalian age-related phenotypes.

Sex-dimorphic gene regulation in youth and during aging

In multi-cellular organisms, the precise control of gene expression patterns is key not only for development, but also for cell/tissue homeostasis in adults, and deregulation of such patterns is associated with aging (Benayoun et al. 2015; Lai et al. 2019; Stegeman and Weake 2017). A complementary layer of the study of gene regulation mechanisms lies at the level of chromatin. Indeed, cellular chromatin states (i.e. the 'epigenome') can regulate transcriptional profiles and are governed in part by post-translational modifications of histones (Dong et al. 2012; Dunham et al. 2012; Hoffman et al. 2013; Jenuwein and Allis 2001; Parker et al. 2013; Whyte et al. 2013). Thus, in line with the prevalence of transcriptional alterations with aging, accumulating observations have noted that the general structure of chromatin and specific patterns of chromatin marks are altered with aging across cell types and species (Benayoun et al. 2015 #410; Ucar and Benayoun 2018 #1605; Pal and Tyler 2016 #813). In addition, perturbations in chromatin-modifying enzymes can impact the lifespan of invertebrates, and even age-related cognitive decline in mice (Benayoun et al. 2015 #410; Ucar

and Benayoun 2018 #1605; Pal and Tyler 2016 #813), which supports the status of 'epigenetic alterations' as a 'hallmark of aging' (López-Otín et al. 2013). Although accumulating studies have started to map genomic remodeling with age, these studies have mainly focused on male individuals, or on pooled male/female samples, thus ignoring potentially sex-dimorphic responses. Indeed, in 70 transcriptomic studies of mouse longevity models (compiled from public repositories), we identified 51 studies including only male samples (~ 73%), 12 including only female samples (~ 17%), and 7 including both sexes (~ 10%). Thus, we will highlight the current knowledge of sex dimorphism in gene expression regulation, and discuss how these differences may drive aspects of sex differences in aging.

Transcriptional signatures of aging across sexes

Thousands of genes can be regulated in a sex-dimorphic manner across a range of youthful, healthy somatic tissues (e.g., brain, liver, heart, muscle) from various mammalian species (Berchtold et al. 2008; Isensee et al. 2008; Naqvi et al. 2019; Qureshi and Mehler 2010; Yang et al. 2006). Genes expressed in a sex-dimorphic manner are located on autosomes as well as on sex chromosomes (Berchtold et al. 2008; Isensee et al. 2008; Qureshi and Mehler 2010; Yang et al. 2006), and many of these genes are not directly targeted by sex hormones (Mayne et al. 2016). Functional enrichment analyses of sex-dimorphic gene regulation have identified differentially enriched pathways between male and female tissue transcriptomes, including immune response, oxidoreductase activity, and lipid metabolism (Yang et al. 2006). The existence of large transcriptional differences between male and female cells holds true in pure cell populations, with evidence that microglia purified from female vs. male brains of young mice show widespread gene expression and functional differences (Guneykaya et al. 2018; Villa et al. 2018). Although these studies only investigated such differences in young adults, since these functional processes are related to "hallmarks of aging" (López-Otín et al. 2013), sex-dimorphic regulation of gene expression could thus have an important impact on the aging process.

Studies in flies have revealed that the sex dimorphism in the expression of the mitochondrial Lon protease mediates sex- and age-specific adaptation to oxidative stress and the sex-dimorphic expression of this protease may be conserved in mice (Pomatto et al. 2017). In landmark studies, high sex dimorphism in the transcriptomic response to dietary restriction (Mitchell et al. 2016) and short-term fasting (Della Torre et al. 2018) were observed in mouse liver. Moreover, DR has been reported to feminize the gene expression profiles of male livers (Estep et al. 2009). Finally, genes expressed in a sex-dimorphic manner in the human brain were proposed to act as mediators of stress susceptibility

and depressive symptoms (Labonte et al. 2017), consistent with the idea that sex-dimorphic gene expression can broadly impact human health and physiology. These observations raise the intriguing possibility that sex-dimorphic gene expression may play a key role in aging and response to longevity interventions. Thus, systematically understanding the transcriptional underpinnings of sex differences in aging and longevity would provide crucial molecular handles to develop therapeutic strategies to slow down age-related functional decline and diseases.

Sex dimorphism in aging: a role for chromatin regulation?

Complementary to pure transcriptional regulation, regulation of chromatin states (i.e. the 'epigenome'), which are governed in part by histone post-translational modifications, can help tune transcriptional programs (Dong et al. 2012; Dunham et al. 2012; Hoffman et al. 2013; Jenuwein and Allis 2001; Parker et al. 2013; Whyte et al. 2013).

The impact of X chromosome inactivation in XX mammalian cells

The most obvious epigenetic impact of sexual differentiation is the inactivation via heterochromatinization of additional X chromosomes into a "Barr body" in cells carrying more than one X chromosome. Although X chromosome inactivation (XCI) has evolved to compensate for a differential dosage of X chromosome genes in XX cells, evidence shows that many X-linked genes can be expressed in a bi-allelic fashion in XX cells: on average ~ 15% of X-linked genes in human and ~ 3% in mice (Berletch et al. 2011). Indeed, a number of genes which are known to "escape" XCI are chromatin remodelers, including histone demethylases *UTX*, *KDM5C*, methyl-CpG-binding protein *MeCP2*, and chromatin remodeler *ATRX* (Chow and Heard 2009; Qureshi and Mehler 2010). The degree of expression of these escape genes varies by tissue, between 5 and 80% in others relative to the active X chromosome (Chow and Heard 2009). Numerous studies have looked at dysregulation of XCI in diseases, including cancers, Alzheimer's disease, and physiological aging.

Sex dimorphism in chromatin modifications throughout life

In line with the prevalence of transcriptional alterations with aging, accumulating evidence suggests that the chromatin landscape may be altered with aging across cell types and species. In addition, perturbations in chromatin-modifying enzymes can impact the lifespan of invertebrates, or even age-related cognitive decline in mice (reviewed in details in Benayoun et al. 2015 #410; Ucar and Benayoun 2018 #1605; Pal and Tyler 2016 #813), which supports the status of

'epigenetic alterations' as a 'hallmark of aging' (López-Otín et al. 2013). Recent studies comparing male and female epigenomic profiles across tissues and cell types have revealed robust sex-dimorphic chromatin features, specifically for chromatin accessibility in human T cells (Qu et al. 2015) and histone modifications across human tissues (Yen and Kellis 2015). Though these differences could result from differential sex chromosome ploidy, a number of the observed differences were identified on autosomes, suggesting that chromatin can indeed be differentially regulated in male vs. female cells (Hadad et al. 2016; Qu et al. 2015; Yen and Kellis 2015). These observations may be explained in part by the presence of genes encoding chromatin regulators on sex chromosomes (e.g., methyl-CpG-binding protein MeCP2, H3K27 demethylases UTX and UTY, H3K4 demethylase KDM5C, etc.) (Qureshi and Mehler 2010).

Sex-specific differences in DNA methylation profiles throughout life

In one of the few studies to examine aging as well as sex differences in epigenetic regulation, Agba et al. (2017) revealed a complex, tissue and sex-specific changes with age at 2 loci, the *Nr3c1* promoter and the *Igf2/H19* imprinting control region. Interestingly, in several tissues (hippocampus, hypothalamus, skin and liver) the most considerable difference was seen at the intermediate age (9 months) as female rats increased methylation at the *Igf2/H19* ICR with the methylation levels becoming most similar at the oldest age (24 months) (Agba et al. 2017). At multiple sites in different tissues, the direction of methylation change with age was opposite between sexes. Few studies have looked at genome-wide, sex-specific DNA methylation divergences with age. In one of these studies, while there no overall change was observed in the level of DNA methylation in male or female mouse hippocampi between 3 and 24 months of age, there was a large amount of change in the methylation of specific CpG and CpH sites (Masser et al. 2017). Importantly, these changes were predominantly sexually divergent (> 90%), with age-related change in methylation going in opposite directions in male and female tissues (Masser et al. 2017). Additionally, many sites were found to maintain sex specificity throughout age (either higher in males than females at both young and old age or vice versa). In contrast, another study of mice hippocampi found more subtle changes in DNA cytosine methylation and hydroxymethylation on autosomal chromosomes and large differences in X-chromosomal methylation and hydroxymethylation (Hadad et al. 2016). Finally, a recent study using the DNA methylation epigenetic clock found an association between age of menopause and "biological" aging, as measured by the DNA methylation profile (Levine et al. 2016).

The extent to which these epigenomic changes are simply mediating hormonal signaling or represent a distinct—if overlapping—mechanism of sex dimorphism remains to be fully elucidated. Further, much of the research done to-date on the epigenetics of sex dimorphism has, with reason, centered on the brain or germ cells, where differences were extremely likely to occur. Whether other tissues demonstrate equivalent divergences with sex and age will be an important future research avenue for the field.

Sex dimorphism in transposable element-driven genomic instability in youth and during aging

Transposable elements (TEs), sometimes called "jumping genes," are a type of repetitive DNA with the ability to move within host genomes (McClintock [1953](#)). Two main classes have been described: (1) class I transposons, or RNA-mediated transposons, act through a "copy and paste" mechanism, and (2) class II transposons, or DNA-mediated transposons, act through a "cut and paste" mechanism (Chénais et al. [2012](#)). More specifically, RNA-mediated transposons have enzymes to reverse transcribe their transcripts and to integrate the resulting complementary DNA (cDNA) into host genomes. DNA-mediated transposons, similarly, have transposases that recognize, cleave, and re-integrate TE DNA (Chénais et al. [2012](#)). In humans, the two most common TE families—long interspersed nuclear elements (LINEs) and short interspersed nuclear elements (SINEs)—compose about 33% of the genome (Lander et al. [2001](#)). Mechanistically, TEs can disrupt protein-coding sequences or alter gene expression through insertion into regulatory sequences (Kidwell and Lisch [1997](#)). Accumulating evidence supports the notion that TEs are progressively de-repressed with organismal aging across several organisms (Benayoun et al. [2019](#); De Cecco et al. [2013](#); Dennis et al. [2012](#); Li et al. [2013](#); Wood et al. [2016](#)). The excessive mobilization of TEs is believed to contribute to age-related genomic instability (De Cecco et al. [2013](#); Li et al. [2013](#); Maxwell et al. [2011](#); Wood et al. [2016](#)). Intriguingly, recent evidence suggests that LINE-1 reactivation may contribute to chronic age-related inflammation by promoting inflammatory cytokine secretion (De Cecco et al. [2019](#); Simon et al. [2019](#)). Although it is now established that TEs may contribute to age-related phenotypes, whether sex may influence their activation and impact on cell health remains largely unknown. Here, we discuss the current knowledge related to the impact of circulating sex hormones and of sex chromosomes on TE activity levels.

A potential role for hormonal regulation in sex-specific TE activation?

As highlighted in previous sections, differences in hormone levels may directly contribute to differences between male and female individuals, partially mediated by sex-steroid signaling (Paterni et al. [2014](#)). Evidence suggests that a tight interaction exists between estrogen receptors and TEs, which may implicate TEs in estrogen-influenced processes, including aging. Specifically, an analysis of chromatin immunoprecipitation (ChIP) data for ER-α in the MCF-7 breast cancer cell line found that a large proportion (~20%) of ERα-binding sites overlapped mammalian-wide interspersed repeat (MIR) sequences, a type of SINE element (Bourque et al. [2008](#)). Similarly, Mason et al. ([2010](#)) conducted a broad characterization of estrogen response element (ERE) sequences in MCF-7 cells using ChIP-on-chip. They estimated that 19–36% of EREs reside in repetitive (repeat-masked) genomic elements. Though the most common elements belonged to the Alu family, EREs were also detected in non-Alu SINE elements, LINEs, long terminal repeat (LTR) retrotransposons, non-LTR retrotransposons, microsatellites, and DNA transposable elements. Mason et al. ([2010](#)) also observed binding of ERα-containing complexes to 2 MIR-b elements in vitro by electrophoretic mobility-shift assay (EMSA) and noted that mutagenesis of either MIR or Alu-EREs reduced readout in their luciferase assays, indicative of their role in modulating transcription of nearby genes. A third study analyzed MCF-7 ChIP-seq datasets corresponding to two modes of estrogen treatment: one where cells were exposed to chronic, low levels of estrogen, and one where cells were treated with an acute higher dose of estrogens (Testori et al. [2012](#)). Consistent with prior studies, they identified an enrichment of ERα at DNA sequences corresponding to a variety of TEs (Testori et al. [2012](#)). Noteworthy, some of these TE-ERα interactions were unique to each dosage scheme, and within TEs that interact with ERα, they identify enrichment of binding sequences corresponding to transcription factors and known cofactors of ERα (Testori et al. [2012](#)). Finally, they note that MIR-like and endogenous retrovirus (ERV)-like elements that interact with ERα are frequently located close to the transcription start site of regulated genes (Testori et al. [2012](#)).

Interactions between TEs and androgen signaling have also been found. A putative androgen response element (ARE) was identified within the promoter of a LINE-1 element family (L1Hs) (Morales et al. [2003](#)). They further demonstrated that this promoter could alter the activity of their *LacZ* reporter gene in the presence of testosterone in the JEG-3 human choriocarcinoma cancer cell line (Morales et al. [2003](#)), suggesting the potential for androgens to alter the expression of genes downstream of ARE-containing TE regulatory elements. Interestingly, LINE-1 ORF1-p, one of

the proteins produced by LINE-1 elements, was found to act as an androgen receptor co-activator with the ability to promote the growth of human prostate carcinoma cells (Lu et al. 2013). Thus, sex-steroid hormones may be directly regulating TE activity in responsive cells.

To add to the complexity, researchers have also sought to characterize TE methylation levels with respect to age, sex, and hormone levels (El-Maarri et al. 2011; Lu et al. 2018). An analysis of peripheral blood mononuclear cells found marginally higher LINE-1 methylation in males compared to females (El-Maarri et al. 2011). However, they did not detect any significant effect on LINE-1 methylation across ages or throughout different stages of the menstrual cycle (El-Maarri et al. 2011). An inverse relationship between methylation levels and age of menopausal onset, however, has been noted (Lu et al. 2018). Thus, the ability of hormones to enhance or initiate gene expression combined with the apparent lack of correlation with TE methylation suggests that their TE-mediated effect may predominantly act at the transcriptional rather than epigenetic level.

Together, these results suggest that the interaction between TEs and sex-steroid hormone signaling can elicit sex-specific regulation of TE levels. On the one hand, TEs may provide the means for enhanced or possibly diminished, expression of neighboring genes, depending on circulating hormone levels and receptor activation. On the other hand, TEs such as LINE-1 and Alu, respectively, contain internal Pol II and Pol III promoters (Elder et al. 1981; Fuhrman et al. 1981; Lavie et al. 2004), and the presence of ERE/ARE motifs within these elements raises the possibility that their transcription may also be influenced by hormonal status. Differences in sex hormone levels are thus likely to drive transcriptional differences through both mechanisms. Moreover, these differences are very likely to be dynamic across time, and especially so within females, as (1) the hormonal cycle is characterized by repeated cyclic fluctuations of circulating estrogens and progesterone (Reed and Carr 2000), and (2) estrogen and testosterone levels tend to decrease throughout life in humans (Ferrini and Barrett-Connor 1998; Harman et al. 2001; Horstman et al. 2012), albeit more dramatically in females. Thus, whether sex-steroid hormone receptors differentially modulate TE transcription/integration or TE-influenced gene expression in males vs. females throughout life deserves further investigation, as it may reveal underlying mechanisms to sex dimorphism in organismal phenotypes.

The contribution sex chromosomes to sex-specific TE regulation

As highlighted in previous sections, sex chromosomes are responsible for determining the gender of an organism, which may impact differences observed between the sexes in organisms with XX/XY sex-determination system (Hodgkin 1992). In the process of understanding the evolution and contents of the Y chromosome in mammals, the field has unraveled many exciting features of this chromosome, including the existence of a large portion of euchromatin in the center, in contrast to its largely heterochromatic ends (Quintana-Murci and Fellous 2001). Indeed, the human Y chromosome, and the Y chromosome in general, is known to be highly repetitive (Hughes and Rozen 2012; Skaletsky et al. 2003; Smith et al. 1987). Research in the field of epigenetics has unraveled the loss of heterochromatin marks with age (Pal and Tyler 2016). Thus, the highly repetitive nature of the Y chromosome, coupled to a prevalent loss of heterochromatin with age, may lead to a sex-specific de-repression of Y-linked TEs (Marais et al. 2018). Indeed, in flies, the Y chromosome was reported to broadly influence the chromatin states of autosomes (Lemos et al. 2010). With age, the Y chromatin becomes de-repressed, and TEs tend to activate, which could further promote age-related phenotypes (Brown and Bachtrog 2017). Intriguingly, studies of longevity in XY, XO, XYY males and XX, XXY females showed that the presence of a Y chromosome accelerates aging in flies (Brown and Bachtrog 2017), which was proposed to be the result of its particularly high TE content (Brown and Bachtrog 2017; Marais et al. 2018).

Thus, although there is still limited information about the link between sex chromosome karyotype, TEs and aging, it is likely that this would be a productive future research avenue.

Current and emerging experimental models for the study of sex-dimorphic mechanisms

The most prevalent genetic model for understanding the relative role of sex chromosome complement (i.e. XX vs. XY) and gonadal sex (i.e. ovary vs. testes) in mammalian phenotypes is the "four core genotype" (FCG) model (Arnold 2009; Arnold and Chen 2009). Thanks to the combination of a null mutation of the Y chromosome testis-determining gene *Sry*, and the insertion of an *Sry* transgene in an unmapped autosomal location, sex chromosome complement (XX vs. XY) is effectively decoupled from the animal's gonadal sex in this model (Arnold 2009; Arnold and Chen 2009). This model has been used to study various aspects of karyotype vs. hormonal effects (Arnold and Chen 2009). Importantly, FCG mice were recently used to demonstrate that the presence of two X chromosomes (and, to a lesser extent, of ovaries) can lead to increased longevity (Davis et al. 2018). Known caveats of the FCG model include potentially incomplete gonadal reprogramming in some genetic backgrounds, and premature gonadal exhaustion has been reported on the C57BL/6 background,

the most common background in aging research (Burgoyne and Arnold 2016). To note, FCG leads to gonadal sex reversal during the initial determination of the bipotential gonad, thus decoupling karyotypic and gonadal sex from the beginning of gonadal development (Arnold 2009; Arnold and Chen 2009). This timeline means that the FCG cannot disentangle the organizational effects of gonadal hormones (i.e. impact on the development of distal somatic sites), from their activational effects (i.e. effects on mature tissues after the end of development, and throughout life) (Arnold and Breedlove 1985).

To address the relative importance of endocrine vs. genetic mechanisms in sex-dimorphic phenotypes, it may become useful to leverage a previously described mouse model of adult somatic sex reprogramming: the adult inducible knock-out (KO) of *Foxl2* (Uhlenhaut et al. 2009). Remarkably, deletion of Foxl2 in adult mice leads to upregulation of testis-specific genes in the gonad, and within 3 weeks of *Foxl2* loss, somatic ovary to testis transdifferentiation occurs (Uhlenhaut et al. 2009). Further, induced *Foxl2* knock-out mice acquire circulating testosterone levels comparable to those of 'normal' XY male littermates (Uhlenhaut et al. 2009). This genetic model could provide a unique opportunity to study the impact of a female vs. male hormonal milieu in adult genetically female XX individuals, thus allowing to study the non-organizational effect of sex-steroids on aging. This model could thus open a window on the post-developmental effects of gonadal hormones regardless of karyotypic sex. To note, the adult *Foxl2* KO model has never been evaluated with aging, and its use could open interesting new research avenues in the field.

Generally, leveraging the power of the FCG and the *Foxl2* inducible KO mice should help dissect the adult contribution of gonadal hormones vs. sex chromosomes karyotype in age-related sex-dimorphic phenotypes.

Conclusion and final remarks

In this review, we discussed recent advances in the research of sex differences in aging and longevity. Although differences between women and men aging have been known for decades, the mechanism by which these disparities among the sexes remains poorly understood. Increasing evidence supports the impact of sex hormones on lifespan. However, the molecular dissections of genetic vs. hormonal contributions to these differences are only starting to be touched upon by researchers. To further understand these differences and the molecular pathways that underlie them, it will be crucial to leverage genetic and surgical models that can decouple specific aspects linked to sex differences, including genetic/hormonal sex swaps (e.g., Four Core Genotype, *Foxl2* somatic sex reprogramming), hormonal signaling

disruptions (e.g., inducible or tissue-specific knock-outs for estrogen receptor or androgen receptor genes), or surgical gonadectomy. Information from these various sources will finally help understand the molecular regulation of sex differences in health and lifespan. Moving forward, leveraging these tools to understand the bases of sex differences in responses to pro-longevity interventions and in the prevalence of age-related diseases will be crucial. In this light, tailoring interventions based on sex will be the first (small) step for aging research toward personalized medicine.

Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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