Review

MOLECULAR METABOLISM

Sex differences in obesity, lipid metabolism, and inflammation—A role for the sex chromosomes?

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ABSTRACT

Background: Sex differences in obesity and related diseases are well established. Gonadal hormones are a major determinant of these sex differences. However, sex differences in body size and composition are evident prior to exposure to gonadal hormones, providing evidence for gonadal-independent contributions attributable to the XX or XY sex chromosome complement. Large-scale genetic studies have revealed male/female differences in the genetic architecture of adipose tissue amount and anatomical distribution. However, these studies have typically neglected the X and Y chromosomes.

Scope of the review: Here we discuss how the sex chromosome complement may influence obesity, lipid levels, and inflammation. Human sex chromosome anomalies such as Klinefelter syndrome (XXY), as well as mouse models with engineered alterations in sex chromosome complement, support an important role for sex chromosomes in obesity and metabolism. In particular, the Four Core Genotypes mouse model—consisting of XX mice with either ovaries or testes, and XY mice with either ovaries or testes—has revealed an effect of X chromosome dosage on adiposity, hyperlipidemia, and inflammation irrespective of male or female gonads. Mechanisms may include enhanced expression of genes that escape X chromosome inactivation.

Major conclusions: Although less well studied than effects of gonadal hormones, sex chromosomes exert independent and interactive effects on adiposity, lipid metabolism, and inflammation. In particular, the presence of two X chromosomes has been associated with increased adiposity and dyslipidemia in mouse models and in XXY men. The enhanced expression of genes that escape X chromosome inactivation may contribute, but more work is required.

1. SEXUAL DIMORPHISM IN DISEASE

The study of sex differences in physiology has gained traction as it pertains to understanding male/female differences in disease susceptibility. Women more often than men suffer from autoimmune diseases (*e.g.*, systemic lupus erythematosus, scleroderma, Sjogren's syndrome), as well as osteoporosis, Alzheimer's disease, and clinical depression [1—6]. Autism occurs at higher rates in boys than girls, and sex differences are also observed in neurological diseases such as Parkinson's disease and schizophrenia, to name a few [7—9]. In cardiovascular disease and stroke, there are differences between the sexes in age of onset, disease pathology, and mortality [10].

Some sex differences in human disease are directly related to the distinct sex chromosome complement in females (XX) and males (XY). Males are more commonly afflicted with X-linked diseases such as color blindness, Duchenne muscular dystrophy, and hemophilia. Women may be protected from (or experience attenuated severity of) these recessive disorders, because they possess two X chromosomes [11]. The random inactivation of one X chromosome in female cells during early development silences the X chromosome carrying a mutant gene in approximately half of female cells, allowing the exclusive expression of a wild-type gene in those cells. An extreme example of the influence of XX *versus* XY genotype on disease severity is Rett syndrome, which results from mutation in the *MECP2* gene on the X chromosome. Females afflicted with Rett mutations experience progressive neuro-developmental deficiencies leading to impaired learning, communication, coordination, and other brain functions. By contrast, males with *MECP2* mutations typically die *in utero* or in infancy [12].

Here we will discuss how the sex chromosome complement may influence factors that underlie metabolic disturbances such as obesity, dyslipidemia, and inflammation. It is well known that gonadal hormones have strong effects on fat storage and susceptibility to related diseases such as cardiovascular disease and type 2 diabetes [13]. Since female gonads are typically found together with XX chromosomes, and male gonads with XY chromosomes, the independent roles of gonadal hormones and sex chromosomes has not been appreciated. However, human sex chromosome anomalies such as Klinefelter syndrome (XXY) and Turner syndrome (XO), as well as mouse models with engineered alterations in sex chromosome complement, support an important role for sex chromosomes in obesity and metabolism.

2. SEX DIFFERENCES IN HUMAN ADIPOSITY AND OBESITY

Adipose tissue serves as an efficient energy storage depot. It also has active roles in fatty acid uptake from circulating lipoproteins produced

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in response to a meal, and in the regulated release of fatty acids for use by other tissues between meals or during physical activity. There are key differences between males and females in adipose tissue distribution, with men accumulating greater amounts of visceral adipose tissue and women typically having greater fat accumulation in subcutaneous (gluteal—femoral) depots [14,15]. Sex-specific fat distribution is influenced by several factors, including diet and hormonal status [16]. One contributor to sex bias in adipose tissue distribution may be the rate of direct fatty acid uptake by tissues, a process that occurs independently of lipoprotein lipase (the enzyme responsible for liberation of fatty acids from lipoproteins). Direct fatty acid uptake is higher in the gluteal—femoral depot in women and in the abdominal depot in men [17].

Both overall fat mass and visceral fat accumulation are strongly associated with the development of cardiovascular disease, stroke, hypertension, and insulin resistance [15,18,19]. Standard measurements for fat accumulation in humans include body mass index (weight as a function of height), which reflects whole body adiposity, and waist-to-hip ratio, which provides an indication of fat distribution, with the waist measurement as a proxy for visceral fat and the hip measurement for gluteal fat [19]. Seminal studies performed in the 1980's provided evidence that overall adiposity, as well as subcutaneous fat mass, have a heritability of approximately 30% [20]. This estimate was corroborated by a 1990 study in Caucasian male twins that showed a 31% heritability of waist-to-hip ratio, while a more recent population-based study estimated heritability of the same trait at 39% [21,22]. Some estimates indicate that heritability of fat distribution is greater in women than in men [19]. Fat distribution and heritability also differ across ethnic groups [23,24]. One approach to identify the genes contributing to sex differences in adipose tissue accumulation and distribution is genome-wide association studies (GWAS) in large human cohorts. This approach types genetic variants across the genome and correlates their occurrence with a trait to identify loci that are associated. GWAS performed in hundreds of thousands of people have identified more than 100 genetic loci that harbor common genetic variants that influence adiposity [25—27]. Importantly, at least 17 loci that are associated with body mass index have also been identified in GWAS for type 2 diabetes [25].

Analysis of accumulated GWAS data has revealed a distinct genetic architecture for loci affecting adiposity in males and females. For example, a meta-analysis of more than 50 GWAS studies with waist-to-hip ratio (adjusted for total fat) in more than 200,000 individuals identified 49 loci, 20 of which showed sex-specific effects, with 19 of these having stronger effects in women [28]. These loci represent a rich resource for the identification of sex-biasing genetic factors for body composition and fat distribution, although at present, these loci together account for only a few percent of the genetic variance in adiposity. Much work remains to be done, including the identification of the causal variants at each locus and their mechanism of action to influence adiposity. Of note, these analyses did not take into account loci on the X or Y chromosomes, leaving a gap in our knowledge regarding how genetic variations on X and Y may contribute to observed sex differences in adiposity. The following sections describe studies outside of GWAS that have informed about the role of the X and Y chromosomes in adiposity and metabolic disease.

3. SEX DIFFERENCES IN ADIPOSE TISSUE EXPANSION

It has been suggested that adipocytes in gluteal—femoral depots (and other subcutaneous depots) confer better metabolic health because of the ability to expand to store more fat by recruiting new adipocytes [16,29,30]. It has previously been thought that male mice exhibit greater diet-induced fat mass expansion (in both visceral and subcutaneous depots) than females, and this is partly due to effects of sex hormones [31—33]. However, a recent study demonstrates that in C57BL/6J mice, the sex differences in diet-induced weight gain depend strongly on the age of the mice when fed a high fat diet. In juvenile mice (aged 6 weeks), feeding a high-fat diet for 3 months led to greater percent weight gain in males than females. However, in adult mice (aged 31 weeks), the trend was reversed, and females gained substantially greater percent body weight in response to high-fat diet [34].

One potential contributor to sex differences in adipose tissue expansion is the numbers of adipocyte precursor cells (pluripotent stem cells that may differentiate into adipocytes, chondrocytes or osteoblasts) in mouse gonadal or subcutaneous fat depots. On a low-fat chow diet, female C57BL/6J mice have more adipocyte precursor cells than males in gonadal (visceral) and inguinal (subcutaneous) fat pads [35—37]. When fed a high-fat diet (45% calories as fat), female mice showed increased adipocyte precursor cells and mature adipocytes in gonadal fat, but males did not increase mature fat cells in the gonadal fat pad [36]. Other studies, which employed pulse-labeling or lineage tracing to follow the fate of proliferating adipocyte progenitor cells, inferred that male gonadal fat exhibits hyperplasia in response to a high-fat diet, whereas females exhibit adipocyte hyperplasia in both gonadal and subcutaneous fat depots [38,39]. The sex-specific patterns were reversed by ovariectomy in female mice, or estrogen administration in male mice, suggesting a role for gonadal hormones [37]. These studies have proved valuable, but additional studies of adipocyte recruitment and turnover in fat depots of both sexes are needed to clarify discrepancies between studies that have used distinct methodologies and to provide additional details.

4. GONADAL AND CHROMOSOMAL INFLUENCES ON ADIPOSITY

Gonadal hormones have major effects on fat storage and related diseases, as evidenced by comparisons of pre-menopausal and post-menopausal women. After menopause and reduction in the levels of estrogen and other gonadal hormones, women typically experience increased fat storage in abdominal depots, and an increased occurrence of cardiovascular diseases, hyperlipidemia, insulin resistance, and hypertension [14,40—43]. However, short-term reduction in estrogen levels (4 weeks) did not lead to altered fat storage, although it did affect post-prandial circulating triglyceride levels [44]. By contrast, short-term (4 weeks) suppression of testosterone levels in men led to increased storage of meal-derived fatty acids in the gluteal—femoral fat depot [45]. The effects of gonadal hormones on fat depot development and metabolism are likely influenced by numerous variables, including hormone levels and estrogen and androgen receptor levels [46].

Beyond the well-established roles of gonadal hormones, accumulating evidence supports a key role for the sex chromosomes in the determination of sex differences in adiposity. The presence of XX chromosomes in females and XY chromosomes in males determines the development of ovaries or testes, respectively [47]. Specifically, the *SRY* (sex-determining region Y) gene present on the Y chromosome encodes a transcription factor that initiates testes development in XY embryos, and subsequent elaboration of testicular hormones. Lack of an *SRY* gene in an embryo (due to XX chromosomes or deletion of the *SRY* gene) leads to the development of ovaries and production of ovarian hormones. Sex differences in body composition are evident prior to exposure to gonadal hormones. For example, during human

