Adipocyte 2:2, 74–79; April/May/June 2013; © 2013 Landes Bioscience

Metabolic impact of sex chromosomes

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Keywords: metabolic disease, sex differences, obesity, food intake, fatty liver, circadian rhythm

Obesity and associated metabolic diseases are sexually dimorphic. To provide better diagnosis and treatment for both sexes, it is of interest to identify the factors that underlie male/female differences in obesity. Traditionally, sexual dimorphism has been attributed to effects of gonadal hormones, which influence numerous metabolic processes. However, the XX/XY sex chromosome complement is an additional factor that may play a role. Recent data using the four core genotypes mouse model have revealed that sex chromosome complement—independently from gonadal sex—plays a role in adiposity, feeding behavior, fatty liver and glucose homeostasis. Potential mechanisms for the effects of sex chromosome complement include differential gene dosage from X chromosome genes that escape inactivation, and distinct genomic imprints on X chromosomes inherited from maternal or paternal parents. Here we review recent data in mice and humans concerning the potential impact of sex chromosome complement on obesity and metabolic disease.

Hormonal and Genetic Factors Contribute to Sex Differences

Obesity and the metabolic syndrome are complex diseases regulated by many genetic and environmental factors. It is well known that risk, development and manifestations of obesity-related conditions such as diabetes and atherosclerosis are sexually dimorphic. Sex differences in obesity are strongly influenced by gonadal hormone effects.[1,2] However, an additional fundamental difference that may contribute to metabolic differences between females and males lies within the nucleus of each cell—the XX and XY sex chromosome complement.

The sex chromosome complement of female and male cells imposes several known genetic differences[3] (**Fig. 1**). For example, female cells with an XX chromosome complement never express any of the 78 protein-coding genes, nor an unknown number of noncoding RNAs, that are present on the Y chromosome. In addition, only XX cells undergo the process of transcriptional inactivation of one of the two X chromosomes during early development as a mechanism to balance gene dosage between males and females.[4-6] X chromosome inactivation involves the expression of X chromosome noncoding RNAs, production of high levels of histones, widespread chromatin remodeling and chromosome condensation, such that XX cells experience a distinct nuclear microenvironment during this process.[4] Furthermore, whereas XY cells inherit only a maternally imprinted X chromosome, XX cells carry one X chromosome with maternal imprints and another with paternal imprints.[5] The random inactivation of one X in XX cells therefore could lead to differential expression of imprinted genes compared with XY cells. Finally, although X-inactivation silences most genes on one X chromosome, some genes escape this process and are expressed at a higher level in tissues of females than males.[6-8]

In humans and standard animal models, it has been difficult to distinguish the contributions of gonadal hormones and sex chromosome complement as determinants of obesity, since female gonads are virtually always present in combination with XX chromosomes, and male gonads with XY chromosomes. To tease apart the influence of sex chromosome complement from gonadal hormones in obesity and related metabolic traits, we have used the four core genotypes mouse model.[9,10] In this model, the testis-determining gene, *Sry*, is deleted from the Y chromosome and an Sry transgene is inserted into an autosome. Thus, the Y chromosome segregates independently from the *Sry* gene and formation of male gonads. As a result, this model allows the generation of mice with four different "sexes" on a C57BL/6 background: XX mice with either male or female gonads, and XY mice with either male or female gonads (**Fig. 2**). In addition, we gonadectomized these mice to remove acute gonadal hormone action and uncover the effects of sex chromosome complement, as well as to detect long-lasting (organizational) effects of gonadal hormones.

In our recent study,[11] we observed dramatic effects of sex chromosome complement on obesity and metabolism (summarized in **Fig. 3**). Male and female mice with two X chromosomes had higher body weight and nearly twice as much body fat than mice with one X and one Y chromosome. XX mice also had increased food intake during the light (inactive) phase of the circadian cycle, potentially contributing to their higher body weight. When placed on a high fat diet, XX mice gained weight at an accelerated pace, and developed fatty liver and insulin resistance. A potential mechanism may be that genes escaping X-inactivation drive these differences observed between XX and XY mice. In support of this, we observed increased expression of X-inactivation escapees in key metabolic tissues (adipose and liver) of XX mice. In this article, we discuss these findings in the context of other reported

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Submitted: 09/25/12; Revised: 12/13/12; Accepted: 12/17/12
http://dx.doi.org/10.4161/adip.23320

sex differences in obesity, metabolic dysregulation, circadian rhythms and food intake.

Sex Chromosomes Influence Obesity and Associated Metabolic Dysregulation

The sexually dimorphic nature of human adipose tissue content and anatomical distribution has been widely documented and reviewed in recent excellent review articles.[12,13] It is well known that pre-menopausal women tend to store fat in subcutaneous depots, while men tend to store fat in visceral depots. After menopause, women begin to accumulate fat in the viscera, commonly associated with increased risk for metabolic diseases such as type 2 diabetes, non-alcoholic fatty liver disease and atherosclerosis. These differences in fat distribution have been attributed largely to the acute action of circulating sex hormones. Studies in the four core genotypes mouse model described above, however, revealed that sex chromosome complement also influences adiposity and metabolism.

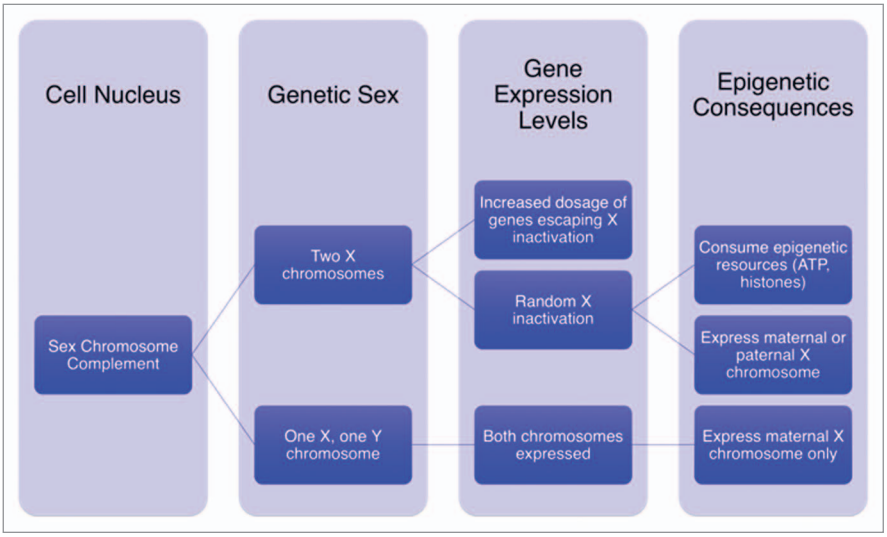

Figure 1. Genetic and epigenetic consequences of sex chromosome complement. XX cells undergo X inactivation, which requires cellular resources to produce histones and non-coding RNAs. Some genes escape X inactivation and are expressed at a higher level in XX compared with XY cells. Additionally, differential genomic imprinting (silencing) of genes on the X chromosome inherited from maternal and paternal parents can lead to gene dosage differences in XX cells and XY cells.

In gonadally intact mice of the four core genotypes, both gonadal sex and sex chromosome complement had effects on body weight.[11] Gonads were subsequently removed in adulthood, thus eliminating acute effects of gonadal hormones. XX mice fed a standard mouse chow diet (~5% fat) had almost double the fat mass of XY mice, regardless of their original gonadal sex. When the mice were fed a high fat diet after gonadectomy, the difference between XX and XY mice was amplified, with XX mice gaining weight more rapidly, and diverging from XY mice after only three days on the high fat diet. Analysis of specific fat depots revealed that XX mice had larger subcutaneous inguinal adipose tissue depots, whereas XY mice had larger gonadal fat pads. This result suggests that sex chromosome complement is a contributing factor to the differences in fat distribution that are observed between females and males.

Obesity causes many complications in tissues other than adipose, such as ectopic accumulation of fat in the liver. In addition to the increased adiposity in XX mice, a high fat diet promoted lipid droplet accumulation in livers of XX mice, whereas XY mice were virtually protected.[11] This was reflected in increased liver mass, increased hepatic triglyceride levels and reduced fatty acid oxidation gene expression in XX mice compared with XY mice. These results implicate sex chromosome complement as a risk factor for fatty liver. Epidemiological data in humans also show that sexual dimorphism exists in susceptibility to non-alcoholic steatohepatitis, but some populations exhibit increased incidence in women, while others report increased incidence in men.[14-16] Data in rodents are also contradictory. Male rats fed a methionine-choline-deficient diet develop more severe hepatic steatosis than females,[17] whereas C57BL/6J mice fed a high fructose diet showed a similar degree of steatosis in males and females, but greater inflammation in females.[18] The different diets used in each of these rodent studies make it difficult to make comparisons and firm conclusions. However, the results in Chen et al.[11] strongly suggest that sex chromosome complement may be an underlying determinant of hepatic steatosis that should be considered in studies of rodents and humans.

Another typical feature of obesity is insulin resistance. In the four core genotypes model, the high fat diet did not alter glucose levels, but induced a 2-fold elevation in fasting insulin levels in XX mice, but not XY mice.[11] Thus, XX chromosome complement appears to be a risk factor for insulin resistance in this model. Interestingly, studies in humans show that pre-menopausal women are more insulin sensitive than men.[19-21] This may be due to the positive effects of estrogen and/or the negative effects of androgens on insulin sensitivity.[22] Thus, while gonadal hormones clearly play a significant role in insulin signaling, our work shows that having two X chromosomes may be an additional genetic determinant, and may become most relevant in a hypogonadal state, such as after menopause.

Determinants of Sex Differences in Food Intake and Circadian Rhythms

To understand why XX mice accumulate more adipose tissue than XY mice, Chen et al.[11] assessed energy expenditure, physical activity, and food intake at a point when body weights among the four genotypes were the same (four weeks post-gonadectomy). No differences were detected in energy expenditure or activity among the genotypes, but XX mice exhibited increased food intake. This was notable because it occurred prior to their

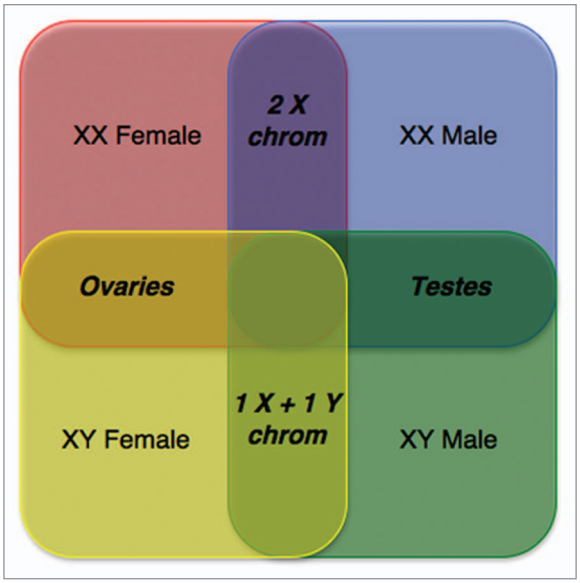

Figure 2. The four core genotypes mouse model. This mouse model generates four different "sexes": mice with female gonads that have either XX or XY sex chromosomes, and mice with male gonads that have either XX or XY sex chromosomes. Differences between gonadal females and gonadal males are attributed to acute or organizational gonadal hormone effects, while differences between XX and XY mice are attributed to the sex chromosome complement.

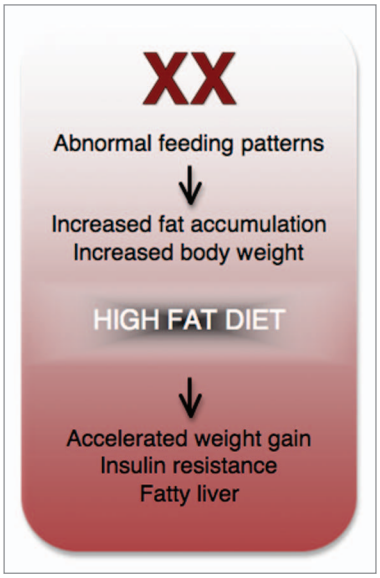

Figure 3. Metabolic impact of two X chromosomes. Mice with two X chromosomes have a higher food intake during the inactive phase, higher body weight and greater adipose tissue content. When placed on a high fat diet, these mice exhibit rapid weight gain and develop insulin resistance and fatty liver.

divergence from XY mice in body weight, and therefore may be a causative factor in the subsequent increased adiposity in XX mice. It was also notable that the increased food intake occurred exclusively during the light phase, during which mice (which are nocturnal) have reduced activity and typically consume only about 30% of their daily food. The increased food intake during the light phase raises the intriguing possibility that sex chromosome complement influences circadian regulation.

There is increasing evidence in mice and humans that disruption in the circadian cycle affects eating patterns and may contribute to obesity.[23,24] The distribution of caloric intake throughout the day is an important factor in human obesity.[25] In particular, eating during the inactive phase of the circadian cycle, such as midnight snacking, is associated with weight gain and greater risk of the metabolic syndrome.[26-28] Genetic disruption of the circadian cycle by mutation of the mouse *Clock* gene, a central transcriptional regulator of circadian rhythm, causes increased feeding during the light (inactive) period and obesity.[29] Furthermore, wild-type mice that eat on a circadian-shifted schedule are also prone to obesity. For example, when mice were fed equivalent amounts of a high fat diet exclusively during the dark phase or exclusively during the light phase, those who ate during the light phase gained double the weight, despite similar activity levels.[30] Additional studies of light-restricted feeding in mice have also shown increased weight gain, as well as altered metabolic gene expression in fat and liver, and higher respiratory exchange ratio, indicating reduced reliance on fatty acid oxidation.[31,32] Interestingly, the increased adiposity in XX mice in the study by Chen et al.[11] was associated with altered metabolic gene expression and higher respiratory exchange ratio. The mechanisms for the increased weight gain with disruption of circadian rhythm are not well understood, but may depend on a rhythmic profile of leptin levels that normally occurs throughout the circadian cycle.[33] It will be interesting to determine whether altered rhythmicity of leptin, or perhaps leptin resistance, is present in XX compared with XY mice, and whether limitation of feeding in XX mice to the dark period may alleviate the increased weight gain.

Sexual dimorphism in eating behavior of male and female rodents has been described, and gonadal hormones have been implicated. Several studies show that food intake and satiety are highly regulated by estradiol.[34] In gonadally intact female rats, a rise in estradiol secretion is followed by a reduction in food intake, whereas ovariectomy results in increased food intake. Furthermore, estradiol interacts with other satiety signals in the central nervous system and in the periphery.[34] It has also been shown that female rats that have been fasted for 48 h activate orexin neurons (which promote feeding) to a greater extent and consume more food than males.[35] Nevertheless, the data in Chen et al.[11] showing that gonadectomized mice with XX chromosomes eat more than XY mice reveals that additional genetic factors beyond gonadal hormones also contribute to sex differences in food intake and meal patterns. The four core genotypes mouse model provides a tool to further dissect the effects of gonadal hormones and sex chromosome effects on feeding behavior and metabolic disease.

Relevance to Humans

With the increasing longevity of humans and thus a longer time spent in a hypogonadal state, it is important to understand non-hormonal regulators of sexual dimorphism. Chen et al.[11] demonstrated that the sex chromosome complement is an important determinant of adiposity, fatty liver, and insulin levels in the absence of sex hormones. These results in the mouse raise the question of whether sex chromosome aneuploidies in humans might be instructive about the role of sex chromosomes in metabolic regulation. Human sex chromosome aneuploidies include 45,X0 females (1/2,500 live female births), 47,XXY males (1/500 live male births), 48,XXYY (1/17,000 live male births), 48,XXXY males (1/50,000 live male births), and 46,XX males (1/20,000 live male births, resulting from translocation of the *SRY* gene to the X chromosome).[36-38] The rarity of most sex chromosome aneuploidies has made it difficult to assess their effects on metabolism. However, some data available for XXY males and X0 females indicate higher incidence of metabolic disease than the general population, as described below.

Compared with XY males, individuals with Klinefelter syndrome (XXY) are more likely to have an atherogenic lipoprotein profile, with elevated low density lipoprotein levels, and reduced high density lipoprotein levels.[39] XXY men may also have increased incidence of type 2 diabetes and metabolic syndrome, defined as the co-occurrence of visceral obesity, insulin resistance and enhanced cardiovascular disease risk.[40,41] These findings in XXY men are consistent with mouse studies in which the presence of two X chromosomes compared with a single X was associated with obesity and metabolic dysregulation.[11] XXY men have lower levels of testicular androgens, which could contribute to the metabolic effects associated with the syndrome, so it is unclear which factors are the most important.

Turner syndrome women (X0) tend to have greater fat mass when adjusted for body weight than XX females.[42,43] X0 women may also experience increased risk for type 2 diabetes mellitus and heart disease.[44] These results appear to contradict the finding in mice that presence of one X chromosome leads to reduced adiposity compared with XX mice.[11] One factor that potentially contributes to increased metabolic dysregulation in Turner syndrome women is that they are hypogonadal throughout their lifetime. In contrast, in the mouse studies, animals had intact, normal gonads until adulthood and therefore may have experienced critical activational and organizational effects of gonadal hormones that are metabolically beneficial and not experienced by X0 humans. Interestingly, an analysis of body fat and lipid levels in a group of Turner syndrome patients showed differences depending on the parental origin of the single, normal X chromosome. Individuals that inherited the maternal X chromosome had 78% more visceral fat than those carrying an X chromosome of paternal origin, and higher triglyceride and low density lipoprotein cholesterol levels.[45] The maternal and paternal X chromosomes carry distinct genomic imprints, which silence the expression of specific genes and result in different expression levels. These results dovetail with those in the mouse showing that X chromosome dosage influences metabolic regulation, and highlight the mechanism of differential imprinting of the X chromosome from the two parents as a potential contributing mechanism.

Future Perspectives

Sexual dimorphism is a critical component that affects numerous aspects of metabolism and, hence, susceptibility to metabolic disease. The pervasive effect of sex on metabolism is strikingly illustrated by a recent metabolomic study of serum from more than 3,000 men and women.[46] An unbiased analysis of 131 blood metabolites (including amino acid, fat and sugar molecules) revealed significant concentration differences between males and females for 102 of the metabolites. Thus, widespread differences in metabolism clearly occur in males and females, and there is a need to better understand the nature and origin of these for effective treatment of metabolic diseases in both sexes.

Studies in humans are valuable, and every effort should be made to perform well-designed, sufficiently powered studies of both sexes. But such studies will always be limited in their ability to provide insight into the underlying mechanisms for sex differences, and it is in this realm that animal models are critical. The four core genotypes mouse model is one such model and is unique in that it allows the discrimination of effects due to gonadal sex or sex chromosome complement.[10] Based on the initial identification of sex chromosome effects on adiposity, feeding behavior, fatty liver and insulin resistance, we anticipate that this model will be useful to provide additional insight into the genetic factors and physiological mechanisms involved. As presented in Chen et al.,[11] genes that escape X chromosome inactivation exhibit increased expression levels in tissues such as adipose and liver, which may lead to phenotypic differences. In addition to the expression of protein coding genes examined thus far, additional potential players include long non-coding RNAs that are known to escape X-inactivation,[8] and potentially some of the 70 microRNAs that are present on the X chromosome, which have not been assessed for potential inactivation escape.

A valid question is whether results obtained in a model such as the four core genotypes mouse will translate to humans. Several factors suggest that they will. The genes on the human and mouse X chromosomes are highly conserved, as is the process of X chromosome inactivation. Furthermore, the genes that are known to escape inactivation in the mouse also escape inactivation in humans.[47] Additional genes have also been shown to escape X-inactivation in humans, suggesting that sex chromosome effects may potentially be amplified in humans compared with mice.[48] And finally, in the mouse studies, sex chromosome effects were most apparent in mice that had been gonadectomized as adults. Although humans are not typically gonadectomized, both women and men experience periods of hypogonadal hormone levels, typically beginning in middle age. It is likely that the sex chromosome effects observed in mice may become more influential in humans with advancing age, which is when the majority of individuals develop metabolic diseases such as type 2 diabetes and cardiovascular disease. It will be interesting to determine the effects on obesity and

dysregulated metabolism when gonadectomy is performed in four core genotype mice at advanced ages, to better parallel the onset of menopause in humans. Moreover, mouse models offer considerable advantages for identifying the X gene(s) responsible for the sex chromosome effect, which can then be tested in studies of humans. Ultimately, the identification of genes or factors that promote or protect against metabolic diseases in a sex-specific manner may suggest novel pathways as targets for therapeutic intervention.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

The authors gratefully acknowledge support from the National Institute of Diabetes and Digestive and Kidney Diseases (National Public Health Service R01 DK83561 to A.P.A., X.C. and K.R.) and Ruth L. Kirschstein National Research Service Award (GM007185 to J.L.).

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