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# The sex-chromosomes related cellular dimorphism in physiology and pathology

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ABSTRACT

Sex-based biological differences have a profound impact on health and disease. Historically, these disparities were primarily attributed to differences in gonadal hormones. Recent advances in biochemistry and molecular biology, however, have revealed additional contributing mechanisms—most notably, the critical role of genes located on the X and Y chromosomes. The expression of Y-linked genes, increased dosage of X-linked genes in XX compared to XY cells due to incomplete X-chromosome inactivation, genomic imprinting, and the presence of non-coding and micro-RNAs on the X chromosome are all factors that require consideration in the development of *in vitro* models addressing sex dimorphism.

In the present narrative review, we propose studies showing sex differences in vascular and cardiac cells, skeletal muscle cells, adipose tissue, liver, immune cells, cancer tissues and brain tissues. Given the absence of appropriate experimental methodologies for reproducing *in vitro* the sex differences observed *in vivo* and the limited research conducted at the cellular and molecular level to elucidate the mechanisms responsible for the observed dimorphism, the present review has two objectives. Firstly, it aims to emphasize the necessity of incorporating sex as a variable in preclinical research. Secondly, it highlights the importance of sex chromosome differences as a biological variable that can influence cell physiology and biological responses, which is crucial when conducting *in vitro* studies.

## 1. Introduction

The identification of the origins of the differences between males and females remains a significant challenge for biomedical research. While there is compelling evidence of sex differences that has been validated by *in vivo* and *ex vivo* data, both in health and disease conditions, mechanistic studies analyzing the origins of these differences at the cellular and molecular levels are still rather limited (Allen et al., 2023; Deegan et al., 2021; Di Luigi et al., 2023; Kim et al., 2018; Márquez et al., 2020; Ortona et al., 2016; Rich-Edwards et al., 2018; Ruggieri and Matarrese, 2020; Young et al., 2023). Both sex (the biological characteristic) and gender (belonging to one of the two sexes from a cultural rather than biological point of view) influence molecular and cellular metabolism, clinical characteristics, as well as the pharmacological response (Rich-Edwards et al., 2018).

Sex hormones influence gene expression primarily through their interaction with specific receptors, including classical nuclear receptors (e.g., estrogen receptor, androgen receptor), orphan nuclear receptors, and G protein-coupled receptors (GPCRs). Through these pathways, they can modulate the expression of autosomal as well as X- and Y-linked genes, and, in some cases, affect gene regulation by interacting with regions of the inactivated X chromosome (Chen et al., 2016; Dadam et al., 2024; Rocks et al., 2022; Xiong et al., 2023). However, in many tissues, no differential expression of estrogen receptor genes (ESR1 and ESR2) was observed between male and female subjects, suggesting that sexually dimorphic effects may be mediated through alterations in gene regulatory networks, independent of sex hormone receptor expression levels (Chen et al., 2016).

In this regard, hormonal pathways (organisational and/or activation effects) may act independently or interact (synergistically/antagonistically) with sex chromosome-associated genes, both inducing and reducing sexually dimorphic phenotypes (Arnold and Chen, 2009; McCarthy, 2023; Vousden et al., 2018).

Although *in vivo* and *ex vivo* studies have started to account for sex as a biological variable, most *in vitro* studies still overlook sex chromosome complement (SCC), and frequently rely on immortalized cell lines rather than primary cells. As a result, a significant number of experiments are conducted using a combination of cells derived from both male and

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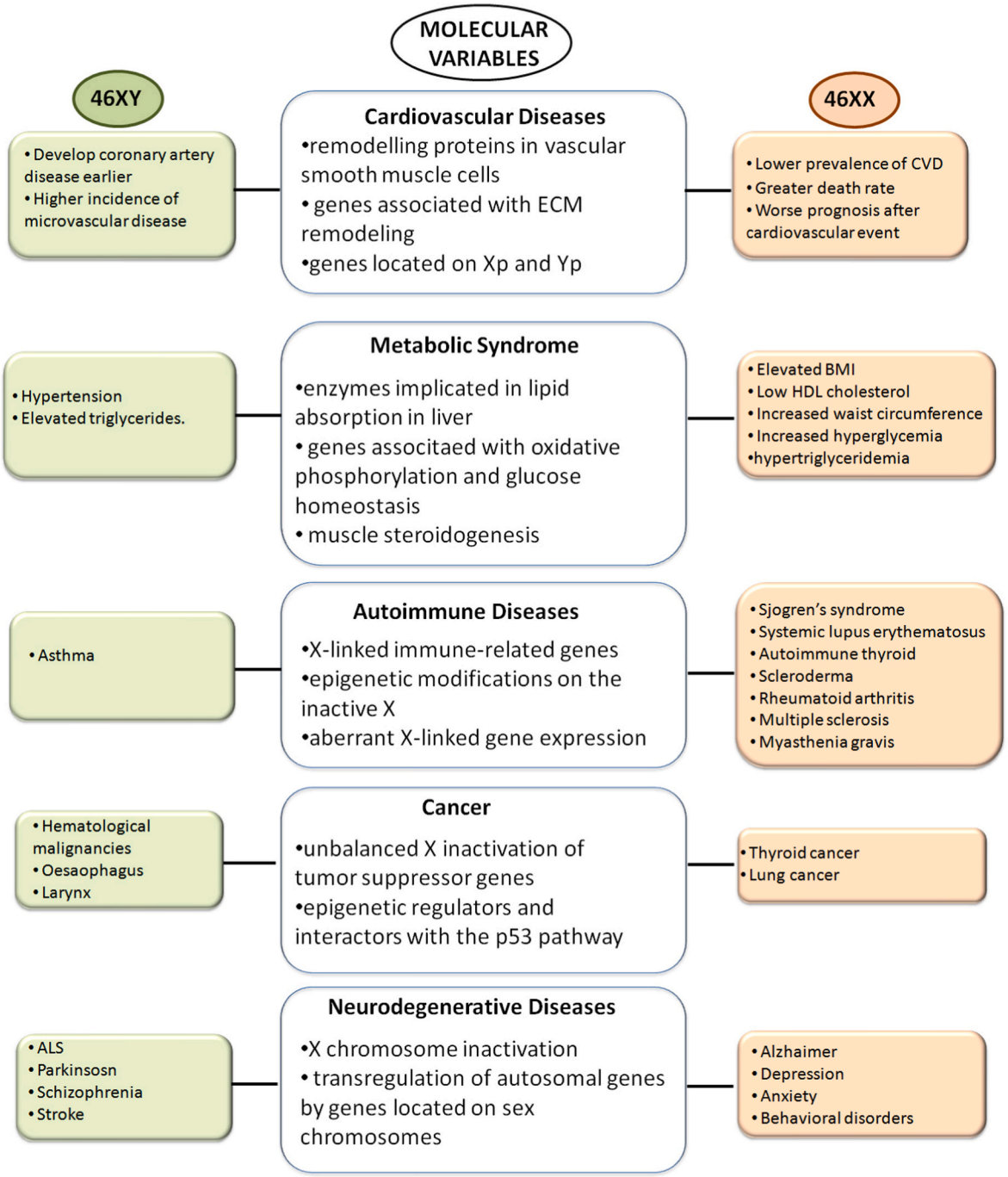


**Fig. 1. Sexual dimorphism in pathological conditions.** The effects of the same molecular variables on the prevalence and characteristics of diseases in male and female individuals related to sex chromosomes. CVD: cardiovascular diseases; BMI: body max index.

female subjects, frequently without the awareness of their chromosomal composition (XX or XY), which introduces variability and restricts reproducibility (Allegra et al., 2023; Flynn et al., 2021). Consequently, the results will be unable to provide a comprehensive analysis of the influence and effects of the sex chromosome complement on dimorphic responses (Aarde et al., 2021; Smiley et al., 2024). Moreover, extensive data demonstrate the importance of sex differences in *in vitro* research: i.e. the presence of Y-related genes, increased dosage of X-related genes in XX *vs*. XY cells, X chromosome inactivation, that turns off entire chromosomes, imprinting, that turns off only specific genes, and the occurrence of non coding ribonucleic acid (RNA) and micro-RNA on X chromosomes (Fedoriw et al., 2012; Rich-Edwards et al., 2018).

It is evident that the development of rigorous *in vitro* models is pivotal in elucidating the underlying mechanisms of the observed sexual dimorphism, with a particular emphasis on pathogenesis and pharmacology, pivotal for ensuring the quality and reliability of studies that contribute to precision medicine.

In this narrative review, we examine *in vitro* studies that highlight sex differences in cellular models and tissues, and explore how these disparities influence pathological conditions where sexual dimorphism plays a dominant role (Fig. 1). In particular, we summarize studies performed in blood vessels and myocardium for cardiovascular diseases; skeletal muscle, adipose tissue and liver concerning metabolic diseases; immune cells for immune- and autoimmune diseases; sexual differences in cancer susceptibility; and, finally, brain tissue for neurodegenerative diseases. Our aim is to emphasize the needed for the inclusion and detail

of sex in preclinical research, and to highlight the importance of sex chromosome differences as a biological variable that *per se* can influence cell physiology and biological responses, which is crucial when conducting *in vitro* studies.

## 2. Sexual dimorphism in cell models for cardiovascular diseases

Sex differences in cardiovascular structure and function are well established in both humans and animal models, and they significantly influence the onset and progression of cardiovascular diseases (CVDs) (On behalf of EVA Collaborators et al., 2020; Prajapati et al., 2022; Raparelli et al., 2020; Shi et al., 2021). In humans, female hearts are typically smaller, have lower stroke volumes, and higher resting heart rates compared to male hearts. Women also exhibit higher ejection fractions, indicating greater ventricular efficiency. Men, by contrast, tend to develop coronary artery disease (CAD) at younger ages and present a higher incidence of microvascular disease. After menopause, women experience increased rates of hypertension, which are further exacerbated by a greater susceptibility to metabolic disorders such as diabetes (AlSiraj et al., 2019; Arnold and Chen, 2009; Lorenz et al., 2015; Prajapati et al., 2022; Regitz-Zagrosek et al., 2013). Although the hormonal environment is crucial in inducing this discrepancy (Morin-Grandmont et al., 2024), the existence of sexual dimorphism at the cellular level, and its potential role in driving these differences, remains a topic of ongoing debate and is the subject of numerous studies (Straface et al., 2012).

In cardiomyocytes, sex-specific gene expression influences both cellular metabolism and contractile function. Female CMs preferentially express genes related to energy metabolism, while male CMs upregulate those involved in cell structure, cell cycle regulation, and motility (Walker et al., 2021). Functionally, male cardiomyocytes contract more forcefully and rapidly, whereas female CMs exhibit slower relaxation kinetics. Notably, female hearts contain a higher proportion of ventricular CMs and display enhanced regenerative capacity, which may contribute to the observed lower incidence of heart failure and myocardial infarction in premenopausal women ((Litviňuková et al., 2020; Parks et al., 2014; Vizgirda et al., 2002). Transcriptomic studies in human tissues implicated in CVDs have revealed widespread sex-biased gene expression, particularly in cardiomyocytes (CMs), endothelial cells, fibroblasts, smooth muscle cells, and immune cells (Reue and Wiese, 2022; Walker et al., 2021).

The molecular basis for these differences likely originates during embryonic development, before gonadal differentiation and sex hormone production, implicating direct genetic effects of sex chromosomes (Shi et al., 2020, 2021). Transcriptomic and proteomic analyses confirm sex-biased expression in both fetal and adult hearts, driven by mechanisms such as X-chromosome inactivation, escape from inactivation, and Y-linked gene expression (Isensee and Noppinger, 2007; Shi et al., 2020).

Genes located on the short arms of the X (Xp) and Y (Yp) chromosomes are expressed in adult human cardiomyocytes and contribute to key aspects of cardiac cell function, including mitochondrial activity, chromatin organization, and stress response. In addition to coding mRNAs, cardiomyocytes express a variety of non-coding RNAs, such as microRNAs (miRNAs), which regulate gene expression post-transcriptionally and play critical roles in cardiac development, function, and repair. The sex-specific expression patterns of these genes and RNAs may underlie differences in cardiomyocyte physiology and disease susceptibility between males and females (Bondy et al., 2013; Luo et al., 2023).

The role of sex chromosomes in cardiovascular pathology has been further elucidated through studies using the Four Core Genotypes (FCG) mouse model. This model decouples chromosomal sex from gonadal sex, allowing investigation of XX vs. XY effects independent of hormonal context. The four genotypes include XX gonadal males or females, and XY gonadal males or females, resulting from the breeding of a female XX with a male XY Sry, in which the Sry gene is located on an autosome. Consequently, the resulting offspring are XY and XX females and XY Sry and XX Sry males, with the sex indicative of the gonadal phenotype (Arnold et al., 2017; Sampson et al., 2012). FCG studies demonstrate that XX mice, regardless of gonadal type, show increased vulnerability to atherosclerosis, angiotensin II-induced hypertension, and ischemia/reperfusion injury (Arnold et al., 2017; Ji et al., 2010; Li et al., 2014). Moreover, gonadectomy in XX mice exacerbates atherosclerosis, while XY females remain unaffected, highlighting a direct role for X chromosome dosage (AlSiraj et al., 2019).

Human studies in Turner syndrome further support the contribution of X chromosome anomalies to cardiovascular malformations such as bicuspid aortic valves and aortic coarctation (Bondy et al., 2013; Caeiro et al., 2011).

At the vascular level, sex differences are also observed in endothelial and smooth muscle cell responses. Female-derived human umbilical vein endothelial cells (HUVEC)s show heightened immune responsiveness, increased expression of complement and major histocompatibility complex (MHC) genes, and greater stress resistance and angiogenic potential (Lista et al., 2011; Lorenz et al., 2015). Vascular smooth muscle cells (SMCs) from male and female rats display sex-specific profiles in extracellular matrix remodeling and contractile gene expression, including differences in matrix metalloproteinase (MMP-1), collagen I, actin alpha (ACTA)2, calponin (CNN1), and transgelin (TAGLN), which may contribute to sex disparities in plaque formation and vascular remodeling (Kennedy et al., 2014; Walker et al., 2021).

Transcriptomic analysis of porcine valvular interstitial cells (VICs) identified 183 genes with sex-biased expression, including those involved in angiogenesis (angiopoietin-like 4 (ANGPTL4)), apoptosis (B-cell lymphoma 2 (BCL2)), calcification (stanniocalcin-1 (STC1), natriuretic peptide precursor C (NPPC)), and lipid metabolism (apolipoprotein E (APOE)) (McCoy et al., 2012). In line with these findings, secreted factors associated with inflammation, angiogenesis, and apoptosis (e.g., interlukin (IL-1)β, tumor necrosis factor (TNF)-α) were found to be elevated in male patients undergoing valve replacement (Aguado et al., 2019; Grim et al., 2020; Parra-Izquierdo et al., 2019).

Collectively, these findings underscore the multifaceted impact of sex chromosomes on cardiovascular structure, function, and disease susceptibility. They highlight the importance of integrating sex as a biological variable in cardiovascular research and emphasize that sex chromosome complement—not only hormones—plays a crucial role in shaping cardiovascular phenotypes.

## 3. Sexual dimorphism in cell models for metabolic diseases

Metabolic syndrome include a group of conditions characterized by the presence of at least 3 of 5 conditions: hyperglycemia, hypertriglyceridemia, hypertension, large waist circumference, low high-density lipoprotein (HDL) cholesterol (Antinozzi et al., 2019). The importance of counteracting this disease lies mainly in the twofold increase in cardiovascular risk associated with type 2 diabetes mellitus and the threefold increase in the risk of developing myocardial infarction (MI), stroke and cardiovascular injury, as well as a 1.5-fold increase in the risk of all-cause mortality (Beigh and Jain, 2012; Mottillo et al., 2010).

The individual components of metabolic syndrome—such as hyperglycemia, hypertension, dyslipidemia, and abdominal obesity—are common in both women and men. However, sex differences exist in the timing of their onset, their relative prevalence, and their contribution to cardiovascular risk (Meloni et al., 2023). In fact, men have a higher percentage of lean mass, visceral adipose tissue, plasma triglyceride levels and myocardial infarction than women, while women have a higher percentage of fat mass, subcutaneous adipose tissue, HDL cholesterol and ischaemic stroke than men (Anna Ciampolillo, 2019). However, when lifestyle factors were analyzed by sex in adults with metabolic syndrome (n = 1066), notable differences emerged.

Women reported healthier dietary patterns, higher levels of moderate-to-vigorous physical activity, and lower rates of smoking and obesity compared to men. In contrast, obese or overweight men were less likely to engage in vigorous physical activity and more likely to consume diets high in salt and fat (Chang et al., 2019). Adipose tissue, liver and skeletal muscle are likely to be the cellular components associated with the onset of metabolic diseases, given their role in energy balance homeostasis and inflammation (Duarte et al., 2022).

With regard to adipose tissue physiology, studies in animal models have shown that sex and sex hormones influence adipogenesis, insulin resistance gene expression, lipolysis, as well as inflammation and obesity. In view of the diverse tissues implicated in metabolic diseases, the paragraph has been divided into subsections, categorized as adipose tissue, muscular tissue, and hepatic tissue.

### 3.1. Adipose tissue

Sex hormones clearly play a central role in sex differences in adipogenesis, adipocyte distribution and inflammation (Pal et al., 2024), However, non-gonadal factors must also be considered in the context of adipose tissue biology. Studies using Four Core Genotype (FCG) mice, as well as XO (Turner syndrome) and XXY (Klinefelter syndrome) models, have shown that the number of X chromosomes significantly influences adiposity. In particular, the presence of two X chromosomes (as in XX and XXY mice) is associated with increased body weight and fat mass compared to animals with a single X chromosome (XY and XO) (Chang et al., 2018; Chen et al., 2012). Gene expression analyses in high-fat diet (HFD)-fed male and female mice have identified thousands of sex-specific genes differentially expressed in adipose tissue, particularly those involved in immune responses, lipid metabolism, and insulin signaling (Grove et al., 2010; Yang et al., 2006). Notably, approximately 100 of these genes appear to be regulated independently of circulating gonadal hormones. Several sexually dimorphic genes have also been found within the cytochrome P450 superfamily—including aromatase and hydroxysteroid dehydrogenases—as well as in genes such as Nr2f1 (nuclear receptor subfamily 2 group F member 1), Thbd (thrombomodulin), HoxA5 and HoxC8 (homeobox proteins), Ddx3x (RNA helicase), Eif2s3x (translation initiation factor), and histone demethylases Kdm6a and Kdm5c (Chang et al., 2019; Link et al., 2020).

In particular, the genomic dosage of Kdm5c, an X-linked gene that escapes X chromosome inactivation, plays a pivotal role in determining the X chromosome's impact on adiposity. Indeed, reducing the dosage of the Kdm5c gene in female XX mice to levels comparable to those observed in males improves body weight, fat content and food intake in XX mice. In addition, Kdmc5 levels have been shown to influence the expression of genes associated with extracellular matrix remodeling, adipocyte differentiation and adipose tissue expansion (Link et al., 2020).

### 3.2. Muscle tissue

Like adipose tissue, muscle tissue constitutes a fundamental element in the regulation of systemic metabolic homeostasis (Antinozzi et al., 2019). Males and females show a sex dimorphism in muscle morphology and fiber type composition, which influences the type and energetic substrates preferentially used during muscle metabolic processes (Lundsgaard and Kiens, 2014).

Gene expression profiling of 15 normal men and 15 normal women using oligonucleotide microarrays revealed sex differences in the expression of several hundred genes, some of which have functions that explain the greater muscle mass of men than women (Welle et al., 2008). These differences involve epigenetic and transcriptional factors in both myoblast and myotube, which in turn could affect overall tissue physiology (Davegårdh et al., 2019).

While men had higher expression of genes encoding mainly mitochondrial proteins, translation initiation factors and ribosomal proteins, women had higher expression of genes involved in growth factor pathways such as growth factor receptor-bound 10 (GRB10) and activin A receptor IIB (ACVR2B), which encode proteins that inhibit insulin-like growth factor-1 (IGF-1) signalling and a myostatin receptor, respectively (Welle et al., 2008).

Using histochemical myosin adenosine triphosphatase (ATPase) staining, Lundsgaard et al. observed a higher number of type I muscle fibres in the vastus lateralis in females compared to males, and a higher percentage of type IIA and IIX in males (Høeg et al., 2009; Lundsgaard and Kiens, 2014; Roepstorff et al., 2006; Steffensen et al., 2002).

In 2019, Davegårdh and colleagues reported sex-specific differences in DNA methylation and gene expression on both autosomes and the X chromosome, particularly in genes involved in oxidative phosphorylation and glucose homeostasis (Davegårdh et al., 2019). These included Lamp2 (lysosome-associated membrane glycoprotein 2), Sirt1, Kdm6a, Creb5 (cAMP responsive element binding protein 5), Rps4x (ribosomal protein S4 X-linked), Syap1 (synapse-associated protein 1), Xist (X-inactive-specific transcript), and Zrsr2 (zinc finger factor).

More recently, sex-related differences have been demonstrated in the expression of steroidogenic enzymes and the androgen receptor (AR) in human neonatal myoblasts with 46XX or 46XY karyotypes (Di Luigi et al., 2023). In particular, 46XY cells showed higher mRNA expression of 5α-reductase (5α-R2) and AR, while 46XX cells exhibited increased expression of aromatase (Cyp19). Moreover, 46XX and 46XY myoblasts responded differently to identical hormonal stimuli, engaging distinct hormone biosynthetic pathways (Sgrò et al., 2024). Female myoblasts were more sensitive to androgens than their male counterparts, and even low doses of testosterone significantly increased AR expression and promoted receptor translocation (Di Luigi et al., 2023). Additionally, following testosterone treatment, 46XY cells produced dihydrotestosterone (DHT) and androstenedione, whereas 46XX myoblasts preferentially converted androgens into estrogens, thereby reducing intracellular androgen levels (Sgrò et al., 2024).

A further significant distinction can be made with regard to satellite cells and their sex-related characteristics. These cells represent the most stem cell component of muscle and become activated in response to stimuli such as acute muscle injury, exercise, or denervation, with the objective of reconstituting damaged tissue.

In 2011, Manzano and colleagues isolated satellite cells from male and female fast extensor digitorum longus (EDL) and slow soleus (SOL) mouse muscles and conducted an *in vitro* analysis of the expression of genes involved in proliferation and differentiation processes. The authors demonstrated that there was a higher expression of Myod1, Myogenin and Mrf4 transcripts in male subjects compared to age-matched females. Conversely, Pax7, which has the potential to block myogenesis, was found to be overexpressed in females compared to males (Manzano et al., 2011).

These data are of particular significance for research in regenerative muscle medicine and neuromuscular disorders, as the source of the regenerative cells must be appropriate to ensure the efficacy of satellite cell-mediated therapy.

### 3.3. Hepatic tissue

Similar to adipose and muscle tissue, the liver exhibits pronounced sexual dimorphism. Sex-specific differences in hepatocytes have been observed in various metabolic processes, including amino acid, lipid, drug, and xenobiotic metabolism (Hochmuth et al., 2021; Jensen-Cody and Potthoff, 2021). A number of studies utilizing rat and mouse liver models have identified in excess of 1000 genes whose expression is sex-dependent, thereby inducing significant sexual dimorphism in liver metabolism and pathophysiology (Waxman and Holloway, 2009).

In 2021, Hochmuth and colleagues isolated primary hepatocytes from male and female mice and examined changes in transcriptome, proteome and extracellular metabolome parameters (Hochmuth et al., 2021). The authors observed that, over the course of 96 h of cell culture,

there were some exceptions to the general pattern of sexual dimorphism (Hochmuth et al., 2021). These included the increased or reversed expression of certain genes, particularly those involved in serotonin and melatonin degradation, amino acid degradation, beta-oxidation, androgen signalling, and hepatic steatosis.

In FCG mouse models, elevated serum lipid levels have been observed in XX males and females (AlSiraj et al., 2019). This phenotype is likely attributable to altered cholesterol and lipid homeostasis in the liver, along with increased expression of enzymes involved in lipid absorption and chylomicron assembly in the small intestine. In addition, the expression of sex chromosome-linked genes appears to be significantly influenced by chromosomal sex. For example, genes located in the male-specific region of the Y chromosome—such as Kdm5d, Eif2s3y, and others—are upregulated in XY livers, while Xist, a non-coding RNA expressed exclusively in XX cells, shows significantly higher expression in XX livers. Pathway analysis has revealed that numerous genes involved in immune response pathways are differentially expressed in the livers of XX versus XY mice, regardless of gonadal sex (AlSiraj et al., 2019; Arnold, 2017; Arnold et al., 2017). More recently, Wiese and colleagues (2022) demonstrated that under hypercholesterolemic conditions, chromosomal sex—independent of gonadal hormones—modulated the expression of nearly 1400 genes across both autosomes and sex chromosomes (Wiese et al., 2022).

Sex differences have also been observed in humans, which are likely due to the female-predominant expression of CYP3A4, the most important P450 catalyst of drug metabolism in the human liver (Waxman and Holloway, 2009). In 2012, Yang et al. demonstrated the sex-dimorphic expression of 77 genes isolated from human male (n = 234) and female (n = 193) liver samples (Yang and Li, 2012). Among these, the authors observed differential expression of the CYP3A7, CYP3A4, and alcohol dehydrogenase (ADH1A) genes, which are involved in phase I metabolism; the acyl-CoA synthetase long chain family member (ACSL) 4, glutathione S-transferase A (GSTA) 1 and2, and UDP-glucuronosyltransferase (UGT2B) 17 genes, which are phase II metabolising enzymes; and the solute carrier family member (SLC3A) 1 and SLC13A1 genes, which are membrane transporters. The dimorphic expression of these genes in males and females results in differences in drug absorption, distribution, metabolism, and excretion.

## 4. Sexual dimorphism in cell models for autoimmune diseases

Autoimmune diseases consist of chronic disorders characterized by an overactive immune response that lead to tissue damage and dysfunction (Ortona et al., 2016). The data indicates a clear sexual dimorphism, with a ratio of women to men patients ranging from 7:1 to 10:1 for Sjogren's syndrome, systemic lupus erythematosus (SLE) autoimmune thyroid disease, and systemic sclerosis, and 2:1–3:1 for rheumatoid arthritis (RA), multiple sclerosis (MS), and myasthenia gravis (Ortona et al., 2016). While the influence of sex hormones on autoimmune pathogenesis is well documented, accumulating evidence points to sex chromosome complement—particularly the presence of two X chromosomes—as a key contributor to these differences. The X chromosome harbors numerous immune-related genes, including cluster of differentiation 40 (CD40) ligand, chemokine receptor (CXCR3), toll-like receptor (TLR)7, TLR8, IL-2Rγ, and IL-9R ((Fairweather et al., 2024).Although many of these genes are subject to X-chromosome inactivation, a subset escapes this process, resulting in higher expression levels in XX individuals. Aberrant expression of such X-linked genes has been associated with autoantibody production and immune hyperactivity, especially in SLE and other female-predominant conditions (Corker et al., 2023; Hewagama et al., 2013). The IL-13Rα2 gene, for instance, exhibits higher expression in XX mice and may act as a decoy receptor, modulating Th2 responses and influencing disease severity (Smith-Bouvier et al., 2008).

Evidence from sex chromosome aneuploidy syndromes further supports this link. Females with Turner syndrome (45,X) display reduced autoimmune susceptibility, while males with Klinefelter syndrome (47, XXY) show increased risk compared to XY males (Jørgensen et al., 2010; Seminog et al., 2015). These findings suggest that X chromosome dosage, rather than hormonal environment alone, contributes substantially to immune dysregulation in females.

Several studies using human immune cell models have provided functional insight into these genetic influences. *In vitro* stimulation of human peripheral blood mononuclear cells (PBMCs) revealed that female $CD8^+$ T cells exhibit stronger activation than male counterparts across multiple subsets, including effector and memory precursors (Abdullah et al., 2012). Female PBMCs also show higher forkhead box (FOXP)3 expression and greater sensitivity to cytokine/chemokine signaling and antigen presenting cell (APC)–T cell interactions. Furthermore, female immune cells, including T and B lymphocytes and macrophages, display enhanced phagocytic activity, toll-like receptor (TLR) expression, and microbial killing via NADPH oxidase (Scotland et al., 2011). Beyond functional immune differences, mitochondrial activity in immune cells also shows sexual dimorphism. Female PBMCs exhibit greater activity of mitochondrial complexes I, I + II, and IV, as well as elevated electron transport system (ETS) capacity and citrate synthase activity, reflecting enhanced cellular metabolism and bioenergetics (Silaidos et al., 2018).

A critical component of post-transcriptional regulation is provided by microRNAs (miRNAs), many of which are encoded on the X chromosome. The X chromosome contains a higher density of miRNAs than any autosome or the Y chromosome, which harbors only four identified miRNAs (Bianchi et al., 2012; Westemeier-Rice et al., 2024). These X-linked miRNAs participate in immune modulation and inflammatory signaling. For instance, miR-18b is associated with multiple sclerosis, miR-98 regulates TLR-mediated epithelial responses, miR-106a modulates IL-10 release, and miR-223 influences granulocyte differentiation and IFNγ production (Florijn et al., 2018). The expression of these miRNAs is influenced both by sex hormones and by incomplete X-inactivation, further reinforcing their contribution to sex-specific immune responses (Morgan and Bale, 2012)

In summary, sexual dimorphism in autoimmune diseases is rooted not only in hormonal differences but also in the genetic and epigenetic effects of sex chromosomes. Cell-based models, particularly PBMCs, have revealed intrinsic sex-related differences in immune activation, metabolism, and post-transcriptional regulation. These findings underscore the need to consider sex chromosome complement as a fundamental variable in both mechanistic and translational immunological research.

## 5. Sexual dimorphism in cell models for cancer

While a gender-based analysis of tissue physiology may be of limited relevance in oncology—given that cancer cells exhibit markedly distinct morphological, metabolic, and genetic profiles compared to healthy cells (Baba et al., 2007)—sex-specific genetic and molecular factors may still influence tumorigenesis (Ornos et al., 2023). Therefore, this paragraph focuses on these intrinsic biological differences between males and females that could impact cancer onset and progression.

Significant sex differences in cancer incidence and outcome have been observed, with most tumors of non-reproductive tissues demonstrating biological sex differences. These differences are characterized by a higher prevalence of incidence and mortality in males than in females (Dart, 2020). In 2017, Grant and colleagues examined the statistical incidence of Hiroshima and Nagasaki atomic bombings survivors and observed a higher prevalence of solid tumors in male survivors (93.7 and 86.9 per 104 person-years, respectively) compared with female survivors (63.7 and 48.8, respectively). Additionally, they noted a ratio of 0.66 for female to male cases of hematological malignancies (Grant et al., 2017).

Among the various factors that may be involved, the potential role of immunity in females (see paragraph 4, page 9) is worthy of

consideration. Indeed, the X chromosome contains over 50 genes that regulate innate and adaptive immunity (Haupt et al., 2021). Despite one of two chromosomes present in females being randomly inactivated during embryogenesis (to avoid double dosage of the same proteins), approximately 15 % of the genes evade this mechanism (Venanzi et al., 2023; Dunford et al., 2017). These include genes involved in adaptive and innate immune responses and self-tolerance. Furthermore, the X chromosome is densely populated of miRNAs, such as miRNA-18 and miRNA-19, identified as pivotal for the optimal functioning of both innate and adaptive immune responses. Acting as post-transcriptional regulators, these miRNAs fine-tune the expression of a range of immune-related genes and modulate key cellular processes such as differentiation, proliferation, and migration (Gareev et al., 2025; Pinheiro et al., 2011). Furthermore, sexual differences have been observed in the metabolism of reactive oxygen species, p53-related pathways, the expression of mutant alleles, and DNA repair mechanisms (Venanzi et al., 2023). Genetic analyses have revealed that the X chromosome in females contains several genes that are not genetically or functionally balanced through X inactivation. These include tumor suppressor genes, epigenetic regulators and interactors with the p53 pathway, Kdm6a, ATP-dependent helicase (ATRX), Kdm5c, connector enhancer of kinase suppressor of Ras (CNKSR2), DEAD-Box Helicase 3 X-Linked (DDX3X) and family member C (MAGEC3) (Wallis et al., 2019), that exhibit higher expression levels in female in comparison to male tissues. These genes are involved in tumor suppressor functions, and mutated alleles of these genes have been more frequently detected in male neoplastic diseases, which contributes to the observed excess of male cancer cases.

## 6. Sex dimorphism in cell models for neurodegenerative diseases

A significant sexual difference has been observed in the brain metabolic environment, which may alter immune cell function and contribute to the clinical outcome of important brain disorders (Lee et al., 2022). Many stress-related neuropsychiatric disorders display pronounced sex differences in their frequency and clinical symptoms (Oakley et al., 2024). Indeed, among several disorders of the central nervous system (CNS), females are more susceptible to multiple sclerosis, Alzheimer's disease, and depression, while males are more frequently diagnosed with Parkinson's disease, schizophrenia, and autism, and have worse clinical outcomes in multiple sclerosis and glioma (Alzheimer's Association, 2015; American Psychiatric Association, 2013; Developmental Disabilities Monitoring Network Surveillance Year 2010 Principal Investigators and Centers for Disease Control and Prevention (CDC), 2014; Gilli et al., 2020; Gillies et al., 2014).

The reason for the sexual dimorphism observed in these diseases is not yet fully understood, however, research has identified significant sex-based differences in gene expression in both animal models and human studies. It is hypothesized that the heightened susceptibility to stress-induced changes in hypothalamic signaling—mediated by glucocorticoids such as cortisol or corticosterone—may be linked to the expression and activation of stress hormone receptors, particularly glucocorticoid receptors (GR) and mineralocorticoid receptors (MR). In this context, both MR and GR are activated by elevated glucocorticoid levels, and the resulting effects depend on the balance between MR and GR activation (Karandrea et al., 2000). Female fish exhibit greater GR expression in preoptic and thalamic nuclei compared to males (Kikuchi et al., 2015). In rats, females show higher GR binding capacity in the hippocampus but lower in the hypothalamus than males (Turner and Debra A., 1985). Sex-specific GR expression patterns are also observed in the prefrontal cortex of rats, with females displaying increased GR expression in infralimbic excitatory neurons following stress (Oakley et al., 2024).

Recent studies have highlighted the significant role of sex chromosomes in cognitive resilience, disease susceptibility, and longevity. The presence of a second X chromosome has been shown to improve cognition in ageing FCG mouse models of both sexes, potentially through increased synaptogenesis signalling in the hippocampus (Marino et al., 2024). This cognitive resilience is also associated with reduced tau pathology in humans (Davis et al., 2021). In multiple sclerosis, sex differences in disease susceptibility and progression may be attributed to X chromosome genes, with maternal versus paternal imprinting and differential expression of genes like Foxp3 and Toll-like receptor 7 playing crucial roles (Voskuhl et al., 2018). Furthermore, the female XX sex chromosome complement has been found to increase survival during aging in both male and female mice, and in combination with ovaries, it extends lifespan (Davis et al., 2018). These findings underscore the importance of sex chromosomes in aging and disease processes.

At the molecular level, gene expression differences in different brain cell types and areas have been demonstrated for approximately 3000 genes, primarily due to escape from X chromosome inactivation and the trans-regulatory effects of sex chromosome-linked genes on autosomal gene expression (Lee et al., 2022; Panda et al., 2020). Moreover, the cerebellum exhibited the lowest degree of sex-biased gene expression among all brain regions analyzed, whereas the spinal cord and hippocampus demonstrated the most pronounced differences in the total number of differentially expressed genes.

Proteomic analysis revealed differential expression of 198 transcripts, several of which are involved in essential neuronal functions. These include transcripts related to protein folding and the unfolded protein response (UPR), which is critical for maintaining proteostasis under stress conditions; microRNAs associated with synaptic plasticity, potentially influencing learning and memory; and key metabolic enzymes such as phosphofructokinase-1 (PFK-1), a rate-limiting enzyme in glycolysis, and glucose/pyruvate transporters, which may reflect sex-specific energy demands in the brain. Additionally, differences in the expression of phosphodiesterases (PDE)4C and PDE7A, which regulate intracellular cAMP signaling, could impact synaptic signaling and neuroplasticity (Lee et al., 2022; Uhl et al., 2022).

The brain is composed of two main types of cells: neurons and glial cells, also known as neuroglia. The metabolism of these cells is integral to brain function (Molnar et al., 2021). Consequently, understanding the differences between these cells is crucial for elucidating sex-related dimorphism in brain function. Moreover, the female brain exhibits augmented mitochondrial activity, elevated levels of the brain energy metabolite N-acetylaspartate, enhanced mitochondrial function of PBMCs, and augmented mitochondrial numbers in comparison to the male brain (Silaidos et al., 2018). The observed sex differences in the brain metabolic environment may contribute to the differing immune cell functions observed between the sexes, which in turn may influence the clinical outcomes of relevant brain disorders. The majority of neurodegenerative diseases are characterized by inflammation and, consequently, microglia activation (Hanamsagar and Bilbo, 2016). Additionally, differences between males and females have been reported for cells of both innate and adaptive immunity (Klein and Flanagan, 2016). As previously stated, females exhibit an enhanced response to TLR7 signalling and T cells that bolster their heightened activation and inflammatory capacity. Conversely, males demonstrate augmented responses to LPS at the macrophage, neutrophil, and dendritic cell (DC) levels (Duan et al., 2022).

## 7. Conclusions and future perspective

A major challenge in translational research today is developing experimental models that reflect the biological sex differences observed in humans. Incorporating sex as a variable improves the rigor, relevance, and inclusivity of biomedical studies and is central to advancing personalized medicine. However, current methodologies often fall short in evaluating sex-based differences, leaving the role of sex chromosome complement (SCC) in cellular responses underexplored. Recognizing sex as a continuous biological variable requires not only new

**Table 1**
Most consistently published genes escaping from X chromosome inactivation (Balaton et al., 2021; Youness et al., 2021). "Diseases associated" were taken from GeneCard website (https://www.genecards.org/).

| GENES | | DISEASES ASSOCIATED |
|---|---|---|
| ACRONYM | FULL NAME | ENDOCRINE & METABOLIC DISEASES |
| *ANOS1* | Anosmin 1 | Hypogonadotropic hypogonadism 1 with or without anosmia and kallmann syndrome |
| *BTK* | Burton tyrosine kinase | Agammaglobulinemia, X-Linked and Isolated Growth Hormone Deficiency, Type Iii, With Agammaglobulinemia |
| *EIF2S3* | Eukaryotic translation initiation factor 2 | Mehmo syndrome and hypogonadism |
| *FAM9C* | Family with sequence similarity 9 member c | 46,xy sex reversal 3 |
| *GYG2* | Glycogenin 2 | Glycogen Storage Disease |
| *HTR2C* | 5-hydroxytryptamine receptor 2c | Anxiety and premature ejaculation |
| *PNPLA4* | Patatin like phospholipase domain containing 4 | Cardiomyopathy, dilated, 1m and cardiomyopathy, familial hypertrophic |
| *TXLNG* | Taxilin gamma | Familial isolated hypoparathyroidism |
| *VAMP7* | Vesicle associated membrane protein 7 | 46,xy partial gonadal dysgenesis |
| | | **INFLAMMATORY & AUTOIMMUNE DISEASES** |
| *CD40*LG | CD40 ligand | Immunodeficiency With Hyper-Igm, Type 1 and Cd40 Ligand Deficiency |
| *CYBB* | Cytochrome *b*-245 beta chain | Immunodeficiency 34 and granulomatous disease, chronic, x-linked |
| *CXCR3* | C-X-C motif chemokine receptor 3 | Cutaneous Lupus Erythematosus and Pulmonary Sarcoidosis |
| *CXorf21/ TASL* | Chromosome X open reading frame 21 or TLR: adaptor interacting with SLC15A4 on the Lysosome | Lupus Erythematosus and Immunodeficiency 33. |
| *GEMIN8* | Gem Nuclear Organelle Associated Protein 8 | Spinal Muscular Atrophy and Muscular Atrophy |
| *IL9R* | Interleukin 9 receptor | Asthma and bronchitis |
| *IL13RA1* | Interleukin 13 receptor subunit alpha 1 | Monofixation syndrome and asthma |
| *IRAK1* | Interleukin 1 receptor associated kinase 1 | Pediatric systemic lupus erythematosus and mumps |
| *PPP2R3B* | Protein phosphatase 2 regulatory subunit beta | Pulmonary systemic sclerosis |
| *SLC25A6* | Solute carrier family 25 member 6 | Influenza and bubonic plague |
| *TLR7* | Toll like receptor 7 | Systemic lupus erythematosus 17 and immunodeficiency 74, covid19-related, x-linked |
| | | **CANCER** |
| *AKAP17A* | A-kinase anchoring protein 17a | Null-cell leukemia and hodgkin's lymphoma, mixed cellularity |
| *ASMT* | Acetylserotonin o-methyltransferase | Pineocytoma and pineoblastoma |
| *ASMTL* | N-acetylserotonin O-methyltransferase-like protein | Melanotic Neurilemmoma. |
| *CD99* | CD99 molecule | Extraosseous Ewing Sarcoma and Lymphoblastic Lymphoma. |
| *CDK16* | Cyclin-dependent kinase 16 | Triple-negative breast cancer |
| *CXorf38* | Chromosome x open reading frame 38 | Myeloid leukemia associated with down syndrome and 46 xx gonadal dysgenesis |
| *EIF1AX* | Eukaryotic translation initiation factor 1A | Thyroid Carcinoma and Choroid Cancer |
| *GPM6B* | Glycoprotein M6B | Subleukemic Leukemia and Acute Erythroid Leukemia |
| *IL3RA* | Interleukin 3 receptor subunit alpha | Diphtheria and hairy cell leukemia |
| *KDM6a* | Lysine demethylase 6A | Cancers of the breast, esophagus, colon, kidney, and brain, and cancers of blood-forming cells called myeloid leukemia and multiple myeloma |
| *MXRA5* | Matrix remodeling associated 5 | Lung cancer and phosphoglycerate dehydrogenase deficiency |
| *P2RY8* | P2y receptor family member 8) | B-lymphoblastic leukemia/ lymphoma with iamp21 and intellectual developmental disorder, autosomal dominant 33 |
| *PRKX* | Protein kinase camp-dependent x-linked catalytic subunit | Asbestos-related lung carcinoma and breast ductal adenoma |
| *RBBP7* | Rb binding protein 7, chromatin remodeling factor | Retinoblastoma and hutchinson-gilford progeria syndrome |
| *JPX* | Non protein-coding RNA | Hepatocellular Carcinoma |
| *ZFX* | Zinc finger protein x-linked | Gastric cancer |
| | | **NERVOUS SYSTEM-ASSOCIATED DISEASES** |
| *AP1S2* | Adaptor related protein complex 1 subunit sigma 2 | Fried-type syndromic mental retardation |
| *CA5B* | Carbonic anhydrase 5b | Carbonic anhydrase va deficiency and mixed sleep apnea |
| *CTP62* | CTP synthase 2 | Parkinson's disease and other neurological disorders |
| *DDX3X* | DEAD-box helicase 3 X-linked | Genetic neurodevelopmental disorder, intellectual disability, autism spectrum disorder, language delays, attention-deficit/hyperactivity disorder, and medical comorbidities |
| *FUNDC1* | Fun14 domain containing 1 | Parkinson's-like movement disorder |
| *IQSEC2* | IQ motif and Sec7 domain 2 | Intellectual disability, autism, and epilepsy |
| *KDM5C* | Lysine demethylase 5C | Intellectual Developmental Disorder, X-Linked, Syndromic, Claes-Jensen Type and Syndromic X-Linked Intellectual Disability Claes-Jensen Type. |
| *NLGN4X* | Neuroligin 4 x-linked | Autistic traits, empathy, and asperger syndrome |
| *UBA1* | Ubiquitin like modifier activating enzyme 1 | X-linked infantile spinal muscular atrophy |
| *OFD1* | Centriole and centriolar satellite protein | Orofaciodigital syndrome i and retinitis pigmentosa 23 |
| *RAB9A* | Member ras oncogene family | Warburg micro syndrome 1 |
| *RPS4X* | Ribosomal protein s4 x-linked | Multiple sclerosis |
| *SMC1A* | Structural maintenance of chromosomes 1a | Developmental and epileptic encephalopathy 85 with or without midline brain defects and cornelia de lange syndrome 2 |
| *SYAP1* | Synapse associated protein 1 | Pettigrew syndrome |
| *SPRY3* | Sprouty rtk signaling antagonist 3 | Intellectual developmental disorder, x-linked 108 and colorblindness, partial, protan series |
| *USP9X* | Ubiquitin specific peptidase 9 X-linked | Neurodevelopmental and neurodegenerative disorders |
| *ZRSR2* | Zinc finger CCCH-type, RNA binding motif and serine/ arginine rich 2 | Holoprosencephaly 1 and Holoprosencephaly |

methodological approaches but also dedicated models, such as Four Core Genotypes (FCG) mice, to disentangle chromosomal and hormonal influences.

While male and female animal models remain useful, their ability to fully capture human sex differences is limited by species-specific mechanisms, such as sex chromosome inactivation. Our review highlights that the presence of two X chromosomes (e.g., in XX individuals) can influence gene expression and biological responses, especially in immune regulation, where genes escaping X-inactivation contribute to

disease risk and phenotypic variability (see Table 1) (Balaton et al., 2015; Youness et al., 2021; Zito et al., 2023).

The inclusion of both XX and XY cells in in vitro models is critical for capturing sex-based responses. However, the use of immortalized cell lines—while practical—poses challenges due to chromosomal instability and undefined karyotypes, which can distort gene expression and cellular behavior. Comprehensive karyotypic characterization is therefore essential to ensure data validity, especially in studies of sex-specific biology, hormone signaling, or drug response. To advance the field, sex and gender must be assessed as independent and interactive variables affecting cell behavior, disease mechanisms, and treatment responses. Integration of clinical and experimental datasets, with clear documentation of sex, age, hormonal status, and living conditions, will improve the interpretation of sex differences. Notably, while "gender" now refers to a psychosocial construct, its complexity cannot be adequately modeled in cells or non-human animals.

Ultimately, ensuring that research is properly designed and powered to detect sex-based differences—and that such data are appropriately analyzed—is essential for translating basic and preclinical findings into effective, equitable patient care.

## CRediT authorship contribution statement

**Cristina Antinozzi:** Writing – original draft, Conceptualization. **Paolo Sgrò:** Writing – review & editing, Supervision. **Luigi Di Luigi:** Writing – review & editing.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Data availability

No data was used for the research described in the article.

## References


Aarde, S.M., Genner, R.M., Hrncir, H., Arnold, A.P., Jentsch, J.D., 2021. Sex chromosome complement affects multiple aspects of reversal-learning task performance in mice. Gene Brain Behav. 20. https://doi.org/10.1111/gbb.12685.

Abdullah, M., Chai, P.-S., Chong, M.-Y., Tohit, E.R.M., Ramasamy, R., Pei, C.P., Vidyadaran, S., 2012. Gender effect on in vitro lymphocyte subset levels of healthy individuals. Cell. Immunol. 272, 214–219. https://doi.org/10.1016/j.cellimm.2011.10.009.

Aguado, B.A., Schuetze, K.B., Grim, J.C., Walker, C.J., Cox, A.C., Ceccato, T.L., Tan, A.-C., Sucharov, C.C., Leinwand, L.A., Taylor, M.R.G., McKinsey, T.A., Anseth, K.S., 2019. Transcatheter aortic valve replacements alter circulating serum factors to mediate myofibroblast deactivation. Sci. Transl. Med. 11, eaav3233. https://doi.org/10.1126/scitranslmed.aav3233.

Allegra, S., Chiara, F., Di Grazia, D., Gaspari, M., De Francia, S., 2023. Evaluation of sex differences in preclinical pharmacology research: how far is left to go? Pharmaceuticals 16, 786. https://doi.org/10.3390/ph16060786.

Allen, J.B., Ludtka, C., James, B.D., 2023. Sex as a biological variable in tissue engineering and regenerative medicine. Annu. Rev. Biomed. Eng. 25, 311–331. https://doi.org/10.1146/annurev-bioeng-092222-030857.

AlSiraj, Y., Chen, X., Thatcher, S.E., Temel, R.E., Cai, L., Blalock, E., Katz, W., Ali, H.M., Petriello, M., Deng, P., Morris, A.J., Wang, X., Lusis, A.J., Arnold, A.P., Reue, K., Thompson, K., Tso, P., Cassis, L.A., 2019. XX sex chromosome complement promotes atherosclerosis in mice. Nat. Commun. 10. https://doi.org/10.1038/s41467-019-10462-z.

Alzheimer's Association, 2015. 2015 Alzheimer's disease facts and figures. Alzheimer's & Dementia 11, 332–384. https://doi.org/10.1016/j.jalz.2015.02.003.

American Psychiatric Association, 2013. Diagnostic and Statistical Manual of Mental Disorders, fifth ed. American Psychiatric Association. https://doi.org/10.1176/appi.books.9780890425596.

Antinozzi, C., Marampon, F., Sgrò, P., Tombolini, V., Lenzi, A., Crescioli, C., Di Luigi, L., 2019. Comparative study of testosterone and vitamin D analogue, elocalcitol, on insulin-controlled signal transduction pathway regulation in human skeletal muscle cells. J. Endocrinol. Investig. 42, 897–907. https://doi.org/10.1007/s40618-018-0998-6.

Arnold, A.P., 2017. A general theory of sexual differentiation. J. Neurosci. Res. 95, 291–300. https://doi.org/10.1002/jnr.23884.

Arnold, A.P., Chen, X., 2009. What does the "four core genotypes" mouse model tell us about sex differences in the brain and other tissues? Front. Neuroendocrinol. 30, 1–9. https://doi.org/10.1016/j.yfrne.2008.11.001.

Arnold, A.P., Cassis, L.A., Eghbali, M., Reue, K., Sandberg, K., 2017. Sex hormones and sex chromosomes cause sex differences in the development of cardiovascular diseases. ATVB 37, 746–756. https://doi.org/10.1161/atvbaha.116.307301.

Baba, A.I., Cătoi, C., Baba, A.I., 2007. Comparative Oncology. Publ. House of the Romanian Academy, Bucharest.

Balaton, B.P., Cotton, A.M., Brown, C.J., 2015. Derivation of consensus inactivation status for X-linked genes from genome-wide studies. Biol. Sex Differ. 6, 35. https://doi.org/10.1186/s13293-015-0053-7.

Balaton, B.P., Fornes, O., Wasserman, W.W., Brown, C.J., 2021. Cross-species examination of X-chromosome inactivation highlights domains of escape from silencing. Epigenetics Chromatin 14. https://doi.org/10.1186/s13072-021-00386-8.

Beigh, S.H., Jain, S., 2012. Prevalence of metabolic syndrome and gender differences. Bioinformation 8, 613–616. https://doi.org/10.6026/97320630008613.

Bianchi, I., Lleo, A., Gershwin, M.E., Invernizzi, P., 2012. The X chromosome and immune associated genes. J. Autoimmun. 38, J187–J192. https://doi.org/10.1016/j.jaut.2011.11.012.

Bondy, C., Bakalov, V.K., Cheng, C., Olivieri, L., Rosing, D.R., Arai, A.E., 2013. Bicuspid aortic valve and aortic coarctation are linked to deletion of the X chromosome short arm in Turner syndrome. J. Med. Genet. 50, 662–665. https://doi.org/10.1136/jmedgenet-2013-101720.

Caeiro, X.E., Mir, F.R., Vivas, L.M., Carrer, H.F., Cambiasso, M.J., 2011. Sex chromosome complement contributes to sex differences in bradycardic baroreflex response. Hypertension 58, 505–511. https://doi.org/10.1161/hypertensionaha.111.175661.

Chang, E., Varghese, M., Singer, K., 2018. Gender and sex differences in adipose tissue. Curr. Diabetes Rep. 18, 69. https://doi.org/10.1007/s11892-018-1031-3.

Chang, S.-H., Chang, Y.-Y., Wu, L.-Y., 2019. Gender differences in lifestyle and risk factors of metabolic syndrome: do women have better health habits than men? J. Clin. Nurs. 28, 2225–2234. https://doi.org/10.1111/jocn.14824.

Chen, X., McClusky, R., Chen, J., Beaven, S.W., Tontonoz, P., Arnold, A.P., Reue, K., 2012. The number of X chromosomes causes sex differences in adiposity in mice. PLoS Genet. 8, e1002709. https://doi.org/10.1371/journal.pgen.1002709.

Chen, C.-Y., Lopes-Ramos, C., Kuijjer, M.L., Paulson, J.N., Sonawane, A.R., Fagny, M., Platig, J., Glass, K., Quackenbush, J., DeMeo, D.L., 2016. Sexual dimorphism in gene expression and regulatory networks across human tissues. https://doi.org/10.1101/082289.

Ciampolillo, Anna, 2019. Metabolic syndrome and gut microbiota: there is a gender difference? Italian. J. Gender-Specific Med. (JGSM). https://doi.org/10.1723/3148.31295.

Corker, A., Learmonth, M., Patrick, D.M., DeLeon-Pennell, K.Y., Van Beusecum, J.P., 2023. Cardiac and vascular complications in lupus: is there a role for sex? Front. Immunol. 14. https://doi.org/10.3389/fimmu.2023.1098383.

Dadam, F.M., Gonzalez, L., Vivas, L., Godino, A., Caeiro, X.E., 2024. Vasopressinergic sexual dimorphism: sex chromosome complement and organizational hormonal effects. Mol. Cell. Endocrinol. 594, 112390. https://doi.org/10.1016/j.mce.2024.112390.

Dart, A., 2020. Sexual dimorphism in cancer. Nat. Rev. Cancer 20, 627. https://doi.org/10.1038/s41568-020-00304-2, 627.

Davegårdh, C., Hall Wedin, E., Broholm, C., Henriksen, T.I., Pedersen, M., Pedersen, B.K., Scheele, C., Ling, C., 2019. Sex influences DNA methylation and gene expression in human skeletal muscle myoblasts and myotubes. Stem Cell Res. Ther. 10, 26. https://doi.org/10.1186/s13287-018-1118-4.

Davis, A.C., Arnocky, S., Vaillancourt, T., 2018. Sex differences, initiating gossip. In: Shackelford, T.K., Weekes-Shackelford, V.A. (Eds.), Encyclopedia of Evolutionary Psychological Science. Springer International Publishing, Cham, pp. 1–8. https://doi.org/10.1007/978-3-319-16999-6_190-1.

Davis, E.J., Solsberg, C.W., White, C.C., Miñones-Moyano, E., Sirota, M., Chibnik, L., Bennett, D.A., De Jager, P.L., Yokoyama, J.S., Dubal, D.B., 2021. Sex-Specific Association of the X chromosome with cognitive change and tau pathology in aging and alzheimer disease. JAMA Neurol. 78, 1249. https://doi.org/10.1001/jamaneurol.2021.2806.

Deegan, D.F., Nigam, P., Engel, N., 2021. Sexual dimorphism of the heart: Genetics, epigenetics, and development. Front. Cardiovasc. Med. 8, 668252. https://doi.org/10.3389/fcvm.2021.668252.

Developmental Disabilities Monitoring Network Surveillance Year 2010 Principal Investigators, Centers for Disease Control and Prevention (CDC), 2014. Prevalence of autism spectrum disorder among children aged 8 years - autism and developmental disabilities monitoring network, 11 sites, United States, 2010. MMWR Surveill Summ 63, 1–21.

Di Luigi, L., Antinozzi, C., Duranti, G., Dimauro, I., Sgrò, P., 2023. Sex-chromosome-related dimorphism in steroidogenic enzymes and androgen receptor in response to testosterone treatment: an in vitro study on human primary skeletal muscle cells. Int. J. Mol. Sci. 24, 17382. https://doi.org/10.3390/ijms242417382.

Duan, T., Du, Y., Xing, C., Wang, H.Y., Wang, R.-F., 2022. Toll-like receptor signaling and its role in cell-mediated immunity. Front. Immunol. 13, 812774. https://doi.org/10.3389/fimmu.2022.812774.

Duarte, A.C.G.D.O., Speretta, G.F., Teixeira, A.M., Lira, F.S., 2022. Editorial: adipose tissue and skeletal muscle as endocrine organs: role of cytokines in health and disease. Front. Physiol. 13, 1069431. https://doi.org/10.3389/fphys.2022.1069431.

Dunford, A., Weinstock, D.M., Savova, V., Schumacher, S.E., Cleary, J.P., Yoda, A., Sullivan, T.J., Hess, J.M., Gimelbrant, A.A., Beroukhim, R., Lawrence, M.S., Getz, G., Lane, A.A., 2017. Tumor-suppressor genes that escape from X-inactivation contribute to cancer sex bias. Nat. Genet. 49, 10–16. https://doi.org/10.1038/ng.3726.

Fairweather, D., Beetler, D.J., McCabe, E.J., Lieberman, S.M., 2024. Mechanisms underlying sex differences in autoimmunity. J. Clin. Investig. 134. https://doi.org/10.1172/jci180076.
Fedoriw, A., Mugford, J., Magnuson, T., 2012. Genomic imprinting and epigenetic control of development. Cold Spring Harbor Perspect. Biol. 4. https://doi.org/10.1101/cshperspect.a008136 a008136–a008136.
Florijn, B.W., Bijkerk, R., Van Der Veer, E.P., Van Zonneveld, A.J., 2018. Gender and cardiovascular disease: are sex-biased microRNA networks a driving force behind heart failure with preserved ejection fraction in women? Cardiovasc. Res. 114, 210–225. https://doi.org/10.1093/cvr/cvx223.
Flynn, E., Chang, A., Altman, R.B., 2021. Large-scale labeling and assessment of sex bias in publicly available expression data. BMC Bioinf. 22, 168. https://doi.org/10.1186/s12859-021-04070-2.
Gareev, I., Beylerli, O., Sufianov, A., Gulieva, L., Pavlov, V., Shi, H., 2025. MicroRNAs in the regulation of immune response in cardiovascular diseases: new diagnostic and therapeutic tools. Gene Expr. https://doi.org/10.14218/ge.2025.00010, 000, 000–000.
Gilli, F., DiSano, K.D., Pachner, A.R., 2020. SeXX matters in multiple sclerosis. Front. Neurol. 11, 616. https://doi.org/10.3389/fneur.2020.00616.
Gillies, G.E., Pienaar, I.S., Vohra, S., Qamhawi, Z., 2014. Sex differences in Parkinson's disease. Front. Neuroendocrinol. 35, 370–384. https://doi.org/10.1016/j.yfrne.2014.02.002.
Grant, E.J., Brenner, A., Sugiyama, H., Sakata, R., Sadakane, A., Utada, M., Cahoon, E.K., Milder, C.M., Soda, M., Cullings, H.M., Preston, D.L., Mabuchi, K., Ozasa, K., 2017. Solid cancer incidence among the life span study of atomic bomb survivors: 1958–2009. Radiat. Res. 187, 513–537. https://doi.org/10.1667/RR14492.1.
Grim, J.C., Aguado, B.A., Vogt, B.J., Batan, D., Andrichik, C.L., Schroeder, M.E., Gonzalez-Rodriguez, A., Yavitt, F.M., Weiss, R.M., Anseth, K.S., 2020. Secreted factors from proinflammatory macrophages promote an osteoblast-like phenotype in valvular interstitial cells. ATVB 40. https://doi.org/10.1161/ATVBAHA.120.315261.
Grove, K.L., Fried, S.K., Greenberg, A.S., Xiao, X.Q., Clegg, D.J., 2010. A microarray analysis of sexual dimorphism of adipose tissues in high-fat-diet-induced obese mice. Int. J. Obes. 34, 989–1000. https://doi.org/10.1038/ijo.2010.12.
Hanamsagar, R., Bilbo, S.D., 2016. Sex differences in neurodevelopmental and neurodegenerative disorders: focus on microglial function and neuroinflammation during development. J. Steroid Biochem. Mol. Biol. 160, 127–133. https://doi.org/10.1016/j.jsbmb.2015.09.039.
Haupt, S., Caramia, F., Klein, S.L., Rubin, J.B., Haupt, Y., 2021. Sex disparities matter in cancer development and therapy. Nat. Rev. Cancer 21, 393–407. https://doi.org/10.1038/s41568-021-00348-y.
Hewagama, A., Gorelik, G., Patel, D., Liyanarachchi, P., Joseph McCune, W., Somers, E., Gonzalez-Rivera, T., The Michigan Lupus Cohort, Strickland, F., Richardson, B., 2013. Overexpression of X-Linked genes in T cells from women with lupus. J. Autoimmun. 41, 60–71. https://doi.org/10.1016/j.jaut.2012.12.006.
Hochmuth, L., Körner, C., Ott, F., Volke, D., Cokan, K.B., Juvan, P., Brosch, M., Hofmann, U., Hoffmann, R., Rozman, D., Berg, T., Matz-Soja, M., 2021. Sex-dependent dynamics of metabolism in primary mouse hepatocytes. Arch. Toxicol. 95, 3001–3013. https://doi.org/10.1007/s00204-021-03118-9.
Høeg, L., Roepstorff, C., Thiele, M., Richter, E.A., Wojtaszewski, J.F.P., Kiens, B., 2009. Higher intramuscular triacylglycerol in women does not impair insulin sensitivity and proximal insulin signaling. J. Appl. Physiol. 107, 824–831. https://doi.org/10.1152/japplphysiol.91382.2008.
Isensee, J., Noppinger, P.R., 2007. Sexually dimorphic gene expression in Mammalian somatic tissue. Gend. Med. 4, S75–S95. https://doi.org/10.1016/s1550-8579(07)80049-0.
Jensen-Cody, S.O., Potthoff, M.J., 2021. Hepatokines and metabolism: deciphering communication from the liver. Mol. Metabol. 44, 101138. https://doi.org/10.1016/j.molmet.2020.101138.
Ji, H., Zheng, W., Wu, X., Liu, J., Ecelbarger, C.M., Watkins, R., Arnold, A.P., Sandberg, K., 2010. Sex chromosome effects unmasked in angiotensin II–Induced hypertension. Hypertension 55, 1275–1282. https://doi.org/10.1161/hypertensionaha.109.144949.
Jørgensen, K.T., Rostgaard, K., Bache, I., Biggar, R.J., Nielsen, N.M., Tommerup, N., Frisch, M., 2010. Autoimmune diseases in women with Turner's Syndrome. Arthritis Rheum. 62, 658–666. https://doi.org/10.1002/art.27270.
Karandrea, D., Kittas, C., Kitraki, E., 2000. Contribution of sex and cellular context in the regulation of brain corticosteroid receptors following restraint stress. Neuroendocrinology 71, 343–353. https://doi.org/10.1159/000054555.
Kennedy, E., Hakimjavadi, R., Greene, C., Mooney, C.J., Fitzpatrick, E., Collins, L.E., Loscher, C.E., Guha, S., Morrow, D., Redmond, E.M., Cahill, P.A., 2014. Embryonic rat vascular smooth muscle cells revisited - a model for neonatal, neointimal SMC or differentiated vascular stem cells? Vasc. Cell 6, 6. https://doi.org/10.1186/2045-824X-6-6.
Kikuchi, Y., Hosono, K., Yamashita, J., Kawabata, Y., Okubo, K., 2015. Glucocorticoid receptor exhibits sexually dimorphic expression in the medaka brain. Gen. Comp. Endocrinol. 223, 47–53. https://doi.org/10.1016/j.ygcen.2015.09.031.
Kim, H.-I., Lim, H., Moon, A., 2018. Sex differences in cancer: epidemiology, genetics and therapy. Biomol Ther (Seoul) 26, 335–342. https://doi.org/10.4062/biomolther.2018.103.
Klein, S.L., Flanagan, K.L., 2016. Sex differences in immune responses. Nat. Rev. Immunol. 16, 626–638. https://doi.org/10.1038/nri.2016.90.
Lee, J.W., Profant, M., Wang, C., 2022. Metabolic sex dimorphism of the brain at the gene, cell, and tissue level. J. Immunol. 208, 212–220. https://doi.org/10.4049/jimmunol.2100853.
Li, J., Chen, X., McClusky, R., Ruiz-Sundstrom, M., Itoh, Y., Umar, S., Arnold, A.P., Eghbali, M., 2014. The number of X chromosomes influences protection from cardiac ischaemia/reperfusion injury in mice: one X is better than two. Cardiovasc. Res. 102, 375–384. https://doi.org/10.1093/cvr/cvu064.
Link, J.C., Wiese, C.B., Chen, X., Avetisyan, R., Ronquillo, E., Ma, F., Guo, X., Yao, J., Allison, M., Chen, Y.-D.I., Rotter, J.I., El -Sayed Moustafa, J.S., Small, K.S., Iwase, S., Pellegrini, M., Vergnes, L., Arnold, A.P., Reue, K., 2020. X chromosome dosage of histone demethylase KDM5C determines sex differences in adiposity. J. Clin. Investig. 130, 5688–5702. https://doi.org/10.1172/JCI140223.
Lista, P., Straface, E., Brunelleschi, S., Franconi, F., Malorni, W., 2011. On the role of autophagy in human diseases: a gender perspective. J. Cell Mol. Med. 15, 1443–1457. https://doi.org/10.1111/j.1582-4934.2011.01293.x.
Litviňuková, M., Talavera-López, C., Maatz, H., Reichart, D., Worth, C.L., Lindberg, E.L., Kanda, M., Polanski, K., Heinig, M., Lee, M., Nadelmann, E.R., Roberts, K., Tuck, L., Fasouli, E.S., DeLaughter, D.M., McDonough, B., Wakimoto, H., Gorham, J.M., Samari, S., Mahbubani, K.T., Saeb-Parsy, K., Patone, G., Boyle, J.J., Zhang, Hongbo, Zhang, Hao, Viveiros, A., Oudit, G.Y., Bayraktar, O.A., Seidman, J.G., Seidman, C.E., Noseda, M., Hubner, N., Teichmann, S.A., 2020. Cells of the adult human heart. Nature 588, 466–472. https://doi.org/10.1038/s41586-020-2797-4.
Lorenz, M., Koschate, J., Kaufmann, K., Kreye, C., Mertens, M., Kuebler, W.M., Baumann, G., Gossing, G., Marki, A., Zakrzewicz, A., Miéville, C., Benn, A., Horbelt, D., Wratil, P.R., Stangl, K., Stangl, V., 2015. Does cellular sex matter? Dimorphic transcriptional differences between female and male endothelial cells. Atherosclerosis 240, 61–72. https://doi.org/10.1016/j.atherosclerosis.2015.02.018.
Lundsgaard, A.-M., Kiens, B., 2014. Gender differences in skeletal muscle substrate metabolism - molecular mechanisms and insulin sensitivity. Front. Endocrinol. 5, 195. https://doi.org/10.3389/fendo.2014.00195.
Luo, Y., Chen, Yapei, Ge, L., Zhou, G., Chen, Yaoyong, Zhu, D., 2023. Competing endogenous RNA network analysis of Turner syndrome patient-specific iPSC-derived cardiomyocytes reveals dysregulation of autosomal heart development genes by altered dosages of X-inactivation escaping non-coding RNAs. Stem Cell Res. Ther. 14. https://doi.org/10.1186/s13287-023-03601-3.
Manzano, R., Toivonen, J.M., Calvo, A.C., Miana-Mena, F.J., Zaragoza, P., Muñoz, M.J., Montarras, D., Osta, R., 2011. Sex, fiber-type, and age dependent in vitro proliferation of mouse muscle satellite cells. J. Cell. Biochem. 112, 2825–2836. https://doi.org/10.1002/jcb.23197.
Marino, F., Wang, D., Merrihew, G.E., MacCoss, M.J., Dubal, D.B., 2024. A second X chromosome improves cognition in aging male and female mice. https://doi.org/10.1101/2024.07.26.605328.
Márquez, E.J., Chung, C.-H., Marches, R., Rossi, R.J., Nehar-Belaid, D., Eroglu, A., Mellert, D.J., Kuchel, G.A., Banchereau, J., Ucar, D., 2020. Sexual-dimorphism in human immune system aging. Nat. Commun. 11, 751. https://doi.org/10.1038/s41467-020-14396-9.
McCarthy, M.M., 2023. Neural control of sexually dimorphic social behavior: connecting development to adulthood. Annu. Rev. Neurosci. 46, 321–339. https://doi.org/10.1146/annurev-neuro-121522-110856.
McCoy, CM, Nicholas, DQ, Masters, KS., 2012. Sex-related differences in gene expression by porcine aortic valvular interstitial cells. PLoS One 7 (7), e39980. https://doi.org/10.1371/journal.pone.0039980. Epub 2012 Jul 10. PMID: 22808080; PMCID: PMC3393722.
Meloni, A., Cadeddu, C., Cugusi, L., Donataccio, M.P., Deidda, M., Sciomer, S., Gallina, S., Vassalle, C., Moscucci, F., Mercuro, G., Maffei, S., 2023. Gender differences and cardiometabolic risk: the importance of the risk factors. IJMS 24, 1588. https://doi.org/10.3390/ijms24021588.
Molnar, C., Gair, J., Rye, C., 2021. Concepts of Biology, 1st Canadian edition. BCcampus, Victoria, B.C.
Morgan, C.P., Bale, T.L., 2012. Sex differences in microRNA regulation of gene expression: no smoke, just miRs. Biol sex dif 3, 22. https://doi.org/10.1186/2042-6410-3-22.
Morin-Grandmont, A., Walsh-Wilkinson, E., Thibodeau, S.-È., Boudreau, D.K., Arsenault, M., Bossé, Y., Couet, J., 2024. A murine model of hypertensive heart disease in older women. PeerJ 12, e17434. https://doi.org/10.7717/peerj.17434.
Mottillo, S., Filion, K.B., Genest, J., Joseph, L., Pilote, L., Poirier, P., Rinfret, S., Schiffrin, E.L., Eisenberg, M.J., 2010. The metabolic syndrome and cardiovascular risk. J. Am. Coll. Cardiol. 56, 1113–1132. https://doi.org/10.1016/j.jacc.2010.05.034.
Oakley, R.H., Riddick, N.V., Moy, S.S., Cidlowski, J.A., 2024. Imbalanced glucocorticoid and mineralocorticoid stress hormone receptor function has sex-dependent and independent regulatory effects in the mouse hippocampus. Neurobiology of Stress 28, 100589. https://doi.org/10.1016/j.ynstr.2023.100589.
On behalf of EVA Collaborators, Raparelli, V., Proietti, M., Lenzi, A., Basili, S., 2020. Sex and gender differences in ischemic heart disease: endocrine vascular disease approach (EVA) study design. J. Cardiovasc. Transl. Res. 13, 14–25. https://doi.org/10.1007/s12265-018-9846-5.
Ornos, E.D., Cando, L.F., Catral, C.D., Quebral, E.P., Tantengco, O.A., Arevalo, MaV.P., Dee, E.C., 2023. Molecular basis of sex differences in cancer: perspective from Asia. iScience 26, 107101. https://doi.org/10.1016/j.isci.2023.107101.
Ortona, E., Pierdominici, M., Maselli, A., Veroni, C., Aloisi, F., Shoenfeld, Y., 2016. Sex-based differences in autoimmune diseases. Ann. Ist. Super Sanita 52, 205–212. https://doi.org/10.4415/ANN_16_02_12.
Pal, P., Maranon, R.O., Rivera Gonzales, O.J., Speed, J.S., Janorkar, A.V., 2024. Sexual Dimorphism's impact on adipogenesis: a three-dimensional in vitro model treated with 17β-estradiol and testosterone. Mol. Cell. Endocrinol. 589, 112249. https://doi.org/10.1016/j.mce.2024.112249.

Panda, A., Zylicz, J.J., Pasque, V., 2020. New insights into X-Chromosome reactivation during reprogramming to pluripotency. Cells 9, 2706. https://doi.org/10.3390/cells9122706.

Parks, R.J., Ray, G., Bienvenu, L.A., Rose, R.A., Howlett, S.E., 2014. Sex differences in SR Ca2+ release in murine ventricular myocytes are regulated by the cAMP/PKA pathway. J. Mol. Cell. Cardiol. 75, 162–173. https://doi.org/10.1016/j.yjmcc.2014.07.006.

Parra-Izquierdo, I., Castaños-Mollor, I., López, J., Gómez, C., San Román, J.A., Sánchez Crespo, M., García-Rodríguez, C., 2019. Lipopolysaccharide and interferon-γ team up to activate HIF-1α via STAT1 in normoxia and exhibit sex differences in human aortic valve interstitial cells. Biochim. Biophys. Acta Mol. Basis Dis. 1865, 2168–2179. https://doi.org/10.1016/j.bbadis.2019.04.014.

Pinheiro, I., Dejager, L., Libert, C., 2011. X-chromosome-located microRNAs in immunity: might they explain male/female differences?: the X chromosome-genomic context may affect x-located miRNAs and downstream signaling, thereby contributing to the enhanced immune response of females. Bioessays 33, 791–802. https://doi.org/10.1002/bies.201100047.

Prajapati, C., Koivumäki, J., Pekkanen-Mattila, M., Aalto-Setälä, K., 2022. Sex differences in heart: from basics to clinics. Eur. J. Med. Res. 27, 241. https://doi.org/10.1186/s40001-022-00880-z.

Raparelli, V., Romiti, G., Spugnardi, V., Borgi, M., Cangemi, R., Basili, S., Proietti, M., the EVA Collaborative Group, 2020. Gender-related determinants of adherence to the Mediterranean diet in adults with ischemic heart disease. Nutrients 12, 759. https://doi.org/10.3390/nu12030759.

Regitz-Zagrosek, V., Dworatzek, E., Kintscher, U., Dragun, D., 2013. Sex and sex hormone–dependent cardiovascular stress responses. Hypertension 61, 270–277. https://doi.org/10.1161/HYPERTENSIONAHA.111.189233.

Reue, K., Wiese, C.B., 2022. Illuminating the mechanisms underlying sex differences in cardiovascular disease. Circ. Res. 130, 1747–1762. https://doi.org/10.1161/circresaha.122.320259.

Rich-Edwards, J.W., Kaiser, U.B., Chen, G.L., Manson, J.E., Goldstein, J.M., 2018. Sex and gender differences research design for basic, clinical, and population studies: essentials for investigators. Endocr. Rev. 39, 424–439. https://doi.org/10.1210/er.2017-00246.

Rocks, D., Shukla, M., Ouldibbat, L., Finnemann, S.C., Kalluchi, A., Rowley, M.J., Kundakovic, M., 2022. Sex-specific multi-level 3D genome dynamics in the mouse brain. Nat. Commun. 13. https://doi.org/10.1038/s41467-022-30961-w.

Roepstorff, C., Thiele, M., Hillig, T., Pilegaard, H., Richter, E.A., Wojtaszewski, J.F.P., Kiens, B., 2006. Higher skeletal muscle $\alpha_2$ AMPK activation and lower energy charge and fat oxidation in men than in women during submaximal exercise. J. Physiol. 574, 125–138. https://doi.org/10.1113/jphysiol.2006.108720.

Ruggieri, A., Matarrese, P., 2020. Male and female cells: same stress, different response. The Italian Journal of Gender-Specific Medicine 6, 1–2. https://doi.org/10.1723/3297.32668.

Sampson, A.K., Jennings, G.L.R., Chin-Dusting, J.P.F., 2012. Y are males So difficult to understand?: a case where "X" does not mark the spot. Hypertension 59, 525–531. https://doi.org/10.1161/HYPERTENSIONAHA.111.187880.

Scotland, R.S., Stables, M.J., Madalli, S., Watson, P., Gilroy, D.W., 2011. Sex differences in resident immune cell phenotype underlie more efficient acute inflammatory responses in female mice. Blood 118, 5918–5927. https://doi.org/10.1182/blood-2011-03-340281.

Seminog, O.O., Seminog, A.B., Yeates, D., Goldacre, M.J., 2015. Associations between Klinefelter's syndrome and autoimmune diseases: english national record linkage studies. Autoimmunity 48, 125–128. https://doi.org/10.3109/08916934.2014.968918.

Sgrò, P., Antinozzi, C., Wasson, C.W., Del Galdo, F., Dimauro, I., Di Luigi, L., 2024. Sexual dimorphism in sex hormone metabolism in human skeletal muscle cells in response to different testosterone exposure. Biology 13, 796. https://doi.org/10.3390/biology13100796.

Shi, S., Qin, M., Shen, B., Cai, Y., Liu, T., Yang, F., Gong, W., Liu, X., Liang, J., Zhao, Q., Huang, H., Yang, B., Huang, C., 2020. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. JAMA Cardiol 5, 802. https://doi.org/10.1001/jamacardio.2020.0950.

Shi, W., Sheng, X., Dorr, K.M., Hutton, J.E., Emerson, J.I., Davies, H.A., Andrade, T.D., Wasson, L.K., Greco, T.M., Hashimoto, Y., Federspiel, J.D., Robbe, Z.L., Chen, X., Arnold, A.P., Cristea, I.M., Conlon, F.L., 2021. Cardiac proteomics reveals sex chromosome-dependent differences between males and females that arise prior to gonad formation. Dev. Cell 56, 3019–3034.e7. https://doi.org/10.1016/j.devcel.2021.09.022.

Silaidos, C., Pilatus, U., Grewal, R., Matura, S., Lienerth, B., Pantel, J., Eckert, G.P., 2018. Sex-associated differences in mitochondrial function in human peripheral blood mononuclear cells (PBMCs) and brain. Biol. Sex Differ. 9, 34. https://doi.org/10.1186/s13293-018-0193-7.

Smiley, K.O., Munley, K.M., Aghi, K., Lipshutz, S.E., Patton, T.M., Pradhan, D.S., Solomon-Lane, T.K., Sun, S.D., 2024. Sex diversity in the 21st century: concepts, frameworks, and approaches for the future of neuroendocrinology. Horm. Behav. 157, 105445. https://doi.org/10.1016/j.yhbeh.2023.105445.

Smith-Bouvier, D.L., Divekar, A.A., Sasidhar, M., Du, S., Tiwari-Woodruff, S.K., King, J.K., Arnold, A.P., Singh, R.R., Voskuhl, R.R., 2008. A role for sex chromosome complement in the female bias in autoimmune disease. J. Exp. Med. 205, 1099–1108. https://doi.org/10.1084/jem.20070850.

Steffensen, C.H., Roepstorff, C., Madsen, M., Kiens, B., 2002. Myocellular triacylglycerol breakdown in females but not in males during exercise. Am. J. Physiol. Endocrinol. Metabol. 282, E634–E642. https://doi.org/10.1152/ajpendo.00078.2001.

Straface, E., Gambardella, L., Brandani, M., Malorni, W., 2012. Sex differences at cellular level: "cells have a sex.". Handb. Exp. Pharmacol. 49–65. https://doi.org/10.1007/978-3-642-30726-3_3.

Turner, B.B., Debra, A.W., 1985. Sexual dimorphism of glucocorticoid binding in rat brain. Brain Res. 343, 16–23. https://doi.org/10.1016/0006-8993(85)91153-9.

Uhl, M., Schmeisser, M.J., Schumann, S., 2022. The sexual dimorphic synapse: from spine density to molecular composition. Front. Mol. Neurosci. 15, 818390. https://doi.org/10.3389/fnmol.2022.818390.

Venanzi, F.M., Bini, M., Nuccio, A., De Toma, A., Lambertini, M., Ogliari, F.R., Oresti, S., Viganò, M.G., Brioschi, E., Polignano, M., Naldini, M.M., Riva, S., Ferrara, M., Fogale, N., Damiano, G., Russo, V., Reni, M., Veronesi, G., Foggetti, G., Conforti, F., Bulotta, A., Ferrara, R., 2023. Sex dimorphism and cancer immunotherapy: may pregnancy solve the puzzle? Cancer Treat Rev. 121, 102648. https://doi.org/10.1016/j.ctrv.2023.102648.

Vizgirda, V.M., Wahler, G.M., Sondgeroth, K.L., Ziolo, M.T., Schwertz, D.W., 2002. Mechanisms of sex differences in rat cardiac myocyte response to β-adrenergic stimulation. Am. J. Physiol. Heart Circ. Physiol. 282, H256–H263. https://doi.org/10.1152/ajpheart.2002.282.1.H256.

Voskuhl, R.R., Sawalha, A.H., Itoh, Y., 2018. Sex chromosome contributions to sex differences in multiple sclerosis susceptibility and progression. Mult. Scler. 24, 22–31. https://doi.org/10.1177/1352458517737394.

Vousden, D.A., Corre, C., Spring, S., Qiu, L.R., Metcalf, A., Cox, E., Lerch, J.P., Palmert, M.R., 2018. Impact of X/Y genes and sex hormones on mouse neuroanatomy. Neuroimage 173, 551–563. https://doi.org/10.1016/j.neuroimage.2018.02.051.

Walker, C.J., Schroeder, M.E., Aguado, B.A., Anseth, K.S., Leinwand, L.A., 2021. Matters of the heart: cellular sex differences. J. Mol. Cell. Cardiol. 160, 42–55. https://doi.org/10.1016/j.yjmcc.2021.04.010.

Wallis, C.J.D., Butaney, M., Satkunasivam, R., Freedland, S.J., Patel, S.P., Hamid, O., Pal, S.K., Klaassen, Z., 2019. Association of patient sex with efficacy of immune checkpoint inhibitors and overall survival in advanced cancers: a systematic review and meta-analysis. JAMA Oncol. 5, 529. https://doi.org/10.1001/jamaoncol.2018.5904.

Waxman, D.J., Holloway, M.G., 2009. Sex differences in the expression of hepatic drug metabolizing enzymes. Mol. Pharmacol. 76, 215–228. https://doi.org/10.1124/mol.109.056705.

Welle, S., Tawil, R., Thornton, C.A., 2008. Sex-related differences in gene expression in human skeletal muscle. PLoS One 3, e1385. https://doi.org/10.1371/journal.pone.0001385.

Westemeier-Rice, E.S., Winters, M.T., Rawson, T.W., Martinez, I., 2024. More than the SRY: the non-coding landscape of the Y chromosome and its importance in human disease. ncRNA 10, 21. https://doi.org/10.3390/ncrna10020021.

Wiese, C.B., Agle, Z.W., Zhang, P., Reue, K., 2022. Chromosomal and gonadal sex drive sex differences in lipids and hepatic gene expression in response to hypercholesterolemia and statin treatment. Biol. Sex Differ. 13. https://doi.org/10.1186/s13293-022-00474-8.

Xiong, L., Liu, J., Han, S.Y., Koppitch, K., Guo, J.-J., Rommelfanger, M., Miao, Z., Gao, F., Hallgrimsdottir, I.B., Pachter, L., Kim, J., MacLean, A.L., McMahon, A.P., 2023. Direct androgen receptor control of sexually dimorphic gene expression in the mammalian kidney. Dev. Cell 58, 2338–2358.e5. https://doi.org/10.1016/j.devcel.2023.08.010.

Yang, L., Li, Y., 2012. Sex differences in the expression of drug-metabolizing and transporter genes in human liver. J. Drug Metabol. Toxicol. 3. https://doi.org/10.4172/2157-7609.1000119.

Yang, X., Schadt, E.E., Wang, S., Wang, H., Arnold, A.P., Ingram-Drake, L., Drake, T.A., Lusis, A.J., 2006. Tissue-specific expression and regulation of sexually dimorphic genes in mice. Genome Res. 16, 995–1004. https://doi.org/10.1101/gr.5217506.

Youness, A., Miquel, C.-H., Guéry, J.-C., 2021. Escape from X chromosome inactivation and the female predominance in autoimmune diseases. IJMS 22, 1114. https://doi.org/10.3390/ijms22031114.

Young, J.E., Wu, M., Hunsberger, H.C., 2023. Editorial: sex and gender differences in neurodegenerative diseases. Front. Neurosci. 17, 1175674. https://doi.org/10.3389/fnins.2023.1175674.

Zito, A., Roberts, A.L., Visconti, A., Rossi, N., Andres-Ejarque, R., Nardone, S., El-Sayed Moustafa, J.S., Falchi, M., Small, K.S., 2023. Escape from X-inactivation in twins exhibits intra- and inter-individual variability across tissues and is heritable. PLoS Genet. 19, e1010556. https://doi.org/10.1371/journal.pgen.1010556.