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The X-quisite X-ception: Sex Differences with Immune Responses

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Abstract

There are significant sex-based differences in immune responses to pathogens and self-antigens, with human females exhibiting increased susceptibility to various autoimmune diseases, and human males displaying preferential susceptibility to some viral, bacterial, parasitic, and fungal infections. While sex hormones clearly contribute to sex differences in immune cell composition and function, the presence of two X chromosomes in human females suggests that differential gene expression of numerous X-linked immune-related genes may also influence sex-biased innate and adaptive immune cell function in health and disease. Here, we review the sex differences in immune system composition and function, examining how hormones and genetics influence the immune system. We focus on the genetic and epigenetic contributions responsible for altered X-linked gene expression, and how this impacts sex-biased immune responses in the context of pathogen infection and systemic autoimmunity.

Keywords

sex hormones; X chromosome inactivation; adaptive immune cells; innate immune cells; female biased autoimmune disease; systemic sclerosis; systemic lupus erythematosus; Sjögren's syndrome; XCI escape

INTRODUCTION

Biological sex contributes to physiological differences between human males and females that can influence pathogen exposure, recognition and clearance, and replication. Recent studies investigating how mammals respond to immunogenic challenges have revealed numerous differences between male and female susceptibility to pathogens such as bacteria, fungi, viruses, and parasites, likely via sex-biased differences in immune responses

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Competing Interests

The authors declare no competing interests.

(Figure 1). In general, human females have greater innate and adaptive immune responses compared to males. Females usually clear infections faster than males, and males exhibit increased mortality rates across all ages, including in pre-term births and infants, after infection[1]. Females often exhibit stronger serologic responses compared to males following vaccination. Even in mice, females are more resistant to bacterial and viral infections and generate stronger and longer-lasting immune responses[2]. This seemingly advantageous female sex bias in the potency of immune responses is juxtaposed by the female-biased proclivity to autoimmunity. Human females are at increased risk for some autoimmune diseases, including systemic lupus erythematosus (SLE), Sjogren's Syndrome, and systemic sclerosis[3]. However, the diverse molecular mechanism underlying these sex biased immune responses remain incompletely understood, and clarifying their origin may help provide new insights into disease pathogenesis.

The molecular origins for sex differences in immune responses originate from the X and Y chromosomes, the reproductive organs, and variations in levels of sex hormones over time. Sex hormones, specifically androgens and estrogens, can have either pro- or anti-inflammatory effects, and many genes with immune functions are regulated by the presence or absence of nuclear hormone receptor binding (BOX 1). The sex chromosomes provide the genetic and epigenetic foundations for altered gene expression in a heritable, sex-specific fashion in immune cells. The X chromosome contains about 50 immune-related genes, including some important for immune cell identity (*FOXP3*), cellular activation and intracellular signaling (*CD40LG, TLR7, IRAK1, IL13RA1/2, NEMO, TASL, IL-9R*), leukocyte trafficking (*CD99, CXCR3*), immune cell differentiation and proliferation (*IL-2RG, BTK*), and cellular metabolism (*OGT, CYBB*). Thus, the X chromosome is likely an important contributor to the molecular basis of female-biased antimicrobial responses and autoimmunity. In this Review, we review current literature on sex differences in immune system composition and function, examining how hormones and genetics of the X-chromosome influence the immune system. We focus on genetic and epigenetic contributions to altered X-linked gene expression and how this impacts female-biased autoimmune disorders and highlight examples of altered X-linked gene expression that influence pathogen susceptibility and disease progression.

Sex differences in immune cell composition

The observed sex-biased differences in innate, humoral, and cellular immunity in humans are accompanied by differential immune composition in males and females. For example, flow cytometric immunophenotyping of healthy volunteers in Europe and Asia have consistently identified female-specific elevations of CD4+ T-cells, specifically naïve cells, which may reflect enhanced thymic function[4,5]. A recent whole blood transcriptional profiling of multiple international and intercontinental cohorts of healthy individuals similarly identified a higher proportion of CD4+ T cells in human females [6]. In addition, human females have more circulating CD19+ B-cells, plasma cells, regulatory T cells (defined by CD25hiCD127lo), and both naïve CD8+ and mucosa-associated invariant T-cells relative to males[4,7-10]. Conversely, human females have lower proportions of both CD14+ and CD16+ monocytes, a generally lower proportion of myeloid cells [6,8] and fewer NK cells

[4,7,8,11] relative to males. Differences in humoral immunity have also been observed between the sexes, with human females having higher quantities of IgM antibodies[12].

Sex differences in immune cell composition have also been observed across mouse strains [13,14]. Within resident immune populations of C57BL/6 mice and Wistar rats, there are greater total leukocyte quantities, and specifically more B and T cells and F4/80+ macrophages in female animals[15]. Consistent with these findings, mesenteric tissues from female animals express higher levels of both innate and adaptive immune cell chemokines and chemokine receptor genes that could enhance recruitment. A recent study found that male mice have higher numbers of splenic NK cells, yet have reduced effector function due to reduced expression of the X-linked gene *Kdm6a* (*Utx*), a histone lysine demethylase. Notably, *Kdm6a* (*Utx*) is expressed in higher levels in female NK cells[16]. Curiously, sex hormones do not significantly influence NK number or effector function, as a female-specific *Utx* deletion in NK cells increases NK cell frequency and reduces effector function through aberrant upregulation of *Bcl2* expression, an anti-apoptosis factor, and downregulation of IFN-gamma[16]. The identification of additional X-linked genes that are capable of influencing both innate and adaptive immune cell frequencies may help further clarify the basis of the observed differences in immune cell composition between the sexes.

Sex hormones influence immune cell function

Sex differences in immune cell function arise from differential gene expression in immune cell subsets of males and females, and sex hormones can contribute towards these observed gene expression differences. Transcriptional profiling of innate and adaptive immune cells – including monocytes, naïve B cells, and various T cell subsets – identified about 1875 transcripts exhibiting sex biased expression, the majority of which were autosomal[17]. Most of these transcripts exhibited sex-biased expression in one type of immune cell, underscoring the cellular specificity of sex-specific gene expression and simultaneously highlighting the broad impact of sex hormonal and trans-acting sex chromosomal elements on the observed gene expression differences[17]. Estrogens can have either pro-inflammatory or anti-inflammatory functions (BOX 1), depending on both the local hormone concentration and the immune cell examined. For example, transcription of *AICDA,* which encodes the AID enzyme which is important for somatic hypermutation and class switch recombination in B cells, is regulated by binding of the estrogen-ER-alpha complex to its promoter region of *AICDA*. In autoimmune disease, AID contributes to the production of high-affinity IgG auto-antibodies[18]. Estrogens also increase the expression of endosomal Toll like Receptors (*TLR*) 3, 7, 9, which are important regulators of Type I interferons (IFNs)[19]. Co-culture of the SLE-derived estrogen-treated CD4+ T cells with B cells from healthy controls resulted increased antibody production *in vitro*[20]. Type I IFN production and antiviral responses downstream of TLRs 3, 7, and 9 are regulated by TRIM21, whose expression is increased by estrogen. *TRIM21* expression also induces IL-23, which promotes Th17-differentiation, an adaptive immune pathway integral to the pathogenesis of several systemic autoimmune diseases, including SLE, SSc, SS, and RA[21]. The female-bias for enhanced type I IFN signaling has also been observed in human plasmacytoid dendritic cells (pDCs), which produce IFNα following TLR stimulation. Female pDCs treated with TLR7 and TLR8 agonists, but not TLR9 agonists, produce more IFNα compared to male pDCs, and more

mRNA transcripts of the IFN-stimulated gene, *IRF5*[22-24]. Although a sex-bias with type I IFN production was not originally observed for TLR9, this could be due to the type of CpG used in the original study[22], as sex biased type I IFN production by pDCs stimulated through TLR9 has been recently reported[25,26]. Both sex chromosomal and sex hormonal mechanisms likely contribute towards this female bias because *TLR7* and *TLR8* are X-linked, and *IRF5* transcription is regulated by estrogen receptor 1 (ESR1)[27].

Sex differences in immune functions, particularly within the context of microbial infection, also reflect sex differences in the cellular expression of pattern recognition receptors. Peritoneal macrophages from female rodents express higher levels of *Tlr2, Tlr3*, and *Tlr4*, and exhibit enhanced phagocytosis and NADPH-mediated bacterial elimination compared to their male counterparts[15]. Accordingly, peritoneal-derived macrophages from female mice also exhibit increased expression of interferon-stimulated genes, and female mice exhibited blunted sepsis severity and fewer recoverable live bacteria in circulation[28,29]. These findings were abrogated by prior ovariectomy and support a role for sex hormones in shaping the tissue resident immunophenotype. The B1 cell-dependent neutralizing antibody response to LPS-O-antigens of enteropathogenic E. coli (EPEC) occurred in sexually mature females, resulting from estrogen-mediated upregulation of BAFF and APRIL cytokines secreted by peritoneal macrophages[29]. Bone marrow-derived macrophages from female mice have higher levels of *Tlr8* compared to male mice[30], and peripheral blood mononuclear cells from human females express more *TLR7* compared to males[31]. Vaccination or viral challenge increases expression of TLR pathway and pro-inflammatory genes in female PBMCs from humans and rats, and it has been suggested that estrogen binding at sex hormone receptor elements in the promoter regions of these genes is responsible for increased gene expression [32]. However, neutrophils from human males have higher expression of *TLR4* and this expression increases following activation with LPS, which results in higher pro-inflammatory cytokine production and may contribute towards the male bias observed with endotoxic shock[33]. Notably, in line with its recognized generally anti-inflammatory role, androgen treatment of male mice decreases *Tlr4* expression in macrophages, and it can also suppress the invasion and colonization of uropathogenic *E.coli* through inhibition of the JAK-STAT signaling pathway and decreased production of IL-1β, IL-6, and IL-8 [34]. Androgens have anti-inflammatory effects (BOX 1) on both humoral and cellular immune responses by reducing T and B cell proliferation and decreasing immunoglobulin and cytokine production[35]. Female mice treated with dihydrotestosterone (DHT) produce more IL-10 and less IL-12 compared to untreated female animals, resulting from increased AR signaling in CD4+ T cells[36].

Androgens also play an important role in central tolerance through regulated expression of *AIRE* in the thymus, the expression of which exhibits a sex bias. While androgens recruit ARs to the AIRE promoter to increase transcription in male mice and humans, estrogens inhibit *AIRE* expression[37,38]. Androgens can also influence expression of *FOXP3*, a transcription factor important for CD4+ regulatory T cells (Tregs) that play an important role in tolerance. Treg-intrinsic AR signaling increases Treg suppression during an allergen challenge, and human Tregs treated with androgen reduced IL-33 induced *ST2* expression and human bronchial epithelial cells produced less IL-33[39]. There is evidence that androgen treatment can increase *FOXP3* expression in Tregs from human females during the ovulation

phase of the menstrual cycle yet had no effect on Tregs from males[40]. Androgens have inhibitory effects on B cell lymphopoiesis and specifically impact B cell progenitors, which express *AR* while mature B cells lacking this receptor were not affected[41]. Unlike estrogen which upregulates expression of B cell activating factor (BAFF), *BAFF* expression is inhibited by androgens[42]. Thus androgens block BAFF-dependent B cell clonal expansion and class switch recombination, and downregulate GC responses, acting through B cell extrinsic mechanisms[43]. Androgens also increase expression of *PTPN1*, which functions in cell growth, differentiation, mitosis and immune cell function. AR-signaling prevents Th1 development by upregulating *Ptpn1*, which is an inhibitory phosphatase of Tyk2 and Jak2 kinases upstream of Sta4, thereby inhibiting IL12/Stat4 signaling [44].

Genetic and epigenetic contributions to sex differences in immune responses: X-Chromosome Inactivation (XCI)

Female mammals regulate X-linked gene expression using XCI (BOX 2), in which one X chromosome (the inactive X chromosome, or Xi) is transcriptionally silenced during development, and a memory of this silencing event is maintained with each cell division and persists into adulthood. Various epigenetic modifications, as well as the long noncoding RNA Xist, are enriched across the Xi, and function to maintain transcriptional repression of most, but not all, of the genes on the Xi. *Xist* expression is required to form the Xi and loss of *Xist* in early development is lethal due to the requirement for an appropriate dosage of X-linked genes in both embryo and placental development [45]. *Xist* deletion or *Xist* gene silencing reduces, and often eliminates, enrichment of heterochromatic modifications from the Xi[46] and results in reactivation of some X-linked genes on the Xi, depending on the cell type and timing relative to XCI initiation. Mouse models with conditional *Xist* deletion in post-XCI somatic cells yields variable phenotypes, including myeloproliferative neoplasia (deletion in hematopoietic stem cells), increased polyp formation (intestinal deletion, following azoxymethane/dextran sulfate treatment), or even the lack of a perceptible phenotype (deletion in neurons, B cells, epithelial cells, intestinal cells) where animals are viable and have normal lifespans[47-49]. Collectively, these studies highlight three fundamental observations: (1) that the identify and number of X-linked genes exhibiting reactivation upon *Xist* deletion varies by cell type; (2) X-linked dosage imbalances are, in fact, variably tolerated in a cell-type-specific manner; (3) inflammatory stress may exacerbate Xi reactivation.

Female mammals are mosaic for the X chromosome, as each individual female cell will contain an inactive X (Xi) that is either maternal or paternal in origin. Most somatic cells examined to date have similar epigenetic features enriched on the Xi, including Xist RNA, heterochromatic histone modifications, and histone variant macroH2A, which can be visualized cytologically[50-53] . However, immune cells lack some hallmark epigenetic features of canonical XCI maintenance. Specifically, splenic B and T cells from mice and circulating lymphocytes from humans lack cytologically visible Xist RNA and heterochromatic mark enrichment at the Xi, despite any significant changes with *Xist* transcription[54-57]. Thus, *Xist* transcription and its localization to the Xi are genetically independent processes. *In vitro* activation of B and T cells stimulates the return of Xist RNA and heterochromatic modifications to the Xi, prior to the first cell division[54,56,58,59].

This dynamic localization of Xist RNA and heterochromatic marks to the Xi is also observed during lymphocyte development, as Xist RNA is lost from the Xi after the common lymphoid progenitor stage, at the pro-B cell and DN1 thymocyte stages, and *Xist* transcription remains constant [56,58].

Surprisingly, non-canonical XCI maintenance is a feature of both adaptive and innate immune cells. Xist RNA exhibits substantial diversity in the robustness of its relocalization to the Xi depending on the type of immune cell. Neutrophils and pDCs lack detectable Xist RNA transcripts at the Xi; in contrast, NK cells exhibit clusters of Xist RNA pinpoints within the Xi territory[60]. Bone marrow-derived macrophages stimulated with either LPS or CpG have dispersed Xist RNA patterns and about half of the nuclei have a H3K27me3 focus that co-localizes with Xist signals. *In vitro* stimulation of mouse pDCs with either CpG or a Tlr7 agonist did not result in detectable Xist RNA localization, despite persistent *Xist* transcription, and both resting and *in vitro* activated pDCs have few H3K27me3 foci[60].

The paucity of epigenetic features on the Xi in many immune cells, including lymphocyte progenitors, supports the hypothesis that the chromatin of the Xi in immune cells is more euchromatic than in fibroblasts, and therefore prone to aberrant reactivation at certain loci. The facultative nature of the chromatin of the Xi may facilitate the increased expression of proinflammatory X-linked genes in response to pathogen infections, which would provide a favorable advantage to females, and yet simultaneously disrupt the balance of self-tolerance resulting in the development of female-biased autoimmune disease (Figure 1).

Female-biased systemic autoimmune disease and the X chromosome

Autoimmune diseases predominantly affect human females, and 80% of all individuals with autoimmune disease are female[61,62,63]. For some autoimmune diseases, such as multiple sclerosis (MS), this sex bias is modest (~65% female), while for other autoimmune diseases such as primary biliary cirrhosis, the sex bias is strongly skewed (~90% female)[64]. The female sex bias with some autoimmune diseases has increased over time. For example, in the mid-twentieth century, MS originally exhibited equal prevalence between the sexes; by the 1980s the sex ratio was 2:1 (female:male); currently, the sex ratio is 3:1[65]. The observed increase in the female-bias of disease likely reflects advancements in the medical classification and diagnosis of these diseases but could also reflect environmental changes. While the female bias for many autoimmune diseases is quite high, the incidence and prevalence across rheumatic autoimmune diseases can vary. For example, the sex bias with SLE is typically ~66-93% female, and the prevalence ranges from 5 - 241 per 100,000 people in the United States; for dermatomyositis (DM) and polymyositis (PM), the sex bias is ~60-75% female yet the prevalence is only about 6 per 100,000 (Table 1). Importantly, beyond disease prevalence, there are also sex differences in disease severity, specifically with respect to the degree of organ involvement, and symptom burden/disability. Male patients with MS, SLE, and SSc typically exhibit greater disease severity[66,67], and male patients with SLE are more likely to exhibit renal and cardiovascular co-morbidities[68]. However, this male-biased increase in autoimmune disease severity is not universal; in RA for example, biological sex does not correlate with articular disease severity[69]. Additional translational studies systematically examining the relationship between biological sex and

both disease manifestations and disease severity are necessary to better understand how biological sex may impact the phenotype, pathogenesis, and natural history of disease.

Dosage imbalances of some X-linked genes are detrimental for cell function and can result in features of systemic autoimmune disease[64] . Because XCI 'escape' (BOX 2) is variable across cell types, it is likely that some of these X-linked genes are biallelically expressed in specific cells (or escape silencing in a portion of the total cell population) in healthy individuals, where they accordingly exhibit sex-biased expression[70]. The X chromosome contains many genes that function, either directly or indirectly, in immune processes[1]. It is therefore likely that these genes are dosage sensitive and therefore subject to XCI silencing in immune cells[59,71], although direct evidence from specific cell types in mice and human samples is lacking. Also unclear is whether any of these genes can become reactivated from the Xi in response to either antigen-mediated stimulation or pathogen infection, or as a result of chronic inflammation during autoimmunity. Aberrant XCI maintenance, where XIST RNA and some heterochromatic histone modifications (H3K27me3, H2AK119-ubiquitin) are missing from the Xi in circulating lymphocytes from female SLE patients, both pediatric and adults, and also in various mouse models of spontaneous lupus-like disease which exhibit a female bias [56,59,72,73]. We have proposed the hypothesis that autoimmune disease, such as SLE, results in reduced enrichment of epigenetic features across the Xi which permits reactivation of immunity-related genes, resulting in the observed abnormal increased expression in lymphocytes (Figure 3). Additional work is necessary to determine whether perturbed XCI maintenance is a feature of other autoimmune diseases that predominantly affect human females.

Individuals with more than one X chromosome, including XX females, patients with Klinefelter Syndrome (XXY), and individuals with polysomy X (XXX), have increased susceptibility to some female biased autoimmune diseases (Figure 2), including SLE, Sjogren's syndrome (SS), SSc, and PM/DM[74,75]. The association between female-biased autoimmunity and X chromosome dosage may also apply more broadly to other autoimmune diseases pending additional karyotype-stratified case-control studies. The contribution of multiple X chromosomes to systemic autoimmune disease risk (independent of sex hormones) is supported by mouse models using the 'four core genotypes': (**1**) ovary-bearing XX mice , (**2**) ovary-bearing XY mice deficient in the Y-linked Sry gene required for sex determination and male gonad formation (XY*Sry* mice), (**3**) testes-bearing XY*Sry*$^{-}$ and (**4**) testes-bearing XX*Sry* transgenic mice[76]. Pristane-induced SLE-like disease, with elevated type I interferon production, and induced experimental autoimmune encephalomyelitis (EAE) results in increased onset and disease severity in XX and XXSry animals[77], reflecting genetic and epigenetic contributions from the X, although the causal genes responsible are unknown. Bone marrow chimera experiments in which hematopoietic stem cells or fetal liver cells from ovariectomized female NZB/W F1 mice, a classic spontaneous mouse model of SLE-like disease exhibiting a female bias (see BOX 3), are injected into hormonally intact lethally irradiated NZB/W F1 males results in the development of lupus-like disease with increased numbers of germinal center B cells, memory B cells, and plasma cells in all male recipients, similar to NZB/W F1 females[78]. Thus X-linked genes expressed in female (XX) immune cells, independent of prior exposure

to female sex hormones, accelerate SLE-like disease onset in male animals predisposed to develop autoimmune disease, underscoring the significance of genetic contributions from the X chromosome in autoimmunity.

X-linked immunity genes that are dosage sensitive in autoimmune disease

There are a number of X-linked immunodeficiencies, thus underscoring the importance of appropriate X-linked gene dosage for immune function and health.[79] Accordingly, X-linked genes that are aberrantly expressed in immune cells of patients with female-biased autoimmune disease suggest perturbations in the regulation of XCI contributes to this bias. Abnormal X-linked gene expression has been observed in both adaptive and innate immune cells from patients with autoimmune rheumatic diseases, including SLE, SS, and SSc (Table 2). Interestingly, transgenic mouse models overexpressing some X-linked immune related genes have altered immune function and result in features of autoimmune disease (see Table 2). The X-linked gene *CD40LG* is primarily expressed by activated $CD4^+$ T cells, and encodes a receptor that binds to CD40, which is expressed by dendritic cells, B cells, and endothelial cells. *CD40LG* is aberrantly overexpressed in T and B cells from female SLE[80,81] and SSc[82] patients relative to healthy female controls. While the biological significance of this overexpression in these patients is not well-established, transgenic overexpression of *Cd40lg* in mice results in autoimmune disease, with increased IgG antibodies, chronic inflammation, glomerulonephritis, thymic atrophy, and increased lethality[83]. *CXCR3* is an inducible chemokine receptor that functions in adaptive immune responses by regulating Th1 cells and T cell trafficking. *CXCR3* is overexpressed in circulating $CD4^+$ T cells of female patients with SLE and the proportion of $CXCR3^+$ $CD4^+$ T cells is increased in the urine and kidneys from patients with lupus nephritis[81,84]. In SS patients, there are also elevated numbers of infiltrating $CXCR3^+$ $CD3^+$ T cells in salivary gland tissue, and the CXCR3 ligands CXCL9 and CXCL10 are overexpressed[85]. BTK is a kinase associated with the B cell receptor and its activation induces a signaling cascade required for B cell proliferation, activation, and survival. SLE patients (samples were not distinguished by sex) with active lupus nephritis overexpress *BTK* in peripheral blood mononuclear cells[86], and *Btk* overexpression in mice increases germinal center B cells, positive ANA staining, and immune complex deposition in kidneys [87]. Decreasing the activity of Btk through small molecule inhibition in both a spontaneous (NZB/W F1 mice) and an inducible mouse model of lupus reduces lupus-like disease phenotypes[88]. FOXP3 is a transcription factor important for differentiation and maintenance of regulatory T cells (Tregs). SLE and SSc patient Tregs express less FOXP3, which likely compromises Treg function, and while there are conflicting reports regarding the abundance of Tregs in the peripheral blood of patients with SLE and SSc, the available evidence suggests that Tregs may be dysfunctional in these diseases [89-91]. Tregs in the skin of SSc patients exhibit abnormal production of Th2 cytokines, indicative of tissue specific Treg cellular effects that may influence localized dysfunction and contribute towards fibrosis[92]. Overexpression of *Foxp3* is protective against renal dysfunction in a mouse model of accelerated crescentic glomerulonephritis due to increased Treg number and function, which blocks Th1, Th2, and Th17 responses systemically[93].

X-linked immune genes also exhibit dosage sensitivity and are overexpressed in female-biased autoimmune diseases. *TLR7* encodes an endosomal pattern recognition receptor that induces Type I IFN production and activates IFN signature genes. Increased *TLR7* expression was observed among female pediatric SLE patients[94], perhaps in part due to its ability to escape XCI and exhibit biallelic expression in immune cells, such as B cells[31]. Indeed, *TLR7* exhibits variable escape from XCI in human immune cells and B cells from female NZB/W F1 mice[73], suggesting that aberrant overexpression resulting from XCI escape is a mechanism that may contribute to the pathogenesis of female-biased autoimmune disease. Biallelic expression of *TLR7* in human female B cells increases cell responsiveness to TLR7 ligands and increased class switching compared to monoallelic *TLR7* expressing B cells[31]. The resulting increase in TLR7 signaling is likely biologically significant. Recently, a gain-of-function mutation in *TLR7* was identified in a young female with SLE. Introduction of this mutation into BL6 mice results in the spontaneous development of lupus-like disease. [95]. Mouse models with two or more copies of *Tlr7*, including the BXSB-Yaa strain (BOX 3), have increased autoantibody production, autoreactive lymphocytes, and glomerulonephritis[96,97]. *TRL7* exhibits variable escape from XCI in human immune cells and B cells from female NZB/W F1 mice[73], suggesting that aberrant overexpression resulting from XCI escape is a mechanism that may contribute towards female-biased autoimmune disease. *TASL* (*CXorf21*), an X-linked adaptor protein critical for Tlr7 signaling is aberrantly overexpressed in SLE patient lymphoblastoid cell lines compared to healthy controls and may escape XCI in immune cells [98]. Thus, abnormal overexpression of *TLR7* and *TASL* due to potential perturbations with XCI escape could represent a mechanism which contributes towards increased IFN signaling in female individuals with autoimmune disease. Retrospective identification of additional disease-related genes abnormally expressed from the X chromosome is challenged by the omission of reads from the sex chromosomes in microarray and transcriptional profiling datasets when normalizing samples between the sexes in many publications. However, many patient datasets for autoimmune diseases with a strong female bias include a female-majority of patient samples and therefore retain X-linked transcript information, permitting future re-analyses of the data to identify additional differentially expressed X-linked genes in patient samples[56,59]. Future translational investigations in well clinically characterized patient cohorts will be instrumental in further defining the spectrum of X-linked genes exhibiting dysregulated expression in a sex-specific and disease-specific manner.

Sex differences with immune responses to pathogens

Sex differences in the incidence or severity of infectious diseases have also been observed across a variety of distinct pathogens (Table 3). Biological sex impacts pathogen replication and transmission, as well as the host immune response to the pathogen. The sex bias of infectious disease is typically explained by the stronger female immune response, which results in higher levels of inflammation. While sexual dimorphism among infectious diseases is likely explained in part by behavioral differences (lifestyle choices, exposures, access to healthcare, etc), underlying physiological differences, both hormonal and genetic, may have an even greater impact. The hormonal and genetic contributions responsible for the sex-biased responses to a variety of pathogens are summarized in Table 3 but have not been well characterized (particularly the genetic component). Mouse and rodent models

often recapitulate the observed sex bias in humans (Table 3) and have been used to identify sex-specific molecular pathways resulting from infection of some pathogens. Pathogen type also influences infection incidence and disease severity, often exhibiting a sex bias in both humans and rodent models. Males typically exhibit greater incidence for most bacterial, parasitic, some viral, and fungal infections (Table 3); females have greater incidence of parasitic worm infections[99-101]. Some pathogens, including HIV, Ebola, *M. tuberculosis, Cryptosporidium*, and Sars-CoV-2, exhibit altered rates of replication, transmission, or incidence of multiple infections of different pathogens between the sexes, which likely influence incidence rates [102-107]. Continued use of relevant mouse models, when they recapitulate some features of human disease, with these different pathogens is likely to reveal genetic and epigenetic mechanisms that contribute to the sex differences following infection by these specific pathogens.

Sex differences in response to vaccination

Females often have greater antibody responses, and typically experience more adverse reactions to vaccinations[108]. Activation of the innate immune system immediately following vaccination often results in localized inflammation of the injection site. Subsequent activation of the adaptive immune system is also critical for generating an effective memory response to inactivated viruses or viral particles. Females often develop more inflammation around the vaccine injection site, which may result from sex differences with innate immune activation and produce stronger class-switched antibody profiles for vaccines against influenza, smallpox, measles mumps and rubella, yellow fever, hepatitis A and B, and herpes simplex (Table 3). Female mice injected with inactivated virus produce higher antibody titers and higher numbers of germinal center B cells and CD8+ and CD4+ T cells in lymph nodes compared to male mice[109]. Because females often have stronger responses to viral and bacterial vaccines and have more severe reactions, it has been suggested that female-specific reductions with vaccine doses should be considered[32].

X-linked genes involved in sex-biased responses to pathogen infections and vaccination

Accumulating evidence suggests that XCI escape of some X-linked immunity genes in innate and adaptive immune cells contributes towards increased female protection from bacteria and parasites. Transcription of *ACE2*, one of the receptors utilized by coronaviruses for cellular entry, is influenced by both genetic and hormonal factors[106,107,110,111], and *ACE2* escapes XCI in human cells and mouse AT2 cells inside alveoli of the lung[71,112]. One study using Cxcr3 dual reporter mice found that *Cxcr3* escapes XCI in activated T cells, and that following *Leishmania* infection, biallelic *Cxcr3*-expressing cells produce more IFN-gamma, IL-2, and CD69 than do monoallelic *Cxcr3* expressing cells[113]. In general, males have less potent antiviral responses (Table 3), which may be influenced by sex-dependent differences in *UTX/Utx* expression levels in NK cells that result in increased numbers of NK cells with reduced functionality in males compared to females[16]. NK cells are necessary for antiviral responses to various viruses including cytomegalovirus (CMV), and *Utx* deletion increases lethality following CMV infection[16]. It is likely that in addition to *Utx* and *Cxcr3,* other X-linked genes that escape XCI in immune cells impact the response to pathogens that exhibit sex biases in infection (Table 3). The identification of these genes may reveal

one pathway which underlies the mechanistic basis for sex-biased immune protection in response to a variety of pathogens.

The importance of X-linked immunity related genes for sex-biased responses to pathogens is underscored by observations of sex-specific phenotypes in genetic deletion models or in patients with specific mutations following infections. For example, the X-linked gene *Ddx3x*, an RNA helicase that impacts RNA processing and transcription and regulates type I IFN production following viral and bacterial infections[114], escapes XCI in female cells. Although male cells contain a Y-linked functional homolog (*Ddx3y*), conditional deletion of *Ddx3x* using VAV-Cre impairs the ability of male mice (female-specific deletion is embryonic lethal) to respond to *listeria monocytogenes*[115]. Consistent with these findings, female bone marrow derived macrophages (BMDMs) with homozygous *Ddx3x* deletion are unable to restrict *listeria* growth[115]. *Ddx3x* deletion in BMDMs exhibits sex-specific gene expression patterns, and female BMDMs lacking *Ddx3x* have greater reductions in cytokine (IL-1, IL-6, Il-12, and TNF-alpha) and chemokine expression compared to male Ddx3x mutants[115]. Additional research investigating other XCI escape genes, especially those that encode for chromatin modifying enzymes, through the use of gain and loss of function mutations in specific immune cell types will reveal other potential genetic contributors to the immune responses to pathogens that exhibit a sex bias (Table 3).

Tuberculosis exhibits a male bias in humans and mouse models, and TB is a leading cause globally of a disease caused by a bacterial pathogen (Table 3). Mutations in two X-linked genes, *CYBB* and *IKBKG (NEMO)*, increase susceptibility to mycobacterial disease. Missense mutations in *CYBB*, which encodes for the gp91 subunit of the NADPH oxidase complex, results in a hypomorphic protein that impairs respiratory burst activity in macrophages necessary for protection from mycobacteria[116]. IKBKG/NEMO is the regulatory subunit of the inhibitor of kappa B kinase (IKK) complex, which regulates canonical NF-kappa B activation of genes involved in inflammation and immunity. While *IKBKG/NEMO* mutations result in incontinentia pigmenti, ectodermal dysplasia, and various immunodeficiencies, there are some NEMO mutations that increase predisposition of male patients to mycobacterial infection through reduction of IL-12 and IFN-gamma production[117].

Despite ample evidence for sex biased responses to vaccinations, few X-linked genes that contribute to this finding have been identified. B cells from female immunized mice do express higher levels of *Tlr7*[109], which may result from increased levels of XCI escape and expression from the Xi in response to flu vaccines. *Tlr7* can recognize single-stranded viruses including SARS-CoV-2, and may contribute to Type I IFN production[118,119]. Loss of function *TLR7* mutations in human males reduce Type I IFN levels and prevent interferon-stimulated gene (ISG) induction, resulting in severe COVID-19 disease[118,120-122]. RNA vaccines for SARS-CoV-2 induce adverse which exhibit sex biases [123], as human females are more susceptible to thrombosis thrombocytopaenia syndrome (from adenoviral vectors)[124], yet young human males appear to be more susceptible to myocarditis and pericarditis from mRNA vaccines[125].

CONCLUSIONS AND PERSPECTIVES

Biological sex is an important factor for immune responses and immune health, and the importance of understanding hormonal and genetic contributions to sex differences in immunity is increasing. In 2009, about >60% of immunology-related research publications using animal models lacked information about biological sex, and over half of human immunology publications included male and female samples, yet >90% of these publications lacked sex-specific analyses[126]. Inclusion rates for both sexes in immunological research was 16% in 2009, and increased to 46% by 2019, but suggests that more work is needed to ensure that sex as a biological variable is addressed in future immunologic research. While the influence of sex hormones on sex-specific immune cell function and cytokine production following infection has been investigated for some of the pathogens in Table 3, the contribution from the X chromosome in biased immune responses is not well understood. Future experiments examining XCI escape genes in specific immune cell populations, and use of genetic gain and loss of function experiments of immunity-related X-linked genes will reveal important mechanisms of sex differences in infection susceptibility and resulting disease severity. While the sensitivity of X-linked gene dosage for some female-biased autoimmune diseases has been examined, whether X-linked gene dosage influences immune responses to pathogens is not well known. Understanding the origins of the sex biases using rodent models that recapitulate sex differences observed in clinical studies of infectious and autoimmune disease are likely to inform sex-specific treatment strategies that could improve patient outcomes.

The interplay of the sex chromosomes and how they influence sex hormones is likely to influence sex differences in immune responses and sex-biased autoimmune disease. In addition to the Y-linked *Sry* gene, which functions in primary sex determination and the formation of the male gonads responsible for testosterone production, the influence of other X- and Y-linked genes on sex hormones in the context of sex-biased immune responses has not been carefully investigated. Given the large number of steroid receptor binding sites across the genome, including on the X chromosome, it is likely that inflammatory pathways resulting from infections and autoimmunity will promote sex hormone receptor binding to promoters of X-linked immunity-related genes, perhaps promoting increased XCI escape in female immune cells. Moreover, AR and ER expression levels change with cellular activation in immune cells[127], potentially impacting X-linked gene expression and contributing to sex-biased gene expression. Hormonally-induced expression changes of X-linked genes are likely to occur on the active X, yet it is possible that XCI escape genes on the Xi could be differentially regulated by AR and ER in the context of immune activation. Investigation of allele-specific transcriptional changes in response to cellular activation and inflammation are necessary to determine the complex interplay of sex hormones and X-linked gene expression for sex differences in immune responses. Understanding the genetic and hormonal contributions for sex differences with immune health will undoubtedly result in novel therapeutic approaches for effective precision medicine.

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REFERENCES

1. Libert C, Dejager L & Pinheiro I The X chromosome in immune functions: when a chromosome makes the difference. Nat Rev Immunol 10, 594–604 (2010). 10.1038/nri2815 [PubMed: 20651746]
2. Pasche B. et al. Sex-dependent susceptibility to Listeria monocytogenes infection is mediated by differential interleukin-10 production. Infect Immun 73, 5952–5960 (2005). 10.1128/IAI.73.9.5952-5960.2005 [PubMed: 16113316]
3. Natri H, Garcia AR, Buetow KH, Trumble BC & Wilson MA The Pregnancy Pickle: Evolved Immune Compensation Due to Pregnancy Underlies Sex Differences in Human Diseases. Trends Genet 35, 478–488 (2019). 10.1016/j.tig.2019.04.008 [PubMed: 31200807]
4. Patin E. et al. Natural variation in the parameters of innate immune cells is preferentially driven by genetic factors. Nat Immunol 19, 302–314 (2018). 10.1038/s41590-018-0049-7 [PubMed: 29476184]
5. Clave E. et al. Human thymopoiesis is influenced by a common genetic variant within the TCRA-TCRD locus. Sci Transl Med 10 (2018). 10.1126/scitranslmed.aao2966
6. Bongen E. et al. Sex Differences in the Blood Transcriptome Identify Robust Changes in Immune Cell Proportions with Aging and Influenza Infection. Cell Rep 29, 1961–1973 e1964 (2019). 10.1016/j.celrep.2019.10.019 [PubMed: 31722210]
7. Abdullah M. et al. Gender effect on in vitro lymphocyte subset levels of healthy individuals. Cell Immunol 272, 214–219 (2012). 10.1016/j.cellimm.2011.10.009 [PubMed: 22078320]
8. Melzer S. et al. Reference intervals for leukocyte subsets in adults: Results from a population-based study using 10-color flow cytometry. Cytometry B Clin Cytom 88, 270–281 (2015). 10.1002/cyto.b.21234 [PubMed: 25704947]
9. Huang Z. et al. Effects of sex and aging on the immune cell landscape as assessed by single-cell transcriptomic analysis. Proc Natl Acad Sci U S A 118 (2021). 10.1073/pnas.2023216118
10. Wikby A, Mansson IA, Johansson B, Strindhall J & Nilsson SE The immune risk profile is associated with age and gender: findings from three Swedish population studies of individuals 20-100 years of age. Biogerontology 9, 299–308 (2008). 10.1007/s10522-008-9138-6 [PubMed: 18369735]
11. Carr EJ et al. The cellular composition of the human immune system is shaped by age and cohabitation. Nat Immunol 17, 461–468 (2016). 10.1038/ni.3371 [PubMed: 26878114]
12. Khan SR et al. Determinants of Serum Immunoglobulin Levels: A Systematic Review and Meta-Analysis. Front Immunol 12, 664526 (2021). 10.3389/fimmu.2021.664526 [PubMed: 33897714]
13. Hensel JA, Khattar V, Ashton R & Ponnazhagan S Characterization of immune cell subtypes in three commonly used mouse strains reveals gender and strain-specific variations. Lab Invest 99, 93–106 (2019). 10.1038/s41374-018-0137-1 [PubMed: 30353130]
14. Breznik JA, Schulz C, Ma J, Sloboda DM & Bowdish DME Biological sex, not reproductive cycle, influences peripheral blood immune cell prevalence in mice. J Physiol 599, 2169–2195 (2021). 10.1113/JP280637 [PubMed: 33458827]
15. Scotland RS, Stables MJ, Madalli S, Watson P & Gilroy DW Sex differences in resident immune cell phenotype underlie more efficient acute inflammatory responses in female mice. Blood 118, 5918–5927 (2011). 10.1182/blood-2011-03-340281 [PubMed: 21911834]

16. Cheng MI et al. The X-linked epigenetic regulator UTX controls NK cell-intrinsic sex differences. Nat Immunol 24, 780–791 (2023). 10.1038/s41590-023-01463-8 [PubMed: 36928413]
17. Schmiedel BJ et al. Impact of Genetic Polymorphisms on Human Immune Cell Gene Expression. Cell 175, 1701–1715 e1716 (2018). 10.1016/j.cell.2018.10.022 [PubMed: 30449622]
18. Pauklin S, Sernandez IV, Bachmann G, Ramiro AR & Petersen-Mahrt SK Estrogen directly activates AID transcription and function. J Exp Med 206, 99–111 (2009). 10.1084/jem.20080521 [PubMed: 19139166]
19. Young NA et al. Estrogen modulation of endosome-associated toll-like receptor 8: an IFNalpha-independent mechanism of sex-bias in systemic lupus erythematosus. Clin Immunol 151, 66–77 (2014). 10.1016/j.clim.2014.01.006 [PubMed: 24525049]
20. Lee J. et al. Oestrogen up-regulates interleukin-21 production by CD4(+) T lymphocytes in patients with systemic lupus erythematosus. Immunology 142, 573–580 (2014). 10.1111/imm.12263 [PubMed: 24495300]
21. Lee S. et al. Interleukin-23 drives expansion of Thelper 17 cells through epigenetic regulation by signal transducer and activators of transcription 3 in lupus patients. Rheumatology (Oxford) 59, 3058–3069 (2020). 10.1093/rheumatology/keaa176 [PubMed: 32375179]
22. Berghofer B. et al. TLR7 ligands induce higher IFN-alpha production in females. J Immunol 177, 2088–2096 (2006). [PubMed: 16887967]
23. Meier A. et al. Sex differences in the Toll-like receptor-mediated response of plasmacytoid dendritic cells to HIV-1. Nat Med 15, 955–959 (2009). 10.1038/nm.2004 [PubMed: 19597505]
24. Seillet C. et al. The TLR-mediated response of plasmacytoid dendritic cells is positively regulated by estradiol in vivo through cell-intrinsic estrogen receptor alpha signaling. Blood 119, 454–464 (2012). 10.1182/blood-2011-08-371831 [PubMed: 22096248]
25. Regis E. et al. Sex differences in innate anti-viral immune responses to respiratory viruses and in their clinical outcomes in a birth cohort study. Sci Rep 11, 23741 (2021). 10.1038/s41598-021-03044-x [PubMed: 34887467]
26. Congy-Jolivet N. et al. Monocytes are the main source of STING-mediated IFN-alpha production. EBioMedicine 80, 104047 (2022). 10.1016/j.ebiom.2022.104047 [PubMed: 35561451]
27. Griesbeck M. et al. Sex Differences in Plasmacytoid Dendritic Cell Levels of IRF5 Drive Higher IFN-alpha Production in Women. J Immunol 195, 5327–5336 (2015). 10.4049/jimmunol.1501684 [PubMed: 26519527]
28. Gal-Oz ST et al. ImmGen report: sexual dimorphism in the immune system transcriptome. Nat Commun 10, 4295 (2019). 10.1038/s41467-019-12348-6 [PubMed: 31541153]
29. Zeng Z. et al. Sex-hormone-driven innate antibodies protect females and infants against EPEC infection. Nat Immunol 19, 1100–1111 (2018). 10.1038/s41590-018-0211-2 [PubMed: 30250184]
30. McDonald G. et al. Female Bias in Systemic Lupus Erythematosus is Associated with the Differential Expression of X-Linked Toll-Like Receptor 8. Front Immunol 6, 457 (2015). 10.3389/fimmu.2015.00457 [PubMed: 26441962]
31. Souyris M. et al. TLR7 escapes X chromosome inactivation in immune cells. Sci Immunol 3 (2018). 10.1126/sciimmunol.aap8855
32. Klein SL & Flanagan KL Sex differences in immune responses. Nat Rev Immunol 16, 626–638 (2016). 10.1038/nri.2016.90 [PubMed: 27546235]
33. Aomatsu M, Kato T, Kasahara E & Kitagawa S Gender difference in tumor necrosis factor-alpha production in human neutrophils stimulated by lipopolysaccharide and interferon-gamma. Biochem Biophys Res Commun 441, 220–225 (2013). 10.1016/j.bbrc.2013.10.042 [PubMed: 24140406]
34. Ho CH et al. Testosterone suppresses uropathogenic Escherichia coli invasion and colonization within prostate cells and inhibits inflammatory responses through JAK/STAT-1 signaling pathway. PLoS One 12, e0180244 (2017). 10.1371/journal.pone.0180244 [PubMed: 28665978]
35. Fish EN The X-files in immunity: sex-based differences predispose immune responses. Nat Rev Immunol 8, 737–744 (2008). 10.1038/nri2394 [PubMed: 18728636]
36. Liva SM & Voskuhl RR Testosterone acts directly on CD4+ T lymphocytes to increase IL-10 production. J Immunol 167, 2060–2067 (2001). 10.4049/jimmunol.167.4.2060 [PubMed: 11489988]

37. Dragin N. et al. Estrogen-mediated downregulation of AIRE influences sexual dimorphism in autoimmune diseases. J Clin Invest 126, 1525–1537 (2016). 10.1172/JCI81894 [PubMed: 26999605]
38. Zhu ML et al. Sex bias in CNS autoimmune disease mediated by androgen control of autoimmune regulator. Nat Commun 7, 11350 (2016). 10.1038/ncomms11350 [PubMed: 27072778]
39. Gandhi VD et al. Androgen receptor signaling promotes Treg suppressive function during allergic airway inflammation. J Clin Invest 132 (2022). 10.1172/JCI153397
40. Walecki M. et al. Androgen receptor modulates Foxp3 expression in CD4+CD25+Foxp3+ regulatory T-cells. Mol Biol Cell 26, 2845–2857 (2015). 10.1091/mbc.E14-08-1323 [PubMed: 26063731]
41. Trigunaite A, Dimo J & Jorgensen TN Suppressive effects of androgens on the immune system. Cell Immunol 294, 87–94 (2015). 10.1016/j.cellimm.2015.02.004 [PubMed: 25708485]
42. Wilhelmson AS et al. Testosterone is an endogenous regulator of BAFF and splenic B cell number. Nat Commun 9, 2067 (2018). 10.1038/s41467-018-04408-0 [PubMed: 29802242]
43. Zhao R. et al. A GPR174-CCL21 module imparts sexual dimorphism to humoral immunity. Nature 577, 416–420 (2020). 10.1038/s41586-019-1873-0 [PubMed: 31875850]
44. Kissick HT et al. Androgens alter T-cell immunity by inhibiting T-helper 1 differentiation. Proc Natl Acad Sci U S A 111, 9887–9892 (2014). 10.1073/pnas.1402468111 [PubMed: 24958858]
45. Marahrens Y, Panning B, Dausman J, Strauss W & Jaenisch R Xist-deficient mice are defective in dosage compensation but not spermatogenesis. Genes Dev 11, 156–166 (1997). [PubMed: 9009199]
46. Anguera MC et al. Molecular signatures of human induced pluripotent stem cells highlight sex differences and cancer genes. Cell Stem Cell 11, 75–90 (2012). https://doi.org:S1934-5909(12)00125-7 [pii] 10.1016/j.stem.2012.03.008 [PubMed: 22770242]
47. Adrianse RL et al. Perturbed maintenance of transcriptional repression on the inactive X-chromosome in the mouse brain after Xist deletion. Epigenetics Chromatin 11, 50 (2018). 10.1186/s13072-018-0219-8 [PubMed: 30170615]
48. Yang L, Yildirim E, Kirby JE, Press W & Lee JT Widespread organ tolerance to Xist loss and X reactivation except under chronic stress in the gut. Proc Natl Acad Sci U S A 117, 4262–4272 (2020). 10.1073/pnas.1917203117 [PubMed: 32041873]
49. Yildirim E. et al. Xist RNA is a potent suppressor of hematologic cancer in mice. Cell 152, 727–742 (2013). 10.1016/j.cell.2013.01.034 [PubMed: 23415223]
50. Boggs BA et al. Differentially methylated forms of histone H3 show unique association patterns with inactive human X chromosomes. Nat Genet 30, 73–76 (2002). 10.1038/ng787ng787 [pii] [PubMed: 11740495]
51. Plath K. et al. Role of histone H3 lysine 27 methylation in X inactivation. Science 300, 131–135 (2003). 10.1126/science.10842741084274 [pii] [PubMed: 12649488]
52. Costanzi C, Stein P, Worrad DM, Schultz RM & Pehrson JR Histone macroH2A1 is concentrated in the inactive X chromosome of female preimplantation mouse embryos. Development 127, 2283–2289 (2000). [PubMed: 10804171]
53. Clemson CM, McNeil JA, Willard HF & Lawrence JB XIST RNA paints the inactive X chromosome at interphase: evidence for a novel RNA involved in nuclear/chromosome structure. J Cell Biol 132, 259–275 (1996). [PubMed: 8636206]
54. Wang J et al. Unusual maintenance of X chromosome inactivation predisposes female lymphocytes for increased expression from the inactive X. Proceedings of the National Academy of Sciences 113, E2029–E2038 (2016). 10.1073/pnas.1520113113
55. Syrett CM et al. Loss of Xist RNA from the inactive X during B cell development is restored in a dynamic YY1-dependent two-step process in activated B cells. PLOS Genetics 13, e1007050–e1007050 (2017). 10.1371/journal.pgen.1007050 [PubMed: 28991910]
56. Syrett CM et al. Altered X-chromosome inactivation in T cells may promote sex-biased autoimmune diseases. JCI Insight 4 (2019). 10.1172/jci.insight.126751
57. Syrett CM et al. Diversity of epigenetic features of the inactive X-chromosome in NK cells, dendritic cells, and macrophages. Frontiers in Immunology (2019). 10.3389/fimmu.2018.03087

58. Syrett CM et al. Loss of Xist RNA from the inactive X during B cell development is restored in a dynamic YY1-dependent two-step process in activated B cells. PLoS Genet 13, e1007050 (2017). 10.1371/journal.pgen.1007050 [PubMed: 28991910]
59. Pyfrom S. et al. The dynamic epigenetic regulation of the inactive X chromosome in healthy human B cells is dysregulated in lupus patients. Proc Natl Acad Sci U S A 118 (2021). 10.1073/pnas.2024624118
60. Syrett CM et al. Diversity of Epigenetic Features of the Inactive X-Chromosome in NK Cells, Dendritic Cells, and Macrophages. Front Immunol 9, 3087 (2018). 10.3389/fimmu.2018.03087 [PubMed: 30671059]
61. Ramos-Casals M et al. Google-driven search for big data in autoimmune geoepidemiology: analysis of 394,827 patients with systemic autoimmune diseases. Autoimmun Rev 14, 670–679 (2015). 10.1016/j.autrev.2015.03.008 [PubMed: 25842074]
62. Jacobson DL, Gange SJ, Rose NR & Graham NM Epidemiology and estimated population burden of selected autoimmune diseases in the United States. Clin Immunol Immunopathol 84, 223–243 (1997). 10.1006/clin.1997.4412 [PubMed: 9281381]
63. Beeson PB Age and sex associations of 40 autoimmune diseases. Am J Med 96, 457–462 (1994). 10.1016/0002-9343(94)90173-2 [PubMed: 8192178]
64. Syrett CM & Anguera MC When the balance is broken: X-linked gene dosage from two X chromosomes and female-biased autoimmunity. J Leukoc Biol 106, 919–932 (2019). 10.1002/JLB.6RI0319-094R [PubMed: 31125996]
65. Ngo ST, Steyn FJ & McCombe PA Gender differences in autoimmune disease. Front Neuroendocrinol 35, 347–369 (2014). 10.1016/j.yfrne.2014.04.004 [PubMed: 24793874]
66. Runmarker B & Andersen O Prognostic factors in a multiple sclerosis incidence cohort with twenty-five years of follow-up. Brain 116 (Pt 1), 117–134 (1993). 10.1093/brain/116.1.117 [PubMed: 8453453]
67. Peoples C, Medsger TA Jr., Lucas M, Rosario BL & Feghali-Bostwick CA Gender differences in systemic sclerosis: relationship to clinical features, serologic status and outcomes. J Scleroderma Relat Disord 1, 177–240 (2016). 10.5301/jsrd.5000209
68. Crosslin KL & Wiginton KL Sex differences in disease severity among patients with systemic lupus erythematosus. Gend Med 8, 365–371 (2011). 10.1016/j.genm.2011.10.003 [PubMed: 22153881]
69. Courvoisier N. et al. Prognostic factors of 10-year radiographic outcome in early rheumatoid arthritis: a prospective study. Arthritis Res Ther 10, R106 (2008). 10.1186/ar2498 [PubMed: 18771585]
70. Sierra I. et al. Unusual X chromosome inactivation maintenance in female alveolar type 2 cells is correlated with increased numbers of X-linked escape genes and sex-biased gene expression. Stem Cell Reports (2022). 10.1016/j.stemcr.2022.12.005
71. Tukiainen T. et al. Landscape of X chromosome inactivation across human tissues. Nature 550, 244–248 (2017). 10.1038/nature24265 [PubMed: 29022598]
72. Jiwrajka N. et al. Impaired dynamic X-chromosome inactivation maintenance in T cells is a feature of spontaneous murine SLE that is exacerbated in female-biased models. J Autoimmun 139, 103084 (2023). 10.1016/j.jaut.2023.103084 [PubMed: 37399593]
73. Syrett CM, Sierra I, Beethem ZT, Dubin AH & Anguera MC Loss of epigenetic modifications on the inactive X chromosome and sex-biased gene expression profiles in B cells from NZB/W F1 mice with lupus-like disease. J Autoimmun 107, 102357 (2020). 10.1016/j.jaut.2019.102357 [PubMed: 31780316]
74. Scofield RH et al. Klinefelter's syndrome (47,XXY) in male systemic lupus erythematosus patients: Support for the notion of a gene-dose effect from the X chromosome. Arthritis and Rheumatism 58, 2511–2517 (2008). 10.1002/art.23701 [PubMed: 18668569]
75. Scofield RH et al. 47XXY and 47XXX in Scleroderma and Myositis. ACR Open Rheumatology (2022). 10.1002/acr2.11413
76. De Vries GJ et al. A Model System for Study of Sex Chromosome Effects on Sexually Dimorphic Neural and Behavioral Traits. The Journal of Neuroscience 22, 9005–9014 (2002). 10.1523/jneurosci.22-20-09005.2002 [PubMed: 12388607]

77. Smith-Bouvier DL et al. A role for sex chromosome complement in the female bias in autoimmune disease. Journal of Experimental Medicine 205, 1099–1108 (2008). 10.1084/jem.20070850 [PubMed: 18443225]

78. David A. et al. Intrinsic autoimmune capacities of hematopoietic cells from female New Zealand hybrid mice. Genes Immun 15, 153–161 (2014). 10.1038/gene.2014.2 [PubMed: 24477163]

79. Geha RS et al. Primary immunodeficiency diseases: an update from the International Union of Immunological Societies Primary Immunodeficiency Diseases Classification Committee. J Allergy Clin Immunol 120, 776–794 (2007). 10.1016/j.jaci.2007.08.053 [PubMed: 17952897]

80. Desai-Mehta A, Lu L, Ramsey-Goldman R & Datta SK Hyperexpression of CD40 ligand by B and T cells in human lupus and its role in pathogenic autoantibody production. J Clin Invest 97, 2063–2073 (1996). 10.1172/JCI118643 [PubMed: 8621796]

81. Hewagama A. et al. Overexpression of X-linked genes in T cells from women with lupus. J Autoimmun 41, 60–71 (2013). 10.1016/j.jaut.2012.12.006 [PubMed: 23434382]

82. Lian X. et al. DNA demethylation of CD40l in CD4+ T cells from women with systemic sclerosis: a possible explanation for female susceptibility. Arthritis Rheum 64, 2338–2345 (2012). 10.1002/art.34376 [PubMed: 22231486]

83. Perez-Melgosa M, Hollenbaugh D & Wilson CB Cutting edge: CD40 ligand is a limiting factor in the humoral response to T cell-dependent antigens. J Immunol 163, 1123–1127 (1999). [PubMed: 10415005]

84. Enghard P. et al. CXCR3+CD4+ T cells are enriched in inflamed kidneys and urine and provide a new biomarker for acute nephritis flares in systemic lupus erythematosus patients. Arthritis Rheum 60, 199–206 (2009). 10.1002/art.24136 [PubMed: 19116922]

85. Ogawa N, Ping L, Zhenjun L, Takada Y & Sugai S Involvement of the interferon-gamma-induced T cell-attracting chemokines, interferon-gamma-inducible 10-kd protein (CXCL10) and monokine induced by interferon-gamma (CXCL9), in the salivary gland lesions of patients with Sjogren's syndrome. Arthritis Rheum 46, 2730–2741 (2002). 10.1002/art.10577 [PubMed: 12384933]

86. Kong W. et al. Increased expression of Bruton's tyrosine kinase in peripheral blood is associated with lupus nephritis. Clin Rheumatol 37, 43–49 (2018). 10.1007/s10067-017-3717-3 [PubMed: 28612243]

87. Kil LP et al. Btk levels set the threshold for B-cell activation and negative selection of autoreactive B cells in mice. Blood 119, 3744–3756 (2012). 10.1182/blood-2011-12-397919 [PubMed: 22383797]

88. Katewa A. et al. Btk-specific inhibition blocks pathogenic plasma cell signatures and myeloid cell-associated damage in IFNalpha-driven lupus nephritis. JCI Insight 2, e90111 (2017). 10.1172/jci.insight.90111 [PubMed: 28405610]

89. Valencia X & Lipsky PE CD4+CD25+FoxP3+ regulatory T cells in autoimmune diseases. Nat Clin Pract Rheumatol 3, 619–626 (2007). 10.1038/ncprheum0624 [PubMed: 17968332]

90. Wang YY et al. DNA hypermethylation of the forkhead box protein 3 (FOXP3) promoter in CD4+ T cells of patients with systemic sclerosis. Br J Dermatol 171, 39–47 (2014). 10.1111/bjd.12913 [PubMed: 24641670]

91. Bonelli M, von Dalwigk K, Savitskaya A, Smolen JS & Scheinecker C Foxp3 expression in CD4+ T cells of patients with systemic lupus erythematosus: a comparative phenotypic analysis. Ann Rheum Dis 67, 664–671 (2008). 10.1136/ard.2007.074690 [PubMed: 17728327]

92. MacDonald KG et al. Regulatory T cells produce profibrotic cytokines in the skin of patients with systemic sclerosis. J Allergy Clin Immunol 135, 946–955 e949 (2015). 10.1016/j.jaci.2014.12.1932 [PubMed: 25678090]

93. Yang C, Huang XR, Fung E, Liu HF & Lan HY The Regulatory T-cell Transcription Factor Foxp3 Protects against Crescentic Glomerulonephritis. Sci Rep 7, 1481 (2017). 10.1038/s41598-017-01515-8 [PubMed: 28469165]

94. Garcia-Ortiz H et al. Association of TLR7 copy number variation with susceptibility to childhood-onset systemic lupus erythematosus in Mexican population. Ann Rheum Dis 69, 1861–1865 (2010). 10.1136/ard.2009.124313 [PubMed: 20525845]

95. Brown GJ et al. TLR7 gain-of-function genetic variation causes human lupus. Nature 605, 349–356 (2022). 10.1038/s41586-022-04642-z [PubMed: 35477763]

96. Deane JA et al. Control of toll-like receptor 7 expression is essential to restrict autoimmunity and dendritic cell proliferation. Immunity 27, 801–810 (2007). 10.1016/j.immuni.2007.09.009 [PubMed: 17997333]

97. Pisitkun P. et al. Autoreactive B cell responses to RNA-related antigens due to TLR7 gene duplication. Science 312, 1669–1672 (2006). 10.1126/science.1124978 [PubMed: 16709748]

98. Harris VM et al. Characterization of cxorf21 Provides Molecular Insight Into Female-Bias Immune Response in SLE Pathogenesis. Front Immunol 10, 2160 (2019). 10.3389/fimmu.2019.02160 [PubMed: 31695690]

99. Kelvin EA et al. The association of host age and gender with inflammation around neurocysticercosis cysts. Annals of tropical medicine and parasitology. 103, 487–499 (2009). 10.1179/000349809x12459740922291 [PubMed: 19695154]

100. Wright JE, Werkman M, Dunn JC & Anderson RM Current epidemiological evidence for predisposition to high or low intensity human helminth infection: a systematic review. Parasites & Vectors 11 (2018). 10.1186/s13071-018-2656-4

101. Tchuem Tchuenté LA, Behnke JM, Gilbert FS, Southgate VR & Vercruysse J Polyparasitism with Schistosoma haematobium and soil-transmitted helminth infections among school children in Loum, Cameroon. Tropical medicine & international health : TM & IH. 8, 975–986 (2003). 10.1046/j.1360-2276.2003.01120.x [PubMed: 14629763]

102. Nicolosi A. et al. The Efficiency of Male-to Female and Female-to-Male Sexual Transmission of the Human Immunodeficiency Virus. Epidemiology. 5, 570–575 (1994). 10.1097/00001648-199411000-00003 [PubMed: 7841237]

103. WHO Ebola Response Team, J. A-A, , Archchun Ariyarajah, Isobel M. Blake, Anne Cori, Christl A. Donnelly, Ilaria Dorigatti, Christopher Dye, Tim Eckmanns, Neil M. Ferguson, Christophe Fraser, Tini Garske, Wes Hinsley, Thibaut Jombart, Harriet L. Mills, Gemma Nedjati-Gilani, Emily Newton, Pierre Nouvellet, Devin Perkins, Steven Riley, Dirk Schumacher, Anita Shah, Lisa J. Thomas, Maria D. Van Kerkhove. Ebola Virus Disease among Male and Female Persons in West Africa. New England Journal of Medicine 374, 96–98 (2016). 10.1056/nejmc1510305 [PubMed: 26736011]

104. Hertz D & Schneider B Sex differences in tuberculosis. Seminars in Immunopathology 41, 225–237 (2019). 10.1007/s00281-018-0725-6 [PubMed: 30361803]

105. Shaheen AAM, Somayaji R, Myers R & Mody CH Epidemiology and trends of cryptococcosis in the United States from 2000 to 2007: A population-based study. International Journal of STD & AIDS 29, 453–460 (2018). 10.1177/0956462417732649 [PubMed: 28971712]

106. Gemmati D. et al. COVID-19 and Individual Genetic Susceptibility/Receptivity: Role of ACE1/ACE2 Genes, Immunity, Inflammation and Coagulation. Might the Double X-Chromosome in Females Be Protective against SARS-CoV-2 Compared to the Single X-Chromosome in Males? International Journal of Molecular Sciences 21, 3474 (2020). 10.3390/ijms21103474 [PubMed: 32423094]

107. Devaux CA, Rolain J-M & Raoult D ACE2 receptor polymorphism: Susceptibility to SARS-CoV-2, hypertension, multi-organ failure, and COVID-19 disease outcome. Journal of microbiology, immunology and infection = Wei mian yu gan ran za zhi. 53, 425–435 (2020). 10.1016/j.jmii.2020.04.015 [PubMed: 32414646]

108. Klein SL, Marriott I & Fish EN Sex-based differences in immune function and responses to vaccination. Trans R Soc Trop Med Hyg 109, 9–15 (2015). 10.1093/trstmh/tru167 [PubMed: 25573105]

109. Fink AL, Engle K, Ursin RL, Tang WY & Klein SL Biological sex affects vaccine efficacy and protection against influenza in mice. Proc Natl Acad Sci U S A 115, 12477–12482 (2018). 10.1073/pnas.1805268115 [PubMed: 30455317]

110. Channappanavar R. et al. Sex-Based Differences in Susceptibility to Severe Acute Respiratory Syndrome Coronavirus Infection. The Journal of Immunology 198, 4046 (2017). 10.4049/jimmunol.1601896 [PubMed: 28373583]

111. Stelzig KE et al. Estrogen regulates the expression of SARS-CoV-2 receptor ACE2 in differentiated airway epithelial cells. American Journal of Physiology-Lung Cellular and Molecular Physiology 318, L1280–L1281 (2020). 10.1152/ajplung.00153.2020 [PubMed: 32432918]

112. Sierra I. et al. Unusual X chromosome inactivation maintenance in female alveolar type 2 cells is correlated with increased numbers of X-linked escape genes and sex-biased gene expression. Stem Cell Reports 18, 489–502 (2023). 10.1016/j.stemcr.2022.12.005 [PubMed: 36638790]
113. Oghumu S. et al. Cutting Edge: CXCR3 Escapes X Chromosome Inactivation in T Cells during Infection: Potential Implications for Sex Differences in Immune Responses. J Immunol 203, 789–794 (2019). 10.4049/jimmunol.1800931 [PubMed: 31253729]
114. Soulat D. et al. The DEAD-box helicase DDX3X is a critical component of the TANK-binding kinase 1-dependent innate immune response. EMBO J 27, 2135–2146 (2008). 10.1038/emboj.2008.126 [PubMed: 18583960]
115. Szappanos D. et al. The RNA helicase DDX3X is an essential mediator of innate antimicrobial immunity. PLoS Pathog 14, e1007397 (2018). 10.1371/journal.ppat.1007397 [PubMed: 30475900]
116. Bustamante J. et al. Germline CYBB mutations that selectively affect macrophages in kindreds with X-linked predisposition to tuberculous mycobacterial disease. Nat Immunol 12, 213–221 (2011). 10.1038/ni.1992 [PubMed: 21278736]
117. Filipe-Santos O. et al. Inborn errors of IL-12/23- and IFN-gamma-mediated immunity: molecular, cellular, and clinical features. Semin Immunol 18, 347–361 (2006). 10.1016/j.smim.2006.07.010 [PubMed: 16997570]
118. Asano T. et al. X-linked recessive TLR7 deficiency in ~1% of men under 60 years old with life-threatening COVID-19. Sci Immunol 6 (2021). 10.1126/sciimmunol.abl4348
119. Onodi F. et al. SARS-CoV-2 induces human plasmacytoid predendritic cell diversification via UNC93B and IRAK4. J Exp Med 218 (2021). 10.1084/jem.20201387
120. Fallerini C. et al. Association of Toll-like receptor 7 variants with life-threatening COVID-19 disease in males: findings from a nested case-control study. Elife 10 (2021). 10.7554/eLife.67569
121. Solanich X. et al. Genetic Screening for TLR7 Variants in Young and Previously Healthy Men With Severe COVID-19. Front Immunol 12, 719115 (2021). 10.3389/fimmu.2021.719115 [PubMed: 34367187]
122. van der Made CI et al. Presence of Genetic Variants Among Young Men With Severe COVID-19. JAMA 324, 663–673 (2020). 10.1001/jama.2020.13719 [PubMed: 32706371]
123. Green MS et al. Gender Differences in Adverse Events Following the Pfizer-BioNTech COVID-19 Vaccine. Vaccines (Basel) 10 (2022). 10.3390/vaccines10020233
124. Tsilingiris D, Vallianou NG, Karampela I & Dalamaga M Vaccine induced thrombotic thrombocytopenia: The shady chapter of a success story. Metabol Open 11, 100101 (2021). 10.1016/j.metop.2021.100101 [PubMed: 34179744]
125. Ling RR et al. Myopericarditis following COVID-19 vaccination and non-COVID-19 vaccination: a systematic review and meta-analysis. Lancet Respir Med 10, 679–688 (2022). 10.1016/S2213-2600(22)00059-5 [PubMed: 35421376]
126. Beery AK & Zucker I Sex bias in neuroscience and biomedical research. Neurosci Biobehav Rev 35, 565–572 (2011). 10.1016/j.neubiorev.2010.07.002 [PubMed: 20620164]
127. Guan X. et al. Androgen receptor activity in T cells limits checkpoint blockade efficacy. Nature 606, 791–796 (2022). 10.1038/s41586-022-04522-6 [PubMed: 35322234]
128. Brown MA & Su MA An Inconvenient Variable: Sex Hormones and Their Impact on T Cell Responses. J Immunol 202, 1927–1933 (2019). 10.4049/jimmunol.1801403 [PubMed: 30885988]
129. Singh RP, Hahn BH & Bischoff DS Interferon Genes Are Influenced by 17beta-Estradiol in SLE. Front Immunol 12, 725325 (2021). 10.3389/fimmu.2021.725325 [PubMed: 34733276]
130. Straub RH The complex role of estrogens in inflammation. Endocr Rev 28, 521–574 (2007). 10.1210/er.2007-0001 [PubMed: 17640948]
131. Mohammad I. et al. Estrogen receptor alpha contributes to T cell-mediated autoimmune inflammation by promoting T cell activation and proliferation. Sci Signal 11 (2018). 10.1126/scisignal.aap9415
132. Kim DH et al. Estrogen receptor alpha in T cells suppresses follicular helper T cell responses and prevents autoimmunity. Exp Mol Med 51, 1–9 (2019). 10.1038/s12276-019-0237-z

133. Goodman WA et al. Impaired estrogen signaling underlies regulatory T cell loss-of-function in the chronically inflamed intestine. Proc Natl Acad Sci U S A 117, 17166–17176 (2020). 10.1073/pnas.2002266117 [PubMed: 32632016]
134. Aggelakopoulou M, Kourepini E, Paschalidis N & Panoutsakopoulou V ERbeta in CD4+ T Cells Is Crucial for Ligand-Mediated Suppression of Central Nervous System Autoimmunity. J Immunol 196, 4947–4956 (2016). 10.4049/jimmunol.1600246 [PubMed: 27183630]
135. Garnier L. et al. Estrogen Signaling in Bystander Foxp3(neg) CD4(+) T Cells Suppresses Cognate Th17 Differentiation in Trans and Protects from Central Nervous System Autoimmunity. J Immunol 201, 3218–3228 (2018). 10.4049/jimmunol.1800417 [PubMed: 30355786]
136. Xiong Y. et al. Estradiol resolves pneumonia via ERbeta in regulatory T cells. JCI Insight 6 (2021). 10.1172/jci.insight.133251
137. Tabor DE & Gould KA Estrogen receptor alpha promotes lupus in (NZBxNZW)F1 mice in a B cell intrinsic manner. Clin Immunol 174, 41–52 (2017). 10.1016/j.clim.2016.10.011 [PubMed: 27989899]
138. Carlsten H. et al. Estrogen accelerates immune complex glomerulonephritis but ameliorates T cell-mediated vasculitis and sialadenitis in autoimmune MRL lpr/lpr mice. Cell Immunol 144, 190–202 (1992). 10.1016/0008-8749(92)90236-i [PubMed: 1394437]
139. Herrmann M, Scholmerich J & Straub RH Influence of cytokines and growth factors on distinct steroidogenic enzymes in vitro: a short tabular data collection. Ann N Y Acad Sci 966, 166–186 (2002). 10.1111/j.1749-6632.2002.tb04213.x [PubMed: 12114270]
140. de Man YA, Dolhain RJ, van de Geijn FE, Willemsen SP & Hazes JM Disease activity of rheumatoid arthritis during pregnancy: results from a nationwide prospective study. Arthritis Rheum 59, 1241–1248 (2008). 10.1002/art.24003 [PubMed: 18759316]
141. Baer AN, Witter FR & Petri M Lupus and pregnancy. Obstet Gynecol Surv 66, 639–653 (2011). 10.1097/OGX.0b013e318239e1ee [PubMed: 22112525]
142. Cutolo M & Straub RH Sex steroids and autoimmune rheumatic diseases: state of the art. Nat Rev Rheumatol 16, 628–644 (2020). 10.1038/s41584-020-0503-4 [PubMed: 33009519]
143. Gubbels Bupp MR & Jorgensen TN Androgen-Induced Immunosuppression. Front Immunol 9, 794 (2018). 10.3389/fimmu.2018.00794 [PubMed: 29755457]
144. Traish A, Bolanos J, Nair S, Saad F & Morgentaler A Do Androgens Modulate the Pathophysiological Pathways of Inflammation? Appraising the Contemporary Evidence. J Clin Med 7 (2018). 10.3390/jcm7120549
145. Lyon MF Gene Action in the X-chromosome of the Mouse (Mus musculus L.). Nature 190, 372–373 (1961). 10.1038/190372a0 [PubMed: 13764598]
146. Brown CJ et al. A gene from the region of the human X inactivation centre is expressed exclusively from the inactive X chromosome. Nature 349, 38–44 (1991). 10.1038/349038a0 [PubMed: 1985261]
147. Brown CJ et al. The human XIST gene: Analysis of a 17 kb inactive X-specific RNA that contains conserved repeats and is highly localized within the nucleus. Cell 71, 527–542 (1992). 10.1016/0092-8674(92)90520-M [PubMed: 1423611]
148. Colognori D, Sunwoo H, Kriz AJ, Wang CY & Lee JT Xist Deletional Analysis Reveals an Interdependency between Xist RNA and Polycomb Complexes for Spreading along the Inactive X. Molecular Cell 74, 101–117.e110 (2019). 10.1016/j.molcel.2019.01.015 [PubMed: 30827740]
149. Simon MD et al. High-resolution Xist binding maps reveal two-step spreading during X-chromosome inactivation. Nature 504, 465–469 (2013). 10.1038/nature12719 [PubMed: 24162848]
150. Żylicz JJ et al. The Implication of Early Chromatin Changes in X Chromosome Inactivation. Cell 176, 182–197.e123 (2019). 10.1016/j.cell.2018.11.041 [PubMed: 30595450]
151. Engreitz JM et al. The Xist lncRNA exploits three-dimensional genome architecture to spread across the X chromosome. Science 341, 1–9 (2013). 10.1126/science.1237973
152. Colognori D, Sunwoo H, Kriz AJ, Wang CY & Lee JT in Molecular Cell Vol. 74 101–117.e110 (Elsevier Inc., 2019). [PubMed: 30827740]
153. Żylicz JJ et al. in Cell Vol. 176 182–197.e123 (2019). [PubMed: 30595450]

154. Simon MD et al. in Nature Vol. 504 465–469 (Nature Publishing Group, 2013). [PubMed: 24162848]
155. Costanzi C & Pehrson JR Histone macroH2A1 is concentrated in the inactive X chromosome of female mammals. Nature 393, 599–601 (1998). 10.1038/31275 [PubMed: 9634239]
156. Gendrel A-V et al. Smchd1-Dependent and -Independent Pathways Determine Developmental Dynamics of CpG Island Methylation on the Inactive X Chromosome. Developmental Cell 23, 265–279 (2012). 10.1016/j.devcel.2012.06.011 [PubMed: 22841499]
157. Lock LF, Takagi N & Martin GR Methylation of the Hprt gene on the inactive X occurs after chromosome inactivation. Cell 48, 39–46 (1987). 10.1016/0092-8674(87)90353-9 [PubMed: 3791414]
158. Norris DP, Brockdorff N & Rastan S Methylation status of CpG-rich islands on active and inactive mouse X chromosomes. Mammalian Genome 1, 78–83 (1991). 10.1007/BF02443782 [PubMed: 1799791]
159. Sharp AJ et al. DNA methylation profiles of human active and inactive X chromosomes. Genome Research 21, 1592–1600 (2011). 10.1101/gr.112680.110 [PubMed: 21862626]
160. Cotton AM et al. Landscape of DNA methylation on the X chromosome reflects CpG density, functional chromatin state and X-chromosome inactivation. Human Molecular Genetics 24, 1528–1539 (2015). 10.1093/hmg/ddu564 [PubMed: 25381334]
161. Carrel L & Willard HF X-inactivation profile reveals extensive variability in X-linked gene expression in females. Nature 434, 400–404 (2005). 10.1038/nature03479 [PubMed: 15772666]
162. Tukiainen T. et al. Landscape of X chromosome inactivation across human tissues. Nature 550, 244–248 (2017). 10.1038/nature24265 [PubMed: 29022598]
163. Berletch JB et al. Escape from X Inactivation Varies in Mouse Tissues. PLoS Genetics 11, 1–26 (2015). 10.1371/journal.pgen.1005079
164. Yang F, Babak T, Shendure J & Disteche CM Global survey of escape from X inactivation by RNA-sequencing in mouse. Genome Research 20, 614–622 (2010). 10.1101/gr.103200.109 [PubMed: 20363980]
165. Berletch JB, Yang F, Xu J, Carrel L & Disteche CM Genes that escape from X inactivation. Hum Genet 130, 237–245 (2011). 10.1007/s00439-011-1011-z [PubMed: 21614513]
166. Aguet F et al. The impact of sex on gene expression across human tissues. Science 369 (2020). 10.1126/SCIENCE.ABA3066
167. Souyris M. et al. TLR7 escapes X chromosome inactivation in immune cells. Science Immunology 3, 1–11 (2018). 10.1126/sciimmunol.aap8855
168. Zhang Y. et al. Genes that escape X-inactivation in humans have high intraspecific variability in expression, are associated with mental impairment but are not slow evolving. Mol Biol Evol 30, 2588–2601 (2013). 10.1093/molbev/mst148 [PubMed: 24023392]
169. Meester I. et al. SeXY chromosomes and the immune system: Reflections after a comparative study. Biology of Sex Differences 11, 1–13 (2020). 10.1186/s13293-019-0278-y [PubMed: 31900228]
170. Berletch JB et al. Escape from X inactivation varies in mouse tissues. PLoS Genet 11, e1005079 (2015). 10.1371/journal.pgen.1005079 [PubMed: 25785854]
171. Berletch JB et al. Identification of genes escaping X inactivation by allelic expression analysis in a novel hybrid mouse model. Data Brief 5, 761–769 (2015). 10.1016/j.dib.2015.10.033 [PubMed: 26693509]
172. Andrews BS et al. Spontaneous murine lupus-like syndromes. Clinical and immunopathological manifestations in several strains. J Exp Med 148, 1198–1215 (1978). [PubMed: 309911]
173. Subramanian S. et al. A Tlr7 translocation accelerates systemic autoimmunity in murine lupus. Proc Natl Acad Sci U S A 103, 9970–9975 (2006). 10.1073/pnas.0603912103 [PubMed: 16777955]
174. Fairhurst AM et al. Yaa autoimmune phenotypes are conferred by overexpression of TLR7. Eur J Immunol 38, 1971–1978 (2008). 10.1002/eji.200838138 [PubMed: 18521959]
175. Haywood ME et al. Identification of intervals on chromosomes 1, 3, and 13 linked to the development of lupus in BXSB mice. Arthritis Rheum 43, 349–355 (2000). 10.1002/1529-0131(200002)43:2<349::AID-ANR14>3.0.CO;2-M [PubMed: 10693874]

176. Burnet FM & Holmes MC The natural history of the NZB/NZW F1 hybrid mouse: a laboratory model of systemic lupus erythematosus. Australas Ann Med 14, 185–191 (1965). 10.1111/imj.1965.14.3.185 [PubMed: 5862644]

177. Helyer BJ & Howie JB Renal disease associated with positive lupus erythematosus tests in a cross-bred strain of mice. Nature 197, 197 (1963). 10.1038/197197a0

178. Kessler HS A laboratory model for Sjogren's syndrome. Am J Pathol 52, 671–685 (1968). [PubMed: 5642928]

179. Roubinian JR, Talal N, Greenspan JS, Goodman JR & Siiteri PK Effect of castration and sex hormone treatment on survival, anti-nucleic acid antibodies, and glomerulonephritis in NZB/NZW F1 mice. J Exp Med 147, 1568–1583 (1978). 10.1084/jem.147.6.1568 [PubMed: 308087]

180. Verheul HA, Verveld M, Hoefakker S & Schuurs AH Effects of ethinylestradiol on the course of spontaneous autoimmune disease in NZB/W and NOD mice. Immunopharmacol Immunotoxicol 17, 163–180 (1995). 10.3109/08923979509052727 [PubMed: 7759769]

181. Waters ST et al. NZM2328: a new mouse model of systemic lupus erythematosus with unique genetic susceptibility loci. Clin Immunol 100, 372–383 (2001). 10.1006/clim.2001.5079 [PubMed: 11513551]

182. Reeves WH, Lee PY, Weinstein JS, Satoh M & Lu L Induction of autoimmunity by pristane and other naturally occurring hydrocarbons. Trends Immunol 30, 455–464 (2009). 10.1016/j.it.2009.06.003 [PubMed: 19699150]

183. Satoh M. et al. Widespread susceptibility among inbred mouse strains to the induction of lupus autoantibodies by pristane. Clin Exp Immunol 121, 399–405 (2000). [PubMed: 10931159]

184. Du S. et al. XY sex chromosome complement, compared with XX, in the CNS confers greater neurodegeneration during experimental autoimmune encephalomyelitis. Proc Natl Acad Sci U S A 111, 2806–2811 (2014). 10.1073/pnas.1307091111 [PubMed: 24550311]

References

1. Rees F, Doherty M, Grainge MJ, Lanyon P & Zhang W The worldwide incidence and prevalence of systemic lupus erythematosus: a systematic review of epidemiological studies. Rheumatology (Oxford) 56, 1945–1961, doi:10.1093/rheumatology/kex260 (2017). [PubMed: 28968809]

2. Ramos-Casals M. et al. Google-driven search for big data in autoimmune geoepidemiology: analysis of 394,827 patients with systemic autoimmune diseases. Autoimmun Rev 14, 670–679, doi:10.1016/j.autrev.2015.03.008 (2015). [PubMed: 25842074]

3. Maciel G, Crowson CS, Matteson EL & Cornec D Prevalence of Primary Sjogren's Syndrome in a US Population-Based Cohort. Arthritis Care Res (Hoboken) 69, 1612–1616, doi:10.1002/acr.23173 (2017). [PubMed: 27998024]

4. Pillemer SR et al. Incidence of physician-diagnosed primary Sjogren syndrome in residents of Olmsted County, Minnesota. Mayo Clin Proc 76, 593–599, doi:10.4065/76.6.593 (2001). [PubMed: 11393497]

5. Mayes MD et al. Prevalence, incidence, survival, and disease characteristics of systemic sclerosis in a large US population. Arthritis Rheum 48, 2246–2255, doi:10.1002/art.11073 (2003). [PubMed: 12905479]

6. Hughes M. et al. Gender-related differences in systemic sclerosis. Autoimmun Rev 19, 102494, doi:10.1016/j.autrev.2020.102494 (2020). [PubMed: 32062031]

7. Meyer A. et al. Incidence and prevalence of inflammatory myopathies: a systematic review. Rheumatology (Oxford) 54, 50–63, doi:10.1093/rheumatology/keu289 (2015). [PubMed: 25065005]

8. Gabriel SE, Crowson CS & O'Fallon WM The epidemiology of rheumatoid arthritis in Rochester, Minnesota, 1955-1985. Arthritis Rheum 42, 415–420, doi:10.1002/1529-0131(199904)42:3<415::AID-ANR4>3.0.CO;2-Z (1999). [PubMed: 10088762]

9. Lawrence RC et al. Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the United States. Arthritis Rheum 41, 778–799, doi:10.1002/1529-0131(199805)41:5<778::AID-ART4>3.0.CO;2-V (1998). [PubMed: 9588729]

References

1. Zhou Y. et al. T cell CD40LG gene expression and the production of IgG by autologous B cells in systemic lupus erythematosus. Clinical Immunology 132, 362–370 (2009). 10.1016/j.clim.2009.05.011 [PubMed: 19520616]
2. Balaton BP, Cotton AM & Brown CJ Derivation of consensus inactivation status for X-linked genes from genome-wide studies. Biol Sex Differ 6, 35 (2015). 10.1186/s13293-015-0053-7 [PubMed: 26719789]
3. Lu Q. et al. in The Journal of Immunology Vol. 179 6352–6358 (2007). [PubMed: 17947713]
4. Clegg CH et al. Thymus dysfunction and chronic inflammatory disease in gp39 transgenic mice. Int Immunol 9, 1111–1122 (1997). 10.1093/intimm/9.8.1111 [PubMed: 9263008]
5. Perez-Melgosa M, Hollenbaugh D & Wilson CB Cutting edge: CD40 ligand is a limiting factor in the humoral response to T cell-dependent antigens. J Immunol 163, 1123–1127 (1999). [PubMed: 10415005]
6. Desai-Mehta A, Lu L, Ramsey-Goldman R & Datta SK Hyperexpression of CD40 ligand by B and T cells in human lupus and its role in pathogenic autoantibody production. Journal of Clinical Investigation 97, 2063–2073 (1996). 10.1172/JCI118643 [PubMed: 8621796]
7. Le Coz C. et al. CD40LG duplication-associated autoimmune disease is silenced by nonrandom X-chromosome inactivation. Journal of Allergy and Clinical Immunology 141, 2308–2311.e2307 (2018). 10.1016/j.jaci.2018.02.010 [PubMed: 29499223]
8. Groom JR & Luster AD CXCR3 in T cell function. Experimental Cell Research 317, 620–631 (2011). 10.1016/j.yexcr.2010.12.017 [PubMed: 21376175]
9. Flier J. et al. Differential expression of CXCR3 targeting chemokines CXCL10, CXCL9, and CXCL11 in different types of skin inflammation. J Pathol 194, 398–405 (2001). 10.1002/1096-9896(200108)194:4<397::aid-path899>3.0.co;2-s [PubMed: 11523046]
10. Hewagama A. et al. Overexpression of X-Linked genes in T cells from women with lupus. Journal of Autoimmunity 41, 60–71 (2013). 10.1016/j.jaut.2012.12.006 [PubMed: 23434382]
11. Oghumu S. et al. Cutting Edge: CXCR3 Escapes X Chromosome Inactivation in T Cells during Infection: Potential Implications for Sex Differences in Immune Responses. The Journal of Immunology 203, 789–794 (2019). 10.4049/jimmunol.1800931 [PubMed: 31253729]
12. Eriksson C, Eneslätt K, Ivanoff J, Rantapää-Dahlqvist S & Sundqvist KG Abnormal expression of chemokine receptors on T-cells from patients with systemic lupus erythematosus. Lupus 12, 766–774 (2003). 10.1191/0961203303lu467oa [PubMed: 14596426]
13. Hewagama A. et al. Overexpression of X-linked genes in T cells from women with lupus. J Autoimmun 41, 60–71 (2013). 10.1016/j.jaut.2012.12.006 [PubMed: 23434382]
14. Ogawa N, Ping L, Zhenjun L, Takada Y & Sugai S Involvement of the interferon-gamma-induced T cell-attracting chemokines, interferon-gamma-inducible 10-kd protein (CXCL10) and monokine induced by interferon-gamma (CXCL9), in the salivary gland lesions of patients with Sjogren's syndrome. Arthritis Rheum 46, 2730–2741 (2002). 10.1002/art.10577 [PubMed: 12384933]
15. Rankin AL et al. Selective inhibition of BTK prevents murine lupus and antibody-mediated glomerulonephritis. J Immunol 191, 4540–4550 (2013). 10.4049/jimmunol.1301553 [PubMed: 24068666]
16. Katewa A. et al. Btk-specific inhibition blocks pathogenic plasma cell signatures and myeloid cell-associated damage in IFNalpha-driven lupus nephritis. JCI Insight 2, e90111 (2017). 10.1172/jci.insight.90111 [PubMed: 28405610]
17. Kil LP et al. Btk levels set the threshold for B-cell activation and negative selection of autoreactive B cells in mice. Blood 119, 3744–3756 (2012). 10.1182/blood-2011-12-397919 [PubMed: 22383797]
18. Cornacchia E. et al. Hydralazine and procainamide inhibit T cell DNA methylation and induce autoreactivity. J Immunol 140, 2197–2200 (1988). [PubMed: 3258330]
19. Kong W. et al. Increased expression of Bruton's tyrosine kinase in peripheral blood is associated with lupus nephritis. Clin Rheumatol 37, 43–49 (2018). 10.1007/s10067-017-3717-3 [PubMed: 28612243]

20. Yang C, Huang XR, Fung E, Liu HF & Lan HY The Regulatory T-cell Transcription Factor Foxp3 Protects against Crescentic Glomerulonephritis. Sci Rep 7, 1481 (2017). 10.1038/s41598-017-01515-8 [PubMed: 28469165]
21. Bonelli M, von Dalwigk K, Savitskaya A, Smolen JS & Scheinecker C Foxp3 expression in CD4+ T cells of patients with systemic lupus erythematosus: a comparative phenotypic analysis. Ann Rheum Dis 67, 664–671 (2008). 10.1136/ard.2007.074690 [PubMed: 17728327]
22. Valencia X & Lipsky PE CD4+CD25+FoxP3+ regulatory T cells in autoimmune diseases. Nat Clin Pract Rheumatol 3, 619–626 (2007). 10.1038/ncprheum0624 [PubMed: 17968332]
23. Wang YY et al. DNA hypermethylation of the forkhead box protein 3 (FOXP3) promoter in CD4+ T cells of patients with systemic sclerosis. Br J Dermatol 171, 39–47 (2014). 10.1111/bjd.12913 [PubMed: 24641670]
24. Golks A, Tran TT, Goetschy JF & Guerini D Requirement for O-linked N-acetylglucosaminyltransferase in lymphocytes activation. EMBO J 26, 4368–4379 (2007). 10.1038/sj.emboj.7601845 [PubMed: 17882263]
25. Wu JL et al. O-GlcNAcylation is required for B cell homeostasis and antibody responses. Nat Commun 8, 1854 (2017). 10.1038/s41467-017-01677-z [PubMed: 29187734]
26. Odhams CA et al. Interferon inducible X-linked gene CXorf21 may contribute to sexual dimorphism in Systemic Lupus Erythematosus. Nature Communications 10, 1–15 (2019). 10.1038/s41467-019-10106-2
27. Heinz LX et al. TASL is the SLC15A4-associated adaptor for IRF5 activation by TLR7–9. Nature 581, 316–322 (2020). 10.1038/s41586-020-2282-0 [PubMed: 32433612]
28. Bentham J. et al. Genetic association analyses implicate aberrant regulation of innate and adaptive immunity genes in the pathogenesis of systemic lupus erythematosus. Nature Genetics 47, 1457–1464 (2015). 10.1038/ng.3434 [PubMed: 26502338]
29. Heil F. et al. Species-Specific Recognition of Single-Stranded RNA via Till-like Receptor 7 and 8. Science 303, 1526–1529 (2004). 10.1126/science.1093620 [PubMed: 14976262]
30. Diebold SS, Kaisho T, Hemmi H, Akira S & Reis E Sousa C Innate Antiviral Responses by Means of TLR7-Mediated Recognition of Single-Stranded RNA. Science 303, 1529–1531 (2004). 10.1126/science.1093616 [PubMed: 14976261]
31. Souyris M. et al. TLR7 escapes X chromosome inactivation in immune cells. Sci Immunol 3 (2018). 10.1126/sciimmunol.aap8855
32. Wang J. et al. Unusual maintenance of X chromosome inactivation predisposes female lymphocytes for increased expression from the inactive X. Proc Natl Acad Sci U S A (2016). 10.1073/pnas.1520113113
33. Abbas F. et al. HIV-1 infection enhances innate function and TLR7 expression in female plasmacytoid dendritic cells. Life Sci Alliance 5 (2022). 10.26508/lsa.202201452
34. Hagen SH et al. Heterogeneous Escape from X Chromosome Inactivation Results in Sex Differences in Type I IFN Responses at the Single Human pDC Level. Cell Rep 33, 108485 (2020). 10.1016/j.celrep.2020.108485 [PubMed: 33296655]
35. Syrett CM et al. Diversity of Epigenetic Features of the Inactive X-Chromosome in NK Cells, Dendritic Cells, and Macrophages. Front Immunol 9, 3087 (2018). 10.3389/fimmu.2018.03087 [PubMed: 30671059]
36. Deane JA et al. Control of Toll-like Receptor 7 Expression Is Essential to Restrict Autoimmunity and Dendritic Cell Proliferation. Immunity 27, 801–810 (2007). 10.1016/j.immuni.2007.09.009 [PubMed: 17997333]
37. Pisitkun P. et al. Autoreactive B cell responses to RNA-related antigens due to TLR7 gene duplication. Science 312, 1669–1672 (2006). 10.1126/science.1124978 [PubMed: 16709748]
38. Deane JA et al. Control of toll-like receptor 7 expression is essential to restrict autoimmunity and dendritic cell proliferation. Immunity 27, 801–810 (2007). 10.1016/j.immuni.2007.09.009 [PubMed: 17997333]
39. Brown GJ et al. TLR7 gain-of-function genetic variation causes human lupus. (2022). 10.1038/s41586-022-04642-z

40. Garcia-Ortiz H. et al. Association of TLR7 copy number variation with susceptibility to childhood-onset systemic lupus erythematosus in Mexican population. Annals of the Rheumatic Diseases 69, 1861–1865 (2010). 10.1136/ard.2009.124313 [PubMed: 20525845]

41. Brown GJ et al. TLR7 gain-of-function genetic variation causes human lupus. Nature 605, 349–356 (2022). 10.1038/s41586-022-04642-z [PubMed: 35477763]

References

1. Alwani M. et al. Sex-based differences in severity and mortality in COVID-19. Reviews in Medical Virology 31 (2021). 10.1002/rmv.2223

2. Haitao T. et al. COVID-19 and Sex Differences. Mayo Clinic Proceedings 95, 2189–2203 (2020). 10.1016/j.mayocp.2020.07.024 [PubMed: 33012349]

3. Jin S et al. Sex- and age-specific clinical and immunological features of coronavirus disease 2019. PLOS Pathogens 17, e1009420 (2021). 10.1371/journal.ppat.1009420 [PubMed: 33770147]

4. Gemmati D. et al. COVID-19 and Individual Genetic Susceptibility/Receptivity: Role of ACE1/ACE2 Genes, Immunity, Inflammation and Coagulation. Might the Double X-Chromosome in Females Be Protective against SARS-CoV-2 Compared to the Single X-Chromosome in Males? International Journal of Molecular Sciences 21, 3474 (2020). 10.3390/ijms21103474 [PubMed: 32423094]

5. Gebhard C, Regitz-Zagrosek V, Neuhauser HK, Morgan R & Klein SL Impact of sex and gender on COVID-19 outcomes in Europe. Biology of Sex Differences 11, 29 (2020). 10.1186/s13293-020-00304-9 [PubMed: 32450906]

6. Scully EP, Haverfield J, Ursin RL, Tannenbaum C & Klein SL Considering how biological sex impacts immune responses and COVID-19 outcomes. Nature Reviews Immunology 20, 442–447 (2020). 10.1038/s41577-020-0348-8

7. Takahashi T. et al. Sex differences in immune responses to SARS-CoV-2 that underlie disease outcomes. medRxiv, 2020.2006.2006.20123414 (2020). 10.1101/2020.06.06.20123414

8. Silva MVR et al. Men are the main COVID-19 transmitters: behavior or biology? Discover Mental Health 2 (2022). 10.1007/s44192-022-00004-3

9. O'Driscoll M. et al. Age-specific mortality and immunity patterns of SARS-CoV-2. Nature 590, 140–145 (2021). 10.1038/s41586-020-2918-0 [PubMed: 33137809]

10. Harwood R. et al. Which children and young people are at higher risk of severe disease and death after hospitalisation with SARS-CoV-2 infection in children and young people: A systematic review and individual patient meta-analysis. eClinicalMedicine 44, 101287 (2022). 10.1016/j.eclinm.2022.101287 [PubMed: 35169689]

11. Sylvester SV et al. Sex differences in sequelae from COVID-19 infection and in long COVID syndrome: a review. Current Medical Research and Opinion, 1–9 (2022). 10.1080/03007995.2022.2081454

12. Taquet M. et al. Incidence, co-occurrence, and evolution of long-COVID features: A 6-month retrospective cohort study of 273,618 survivors of COVID-19. PLoS Med 18, e1003773 (2021). 10.1371/journal.pmed.1003773 [PubMed: 34582441]

13. Channappanavar R. et al. Sex-Based Differences in Susceptibility to Severe Acute Respiratory Syndrome Coronavirus Infection. The Journal of Immunology 198, 4046 (2017). 10.4049/jimmunol.1601896 [PubMed: 28373583]

14. Sohn S-Y et al. Interferon-Lambda Intranasal Protection and Differential Sex Pathology in a Murine Model of SARS-CoV-2 Infection. mBio 12 (2021). 10.1128/mbio.02756-21

15. Francis ME et al. Sex and age bias viral burden and interferon responses during SARS-CoV-2 infection in ferrets. Scientific Reports 11 (2021). 10.1038/s41598-021-93855-9

16. Stelzig KE et al. Estrogen regulates the expression of SARS-CoV-2 receptor ACE2 in differentiated airway epithelial cells. American Journal of Physiology-Lung Cellular and Molecular Physiology 318, L1280–L1281 (2020). 10.1152/ajplung.00153.2020 [PubMed: 32432918]

17. Devaux CA, Rolain J-M & Raoult D ACE2 receptor polymorphism: Susceptibility to SARS-CoV-2, hypertension, multi-organ failure, and COVID-19 disease outcome. Journal of

microbiology, immunology and infection = Wei mian yu gan ran za zhi. 53, 425–435 (2020). 10.1016/j.jmii.2020.04.015 [PubMed: 32414646]

18. Klein SL, Pekosz A, Passaretti C, Anker M & Olukoya P. (World Health Organization, 2010).
19. Noymer A & Garenne M The 1918 influenza epidemic's effects on sex differentials in mortality in the United States. Popul Dev Rev 26, 565–581 (2000). 10.1111/j.1728-4457.2000.00565.x [PubMed: 19530360]
20. Eshima N. et al. Sex- and age-related differences in morbidity rates of 2009 pandemic influenza A H1N1 virus of swine origin in Japan. PLoS One 6, e19409 (2011). 10.1371/journal.pone.0019409 [PubMed: 21559366]
21. Jacobs JH et al. Searching for sharp drops in the incidence of pandemic A/H1N1 influenza by single year of age. PLoS One 7, e42328 (2012). 10.1371/journal.pone.0042328 [PubMed: 22876316]
22. Jensen-Fangel S. et al. Gender differences in hospitalization rates for respiratory tract infections in Danish youth. Scand J Infect Dis 36, 31–36 (2004). 10.1080/00365540310017618 [PubMed: 15000556]
23. Vom Steeg LG & Klein SL Sex and sex steroids impact influenza pathogenesis across the life course. Semin Immunopathol 41, 189–194 (2019). 10.1007/s00281-018-0718-5 [PubMed: 30298431]
24. Cervantes O. et al. Role of hormones in the pregnancy and sex-specific outcomes to infections with respiratory viruses*. Immunological Reviews 308, 123–148 (2022). 10.1111/imr.13078 [PubMed: 35373371]
25. Herold S, Becker C, Ridge KM & Budinger GR Influenza virus-induced lung injury: pathogenesis and implications for treatment. Eur Respir J 45, 1463–1478 (2015). 10.1183/09031936.00186214 [PubMed: 25792631]
26. Kumar A. et al. Critically ill patients with 2009 influenza A(H1N1) infection in Canada. JAMA 302, 1872–1879 (2009). 10.1001/jama.2009.1496 [PubMed: 19822627]
27. Vom Steeg LG et al. Age and testosterone mediate influenza pathogenesis in male mice. Am J Physiol Lung Cell Mol Physiol 311, L1234–L1244 (2016). 10.1152/ajplung.00352.2016 [PubMed: 27815260]
28. Geurs TL, Hill EB, Lippold DM & French AR Sex differences in murine susceptibility to systemic viral infections. J Autoimmun 38, J245–253 (2012). 10.1016/j.jaut.2011.12.003 [PubMed: 22209097]
29. Fink AL, Engle K, Ursin RL, Tang W-Y & Klein SL Biological sex affects vaccine efficacy and protection against influenza in mice. Proceedings of the National Academy of Sciences 115, 12477 (2018). 10.1073/pnas.1805268115
30. Lorenzo ME et al. Antibody responses and cross protection against lethal influenza A viruses differ between the sexes in C57BL/6 mice. Vaccine. 29, 9246–9255 (2011). 10.1016/j.vaccine.2011.09.110 [PubMed: 21983155]
31. Vermillion MS et al. Production of amphiregulin and recovery from influenza is greater in males than females. Biol Sex Differ 9, 24 (2018). 10.1186/s13293-018-0184-8 [PubMed: 30012205]
32. vom Steeg LG, Attreed SE, Zirkin B & Klein SL Testosterone treatment of aged male mice improves some but not all aspects of age-associated increases in influenza severity. Cellular Immunology 345, 103988 (2019). https://doi.org:10.1016/j.cellimm.2019.103988 [PubMed: 31540670]
33. Vom Steeg LG et al. Androgen receptor signaling in the lungs mitigates inflammation and improves the outcome of influenza in mice. PLoS Pathog 16, e1008506 (2020). 10.1371/journal.ppat.1008506 [PubMed: 32645119]
34. Vermillion MS, Ursin RL, Attreed SE & Klein SL Estriol Reduces Pulmonary Immune Cell Recruitment and Inflammation to Protect Female Mice From Severe Influenza. Endocrinology 159, 3306–3320 (2018). 10.1210/en.2018-00486 [PubMed: 30032246]
35. Peretz J, Pekosz A, Lane AP & Klein SL Estrogenic compounds reduce influenza A virus replication in primary human nasal epithelial cells derived from female, but not male, donors. American Journal of Physiology-Lung Cellular and Molecular Physiology 310, L415–L425 (2015). 10.1152/ajplung.00398.2015 [PubMed: 26684252]

36. Chen CM, Chen SCC, Yang HY, Yang ST & Wang CM Hospitalization and mortality due to hepatitis A in Taiwan: a 15-year nationwide cohort study. Journal of Viral Hepatitis 23, 940–945 (2016). 10.1111/jvh.12564 [PubMed: 27386835]
37. Baden R, Rockstroh JK & Buti M Natural history and management of hepatitis C: does sex play a role? J Infect Dis 209 Suppl 3, S81–85 (2014). 10.1093/infdis/jiu057 [PubMed: 24966194]
38. Jean CM, Honarmand S, Louie JK & Glaser CA Risk factors for West Nile virus neuroinvasive disease, California, 2005. Emerg Infect Dis 13, 1918–1920 (2007). 10.3201/eid1312.061265 [PubMed: 18258047]
39. Hegdahl HK, Fylkesnes KM, Sandøy IF & Faragher EB Sex Differences in HIV Prevalence Persist over Time: Evidence from 18 Countries in Sub-Saharan Africa. PloS one. 11, e0148502 (2016). 10.1371/journal.pone.0148502 [PubMed: 26841112]
40. Griesbeck M, Scully E & Altfeld M Sex and gender differences in HIV-1 infection. Clinical science. 130, 1435–1451 (2016). 10.1042/cs20160112 [PubMed: 27389589]
41. Meier A. et al. Sex differences in the Toll-like receptor-mediated response of plasmacytoid dendritic cells to HIV-1. Nat Med 15, 955–959 (2009). 10.1038/nm.2004 [PubMed: 19597505]
42. Nicolosi A. et al. The Efficiency of Male-to Female and Female-to-Male Sexual Transmission of the Human Immunodeficiency Virus. Epidemiology. 5, 570–575 (1994). 10.1097/00001648-199411000-00003 [PubMed: 7841237]
43. Cobelens F, Nagelkerke N & Fletcher H The convergent epidemiology of tuberculosis and human cytomegalovirus infection. F1000Research 7, 280 (2018). 10.12688/f1000research.14184.2 [PubMed: 29780582]
44. Yousuf W, Ibrahim H, Harfouche M, Abu Hijleh F & Abu-Raddad L Herpes simplex virus type 1 in Europe: systematic review, meta-analyses and meta-regressions. BMJ global health. 5, e002388 (2020). 10.1136/bmjgh-2020-002388
45. McQuillan G, Kruszon-Moran D, Flagg EW & Paulose-Ram R Prevalence of Herpes Simplex Virus Type 1 and Type 2 in Persons Aged 14-49: United States, 2015-2016. NCHS Data Brief, 1–8 (2018).
46. Han X. et al. Gender influences herpes simplex virus type 1 infection in normal and gamma interferon-mutant mice. J Virol 75, 3048–3052 (2001). 10.1128/JVI.75.6.3048-3052.2001 [PubMed: 11222734]
47. Huber SA & Pfaeffle B Differential Th1 and Th2 cell responses in male and female BALB/c mice infected with coxsackievirus group B type 3. J Virol 68, 5126–5132 (1994). 10.1128/JVI.68.8.5126-5132.1994 [PubMed: 8035512]
48. WHO Ebola Response Team, J. A-A, , Archchun Ariyarajah, Isobel M. Blake, Anne Cori, Christl A. Donnelly, Ilaria Dorigatti, Christopher Dye, Tim Eckmanns, Neil M. Ferguson, Christophe Fraser, Tini Garske, Wes Hinsley, Thibaut Jombart, Harriet L. Mills, Gemma Nedjati-Gilani, Emily Newton, Pierre Nouvellet, Devin Perkins, Steven Riley, Dirk Schumacher, Anita Shah, Lisa J. Thomas, Maria D. Van Kerkhove. Ebola Virus Disease among Male and Female Persons in West Africa. New England Journal of Medicine 374, 96–98 (2016). 10.1056/nejmc1510305 [PubMed: 26736011]
49. Garenne M. Sex Differences in Measles Mortality: A World Review. International journal of epidemiology. 23, 632–642 (1994). 10.1093/ije/23.3.632 [PubMed: 7960393]
50. Green MS, Schwartz N & Peer V Gender differences in measles incidence rates in a multi-year, pooled analysis, based on national data from seven high income countries. BMC Infectious Diseases 22 (2022). 10.1186/s12879-022-07340-3
51. Schuurhof A. et al. Interleukin-9 polymorphism in infants with respiratory syncytial virus infection: An opposite effect in boys and girls. Pediatric pulmonology. 45, 608–613 (2010). 10.1002/ppul.21229 [PubMed: 20503287]
52. Pisesky A. et al. Incidence of Hospitalization for Respiratory Syncytial Virus Infection amongst Children in Ontario, Canada: A Population-Based Study Using Validated Health Administrative Data. PLOS ONE 11, e0150416 (2016). 10.1371/journal.pone.0150416 [PubMed: 26958849]
53. Kenmoe S. et al. Prevalence of human respiratory syncytial virus infection in people with acute respiratory tract infections in Africa: A systematic review and meta-analysis. Influenza and Other Respiratory Viruses 12, 793–803 (2018). 10.1111/irv.12584 [PubMed: 29908103]

54. Malinczak CA et al. Sex-associated TSLP-induced immune alterations following early-life RSV infection leads to enhanced allergic disease. Mucosal Immunol 12, 969–979 (2019). 10.1038/s41385-019-0171-3 [PubMed: 31076663]
55. Ferro A. et al. Sex differences in the prevalence of Helicobacter pylori infection: an individual participant data pooled analysis (StoP Project). Eur J Gastroenterol Hepatol 31, 593–598 (2019). 10.1097/MEG.0000000000001389 [PubMed: 30839435]
56. Murray LJ, McCrum EE, Evans AE & Bamford KB Epidemiology of Helicobacter pylori infection among 4742 randomly selected subjects from Northern Ireland. Int J Epidemiol 26, 880–887 (1997). 10.1093/ije/26.4.880 [PubMed: 9279623]
57. Vazquez-Martinez ER, Garcia-Gomez E, Camacho-Arroyo I & Gonzalez-Pedrajo B Sexual dimorphism in bacterial infections. Biol Sex Differ 9, 27 (2018). 10.1186/s13293-018-0187-5 [PubMed: 29925409]
58. Ohtani M. et al. 17 beta-estradiol suppresses Helicobacter pylori-induced gastric pathology in male hypergastrinemic INS-GAS mice. Carcinogenesis 32, 1244–1250 (2011). 10.1093/carcin/bgr072 [PubMed: 21565825]
59. FitzSimmons SC The changing epidemiology of cystic fibrosis. J Pediatr 122, 1–9 (1993). 10.1016/s0022-3476(05)83478-x [PubMed: 8419592]
60. Guilbault C. et al. Influence of gender and interleukin-10 deficiency on the inflammatory response during lung infection with Pseudomonas aeruginosa in mice. Immunology 107, 297–305 (2002). 10.1046/j.1365-2567.2002.01508.x [PubMed: 12423305]
61. Peer V, Schwartz N & Green MS Sex Differences in Salmonellosis Incidence Rates-An Eight-Country National Data-Pooled Analysis. J Clin Med 10 (2021). 10.3390/jcm10245767
62. Blasi F, Tarsia P, Arosio C, Fagetti L & Allegra L Epidemiology of Chlamydia pneumoniae. Clin Microbiol Infect 4 Suppl 4, S1–S6 (1998).
63. Matteelli A. et al. Prevalence of Chlamydia trachomatis and Neisseria gonorrhoeae infection in adolescents in Northern Italy: an observational school-based study. BMC Public Health 16, 200 (2016). 10.1186/s12889-016-2839-x [PubMed: 26927226]
64. Dias SP, Brouwer MC & van de Beek D Sex and Gender Differences in Bacterial Infections. Infect Immun 90, e0028322 (2022). 10.1128/iai.00283-22 [PubMed: 36121220]
65. Dielissen PW, Teunissen DA & Lagro-Janssen AL Chlamydia prevalence in the general population: is there a sex difference? a systematic review. BMC Infect Dis 13, 534 (2013). 10.1186/1471-2334-13-534 [PubMed: 24215287]
66. Hannu T. Reactive arthritis. Best Pract Res Clin Rheumatol 25, 347–357 (2011). 10.1016/j.berh.2011.01.018 [PubMed: 22100285]
67. Zheng R. et al. A Systematic Review and Meta-Analysis of Epidemiology and Clinical Manifestations of Human Brucellosis in China. Biomed Res Int 2018, 5712920 (2018). 10.1155/2018/5712920 [PubMed: 29850535]
68. Alkahtani AM, Assiry MM, Chandramoorthy HC, Al-Hakami AM & Hamid ME Sero-prevalence and risk factors of brucellosis among suspected febrile patients attending a referral hospital in southern Saudi Arabia (2014-2018). BMC Infect Dis 20, 26 (2020). 10.1186/s12879-020-4763-z [PubMed: 31918671]
69. Orloski KA, Hayes EB, Campbell GL & Dennis DT Surveillance for Lyme disease--United States, 1992-1998. MMWR CDC Surveill Summ 49, 1–11 (2000).
70. Jarefors S. et al. Lyme borreliosis reinfection: might it be explained by a gender difference in immune response? Immunology 118, 224–232 (2006). 10.1111/j.1365-2567.2006.02360.x [PubMed: 16771857]
71. Berglund J. et al. An epidemiologic study of Lyme disease in southern Sweden. N Engl J Med 333, 1319–1327 (1995). 10.1056/NEJM199511163332004 [PubMed: 7566023]
72. Schwartz AM et al. Epidemiology and cost of Lyme disease-related hospitalizations among patients with employer-sponsored health insurance-United States, 2005-2014. Zoonoses Public Health 67, 407–415 (2020). 10.1111/zph.12699 [PubMed: 32462811]
73. Kwit NA, Nelson CA, Max R & Mead PS Risk Factors for Clinician-Diagnosed Lyme Arthritis, Facial Palsy, Carditis, and Meningitis in Patients From High-Incidence States. Open Forum Infect Dis 5, ofx254 (2018). 10.1093/ofid/ofx254 [PubMed: 29326960]

74. Zinck CB et al. Borrelia burgdorferi strain and host sex influence pathogen prevalence and abundance in the tissues of a laboratory rodent host. Mol Ecol 31, 5872–5888 (2022). 10.1111/mec.16694 [PubMed: 36112076]
75. Hertz D & Schneider B Sex differences in tuberculosis. Semin Immunopathol 41, 225–237 (2019). 10.1007/s00281-018-0725-6 [PubMed: 30361803]
76. Tan W. et al. Sex influences the association between haemostasis and the extent of lung lesions in tuberculosis. Biol Sex Differ 9, 44 (2018). 10.1186/s13293-018-0203-9 [PubMed: 30305157]
77. Miele K, Bamrah Morris S & Tepper NK Tuberculosis in Pregnancy. Obstet Gynecol 135, 1444–1453 (2020). 10.1097/AOG.0000000000003890 [PubMed: 32459437]
78. Dibbern J, Eggers L & Schneider BE Sex differences in the C57BL/6 model of Mycobacterium tuberculosis infection. Sci Rep 7, 10957 (2017). 10.1038/s41598-017-11438-z [PubMed: 28887521]
79. Yancey AL, Watson HL, Cartner SC & Simecka JW Gender is a major factor in determining the severity of mycoplasma respiratory disease in mice. Infect Immun 69, 2865–2871 (2001). 10.1128/IAI.69.5.2865-2871.2001 [PubMed: 11292700]
80. Raoult D, Marrie T & Mege J Natural history and pathophysiology of Q fever. Lancet Infect Dis 5, 219–226 (2005). 10.1016/S1473-3099(05)70052-9 [PubMed: 15792739]
81. Leone M. et al. Effect of sex on Coxiella burnetii infection: protective role of 17beta-estradiol. J Infect Dis 189, 339–345 (2004). 10.1086/380798 [PubMed: 14722900]
82. Textoris J. et al. Sex-related differences in gene expression following Coxiella burnetii infection in mice: potential role of circadian rhythm. PLoS One 5, e12190 (2010). 10.1371/journal.pone.0012190 [PubMed: 20730052]
83. Strachan NJ et al. Sexual dimorphism in campylobacteriosis. Epidemiol Infect 136, 1492–1495 (2008). 10.1017/S0950268807009934 [PubMed: 18062834]
84. Turner NA et al. Epidemiologic Trends in Clostridioides difficile Infections in a Regional Community Hospital Network. JAMA Netw Open 2, e1914149 (2019). 10.1001/jamanetworkopen.2019.14149 [PubMed: 31664443]
85. Pohl AM et al. Differences Among Incidence Rates of Invasive Listeriosis in the U.S. FoodNet Population by Age, Sex, Race/Ethnicity, and Pregnancy Status, 2008-2016. Foodborne Pathog Dis 16, 290–297 (2019). 10.1089/fpd.2018.2548 [PubMed: 30735066]
86. Pasche B. et al. Sex-dependent susceptibility to Listeria monocytogenes infection is mediated by differential interleukin-10 production. Infect Immun 73, 5952–5960 (2005). 10.1128/IAI.73.9.5952-5960.2005 [PubMed: 16113316]
87. Salem ML, Matsuzaki G, Madkour GA & Nomoto K Beta-estradiol-induced decrease in IL-12 and TNF-alpha expression suppresses macrophage functions in the course of Listeria monocytogenes infection in mice. Int J Immunopharmacol 21, 481–497 (1999). 10.1016/s0192-0561(99)00027-2 [PubMed: 10458538]
88. Bremer V, Marcus U & Hamouda O Syphilis on the rise again in Germany – results from surveillance data for 2011. Eurosurveillance 17 (2012). 10.2807/ese.17.29.20222-en
89. Peeling RW et al. Syphilis. Nature Reviews Disease Primers 3 (2017). 10.1038/nrdp.2017.73
90. Nudel K. et al. Transcriptome Analysis of Neisseria gonorrhoeae during Natural Infection Reveals Differential Expression of Antibiotic Resistance Determinants between Men and Women. mSphere 3 (2018). 10.1128/mSphereDirect.00312-18
91. Xiong M. et al. Analysis of the sex ratio of reported gonorrhoea incidence in Shenzhen, China. BMJ Open 6, e009629 (2016). 10.1136/bmjopen-2015-009629
92. Jerse AE et al. Estradiol-Treated Female Mice as Surrogate Hosts for Neisseria gonorrhoeae Genital Tract Infections. Front Microbiol 2, 107 (2011). 10.3389/fmicb.2011.00107 [PubMed: 21747807]
93. Farnham A, Alleyne L, Cimini D & Balter S Legionnaires' disease incidence and risk factors, New York, New York, USA, 2002-2011. Emerg Infect Dis 20, 1795–1802 (2014). 10.3201/eid2011.131872 [PubMed: 25513657]
94. Kadioglu A. et al. Sex-based differences in susceptibility to respiratory and systemic pneumococcal disease in mice. J Infect Dis 204, 1971–1979 (2011). 10.1093/infdis/jir657 [PubMed: 22021621]

95. Yang Z. et al. Female resistance to pneumonia identifies lung macrophage nitric oxide synthase-3 as a therapeutic target. Elife 3 (2014). 10.7554/eLife.03711

96. Rosner BM, Stark K & Werber D Epidemiology of reported Yersinia enterocolitica infections in Germany, 2001-2008. BMC Public Health 10, 337 (2010). 10.1186/1471-2458-10-337 [PubMed: 20546575]

97. Pietropaoli AP, Glance LG, Oakes D & Fisher SG Gender differences in mortality in patients with severe sepsis or septic shock. Gend Med 7, 422–437 (2010). 10.1016/j.genm.2010.09.005 [PubMed: 21056869]

98. Zeng Z. et al. Sex-hormone-driven innate antibodies protect females and infants against EPEC infection. Nat Immunol 19, 1100–1111 (2018). 10.1038/s41590-018-0211-2 [PubMed: 30250184]

99. Ng-Nguyen D. et al. The epidemiology of Taenia spp. infection and Taenia solium cysticerci exposure in humans in the Central Highlands of Vietnam. BMC Infect Dis 18, 527 (2018). 10.1186/s12879-018-3434-9 [PubMed: 30348095]

100. Kelvin EA et al. The association of host age and gender with inflammation around neurocysticercosis cysts. Ann Trop Med Parasitol 103, 487–499 (2009). 10.1179/000349809X12459740922291 [PubMed: 19695154]

101. Morales-Montor J & Larralde C The role of sex steroids in the complex physiology of the host-parasite relationship: the case of the larval cestode of Taenia crassiceps. Parasitology 131, 287–294 (2005). 10.1017/s0031182005007894 [PubMed: 16178349]

102. Wright JE, Werkman M, Dunn JC & Anderson RM Current epidemiological evidence for predisposition to high or low intensity human helminth infection: a systematic review. Parasit Vectors 11, 65 (2018). 10.1186/s13071-018-2656-4 [PubMed: 29382360]

103. Ayabina DV et al. Gender-related differences in prevalence, intensity and associated risk factors of Schistosoma infections in Africa: A systematic review and meta-analysis. PLoS Negl Trop Dis 15, e0009083 (2021). 10.1371/journal.pntd.0009083 [PubMed: 34788280]

104. Nakazawa M. et al. Schistosoma mansoni: susceptibility differences between male and female mice can be mediated by testosterone during early infection. Exp Parasitol 85, 233–240 (1997). 10.1006/expr.1997.4148 [PubMed: 9085920]

105. Bernin H & Lotter H Sex Bias in the Outcome of Human Tropical Infectious Diseases: Influence of Steroid Hormones. Journal of Infectious Diseases 209, S107–S113 (2014). 10.1093/infdis/jit610 [PubMed: 24966190]

106. Hajjeh RA, Brandt ME & Pinner RW Emergence of cryptococcal disease: epidemiologic perspectives 100 years after its discovery. Epidemiol Rev 17, 303–320 (1995). 10.1093/oxfordjournals.epirev.a036195 [PubMed: 8654513]

107. Shaheen AA, Somayaji R, Myers R & Mody CH Epidemiology and trends of cryptococcosis in the United States from 2000 to 2007: A population-based study. Int J STD AIDS 29, 453–460 (2018). 10.1177/0956462417732649 [PubMed: 28971712]

108. Acuna-Soto R, Maguire JH & Wirth DF Gender distribution in asymptomatic and invasive amebiasis. Am J Gastroenterol 95, 1277–1283 (2000). 10.1111/j.1572-0241.2000.01525.x [PubMed: 10811339]

109. Sellau J. et al. Androgens predispose males to monocyte-mediated immunopathology by inducing the expression of leukocyte recruitment factor CXCL1. Nat Commun 11, 3459 (2020). 10.1038/s41467-020-17260-y [PubMed: 32651360]

110. Lockard RD, Wilson ME & Rodriguez NE Sex-Related Differences in Immune Response and Symptomatic Manifestations to Infection with Leishmania Species. J Immunol Res 2019, 4103819 (2019). 10.1155/2019/4103819 [PubMed: 30756088]

111. Soares L, Abad-Franch F & Ferraz G Epidemiology of cutaneous leishmaniasis in central Amazonia: a comparison of sex-biased incidence among rural settlers and field biologists. Trop Med Int Health 19, 988–995 (2014). 10.1111/tmi.12337 [PubMed: 24862350]

112. Layegh P, Moghiman T & Ahmadian Hoseini SA Children and cutaneous leishmaniasis: a clinical report and review. J Infect Dev Ctries 7, 614–617 (2013). 10.3855/jidc.2939 [PubMed: 23949297]

113. Cloots K. et al. Male predominance in reported Visceral Leishmaniasis cases: Nature or nurture? A comparison of population-based with health facility-reported data. PLoS Negl Trop Dis 14, e0007995 (2020). 10.1371/journal.pntd.0007995 [PubMed: 31995564]
114. Layegh P, Moghiman T & Ahmadian Hoseini SA Children and cutaneous leishmaniasis: a clinical report and review. The Journal of Infection in Developing Countries 7, 614–617 (2013). 10.3855/jidc.2939 [PubMed: 23949297]
115. Rodriguez NE et al. Epidemiological and Experimental Evidence for Sex-Dependent Differences in the Outcome of Leishmania infantum Infection. Am J Trop Med Hyg 98, 142–145 (2018). 10.4269/ajtmh.17-0563 [PubMed: 29165220]
116. Kobets T. et al. Genetics of host response to Leishmania tropica in mice - different control of skin pathology, chemokine reaction, and invasion into spleen and liver. PLoS Negl Trop Dis 6, e1667 (2012). 10.1371/journal.pntd.0001667 [PubMed: 22679519]
117. Bryson KJ et al. BALB/c mice deficient in CD4 T cell IL-4Ralpha expression control Leishmania mexicana Load although female but not male mice develop a healer phenotype. PLoS Negl Trop Dis 5, e930 (2011). 10.1371/journal.pntd.0000930 [PubMed: 21245915]
118. Travi BL et al. Gender is a major determinant of the clinical evolution and immune response in hamsters infected with Leishmania spp. Infect Immun 70, 2288–2296 (2002). 10.1128/IAI.70.5.2288-2296.2002 [PubMed: 11953362]
119. Oghumu S. et al. Transgenic expression of CXCR3 on T cells enhances susceptibility to cutaneous Leishmania major infection by inhibiting monocyte maturation and promoting a Th2 response. Infect Immun 83, 67–76 (2015). 10.1128/IAI.02540-14 [PubMed: 25312956]
120. Lindova J. et al. Gender differences in behavioural changes induced by latent toxoplasmosis. Int J Parasitol 36, 1485–1492 (2006). 10.1016/j.ijpara.2006.07.008 [PubMed: 16978630]
121. Roberts CW, Cruickshank SM & Alexander J Sex-determined resistance to Toxoplasma gondii is associated with temporal differences in cytokine production. Infect Immun 63, 2549–2555 (1995). 10.1128/iai.63.7.2549-2555.1995 [PubMed: 7790068]
122. Sun KS, Tsai CF, Chen SC, Chen YY & Huang WC Galactomannan Testing and the Incidence of Invasive Pulmonary Aspergillosis: A 10-Year Nationwide Population-Based Study in Taiwan. PLoS One 11, e0149964 (2016). 10.1371/journal.pone.0149964 [PubMed: 26900697]
123. vom Steeg LG & Klein SL SeXX Matters in Infectious Disease Pathogenesis. PLoS Pathog 12, e1005374 (2016). 10.1371/journal.ppat.1005374 [PubMed: 26891052]
124. Schaefer AL et al. Factors Contributing to Sex Differences in Mice Inhaling Aspergillus fumigatus. Int J Environ Res Public Health 17 (2020). 10.3390/ijerph17238851
125. Guess TE, Rosen J, Castro-Lopez N, Wormley FL Jr. & McClelland EE An inherent T cell deficit in healthy males to C. neoformans infection may begin to explain the sex susceptibility in incidence of cryptococcosis. Biol Sex Differ 10, 44 (2019). 10.1186/s13293-019-0258-2 [PubMed: 31477151]
126. Lortholary O, Improvisi L, Fitting C, Cavaillon JM & Dromer F Influence of gender and age on course of infection and cytokine responses in mice with disseminated Cryptococcus neoformans infection. Clin Microbiol Infect 8, 31–37 (2002). 10.1046/j.1469-0691.2002.00375.x [PubMed: 11906498]
127. Bellissimo-Rodrigues F, Bollela VR, Da Fonseca BA & Martinez R Endemic paracoccidioidomycosis: relationship between clinical presentation and patients' demographic features. Med Mycol 51, 313–318 (2013). 10.3109/13693786.2012.714529 [PubMed: 22928923]
128. Shankar J, Restrepo A, Clemons KV & Stevens DA Hormones and the resistance of women to paracoccidioidomycosis. Clin Microbiol Rev 24, 296–313 (2011). 10.1128/CMR.00062-10 [PubMed: 21482727]
129. Pinzan CF, Ruas LP, Casabona-Fortunato AS, Carvalho FC & Roque-Barreira MC Immunological basis for the gender differences in murine Paracoccidioides brasiliensis infection. PLoS One 5, e10757 (2010). 10.1371/journal.pone.0010757 [PubMed: 20505765]
130. Shemer Avner and Meir B (2018).
131. d'Enfert C. et al. The impact of the Fungus-Host-Microbiota interplay upon Candida albicans infections: current knowledge and new perspectives. FEMS Microbiol Rev 45 (2021). 10.1093/femsre/fuaa060

132. Severance EG et al. Candida albicans exposures, sex specificity and cognitive deficits in schizophrenia and bipolar disorder. NPJ Schizophr 2, 16018 (2016). 10.1038/npjschz.2016.18 [PubMed: 27336058]

Text Box 1:

Sex hormones and inflammation

Estrogens (estrone, 17β-estradiol, estriol), progesterone, and androgens (testosterone, dihydrotestosterone) are the predominant gonadal sex hormones. The sex hormone receptors – estrogen receptors (ER alpha, beta), progesterone receptor (PR), and androgen receptor (AR) – are hormone-activated transcription factors that bind to hormone response elements to regulate gene expression. ERs, PRs, and ARs are expressed by a variety of immune cells (T cells, B cells, dendritic cells, monocytes and macrophages, NK cells, type 2 innate lymphoid cells, and granulocytes) and cells at the interface of skin and mucosal barrier sites, such as thymic epithelial cells[128]. Sex-biased gene expression can result from sex-specific differences in steroid production. For example, numerous ER response elements in the IFN-gamma promoter allow for increased downstream gene expression when 17β-estradiol levels are increased, thereby contributing to female biased increased production of IFN-gamma[129].

Estrogens can exhibit either anti-inflammatory (at high concentrations) or pro-inflammatory effects (at low concentrations)[130]. During pregnancy or periovulation when estrogen concentrations are high, estrogens exert inhibitory effects on T cells (specifically Th1 and Th17-polarized cells), M1 macrophages, dendritic cells, neutrophils, and microglia through NF-kB inhibition, and can also increase Treg function. ERalpha in T cells can promote T cell activation induced apoptosis and downregulates Foxp3 expression[131], and can also suppress TFH cell development[132]. Estrogens can also signal through ER-beta in Treg cells in the intestine to regulate immune suppression[133]. Both ER-alpha and ER-beta in CD4+ T cells are important for ligand-mediated suppression of autoimmunity of the central nervous system (Multiple Sclerosis; MS), specially targeting pathogenic Th17 cells[134,135]. ER-beta is also required for Tregs to regulate macrophage proinflammatory responses for resolving lung inflammation resulting from pneumonia[136].

The impact of estrogen on the immune response is also influenced by the immune microenvironment. In animal models of lupus-like disease, estrogens can be pro- or anti-inflammatory, depending on the proinflammatory milieu responsible for the observed lupus-like phenotypes. Deletion of ER-alpha in B cells reduced autoantibody production and nephritis in lupus-prone NZB/W F1 mice[137]. In the MRL/lpr model of spontaneous lupus-like disease, exogenous estrogen administration resulted in accelerated immune-complex glomerulonephritis, reflecting a proinflammatory effect via B-cell activation and autoantibody production; however, T-cell mediated disease, including periarticular inflammation, focal sialadenitis, and renal vasculitis, was significantly reduced[130,138]. Inflammatory cytokines including TNF-alpha, IL-1, and IL-6 can stimulate the activity of aromatase, an enzyme required for estrogen biosynthesis. Thus, the inflammatory milieu may confer contextual effects by altering the local concentrations of estrogen[139]. The concentration- and context-dependent effects of estrogen are also apparent in examples of systemic autoimmune disease. In rheumatoid arthritis and MS, disease activity often spontaneously decreases during pregnancy, a phenomenon which has been attributed to the anti-inflammatory effects of high concentrations of estrogen[134,135,140]. Nevertheless,

the cumulative effects of local estrogen abundance are not so straightforward, as disease activity in systemic lupus erythematosus often spontaneously increases during pregnancy[141]. These observations from disease activity in pregnancy highlight the complex interactions between sex hormones, immune cells, immune tolerance, and the developing fetus.

Androgens have anti-inflammatory effects on immune responses *in vivo* and *in vitro*, through diverse mechanisms. In the context of their effects on the innate immune system, they have been shown to modify signal transduction through pattern recognition receptors, suppressing both NF-kB and *Tlr4* expression[142]. Androgens also lower cytokine secretion of TNF-alpha, IL-1β, and IL-6 from monocytes and macrophages, and IL-33 production from mast cells[41,143,144]. Androgens impact adaptive immune responses, and can inhibit both humoral and cellular immune responses by reducing T and B cell proliferation and decreasing immunoglobulin and cytokine production[35 41,143,144]. In terms of B cells, androgens have inhibitory effects on B cell lymphopoiesis and specifically affect the production of B cell precursors, which express AR; conversely, mature B cells, which lack this receptor, are not directly impacted by androgens[41]. CD4+ T cells from female mice treated with dihydrotestosterone (DHT) produce more IL-10 compared to untreated female animals [36].

BOX 2:

X-Chromosome Inactivation (XCI) & 'Escape' from XCI

Female eutherian mammals use XCI for dosage compensation of X-linked genes between the sexes[145]. XCI is initiated during early embryonic development, during which one X chromosome is randomly selected for transcriptional silencing. The process begins with upregulation of the long non-coding RNA Xist, which spreads across the future inactive X chromosome (Xi) in *cis* together with Polycomb Repressive Complexes (PRCs)[146-151]. X-linked gene promoters and enhancers rapidly lose active histone acetylation marks concurrently with transcriptional repression[148-150]. The repressive histone modifications H2AK119Ub and H3K27me3 are deposited on the Xi by PRC1 and PRC2, respectively, and the histone variant macroH2A becomes enriched[152-155], together creating a heterochromatic environment across the Xi. As a final layer of regulation to maintain transcriptional repression of the Xi, DNA methylation becomes enriched at promoters and enhancers[156-160]. Thus, in most somatic cells, transcriptional silencing of the Xi is maintained with each cell division through Xi enrichment of Xist RNA, heterochromatic histone marks, and DNA methylation, some of which can be visualized cytologically using RNA FISH and immunofluorescence.

Although most genes on the Xi are silenced, about 15-23% of X-linked genes in humans and ~3-7% of X-linked genes in mice are transcribed from the Xi and 'escape' XCI, either constitutively or in a cell type-specific manner[161-164]. The promoter regions of XCI escape genes lack Xist RNA enrichment[148,149,151], heterochromatic histone marks[148,150], and DNA methylation[159,160], and are enriched for RNA Polymerase II, DNAse I hypersensitivity sites, and CTCF occupancy, which collectively allow for gene expression from a highly heterochromatic environment. X-linked genes with a Y-linked counterpart (XY gene pairs) commonly escape XCI silencing and are expressed from the active (Xa) and inactive X (Xi) chromosomes, although transcript levels from the Xi are typically less than levels from the Xa[165]. Importantly, X-linked genes lacking a Y-linked homolog can also escape XCI. Both the magnitude and extent of XCI gene escape vary considerably by cell type, as well as between individual cells, and among individuals. Additionally, some escape genes display sex-biased expression [162,166-168]. Of the approximately 54 immunity-related genes located on the mouse and human X chromosomes, 20.4% are expressed more highly in females and 16.7% are expressed more highly in males[169]. However, these values are likely underestimates due to the methodological challenges associated with measuring transcription specifically from the Xi. Because XCI is random and because expression from the Xi is typically less than that of the Xa, the identification of XCI escape genes requires single-cell approaches with high sequencing depth, or bulk cell analyses using F1 hybrid mice with skewed XCI[70,170,171]. Nevertheless, ongoing efforts to identify additional escape genes are likely to provide important insights into sex-biased immune responses—to date, several proinflammatory genes have been found to aberrantly escape XCI in SLE and other autoimmune diseases, suggesting a key role for the transcription of X-linked genes from the Xi in the context of female-biased immunological processes (see Table 1).

Box 3:

Mouse models of autoimmune disease exhibiting a sex bias

Spontaneous and induced mouse models of lupus-like disease recapitulate some features of human autoimmune disease (primarily autoantibody production, lymphoid activation and hyperplasia, and lupus nephritis), and some of these models exhibit a sex bias. Male BXSB/*Yaa* bear a translocation of the telomeric end of the X chromosome containing *Tlr7* region and 15 neighboring genes onto the Y-chromosome (*Yaa* mutation)[172,173] and acquire a lupus-like phenotype over time. Notably, *Tlr7* knockdown in BXSB/Yaa mice abrogates disease development[174], and transgenic overexpression of *Tlr7* on a non-lupus prone background results in lupus-like disease[96]. The BXSB strain also contains mutations in the MHC locus, and loci on chromosomes 1, 3, and 13 (*Bsx1-6*) that contribute to disease activity[175]. The F1 hybrid NZB/W mouse model develops spontaneous lupus-like disease that exhibits a female bias (100% females and < 40% males develop disease phenotypes by 1 year)[176,177]. NZB/W mice also develop features of SS and female mice exhibit more extensive salivary gland lesions compared to male mice[178]. Both X chromosome number and hormones appear to influence disease onset and severity in NZM/W F1 mice, as estrogen accelerates disease and testosterone provides anti-inflammatory protection in some studies, but not others [179,180]. *In vitro* activated lymphocytes from female NZB/W F1 mice with lupus-like disease exhibit mislocalized Xist RNA and reduced enrichment of H3K27me3 at the Xi, and sex biased gene expression differences[56,73]. Backcrosses between NZB/W F1 and NZW generated various recombinant inbred strains of New Zealand Mixed (NZM) mice, among which NZM2328 and NZM2410 have earlier disease onset, and NZM2328 displaying a stronger female bias than NZM2410[181]. Lupus-like disease can be induced in various mouse strains (with variable efficiency) using intraperitoneal injections of pristane, during which females develop more severe disease phenotypes including anti-Sm, anti-dsDNA, anti-ribosomal P, anti-Su autoantibodies, arthritis, immune complex-mediated glomerulonephritis, and pulmonary capillaritis[182,183]. Finally, there is a female bias with the experimental autoimmune encephalomyelitis model of MS [184].

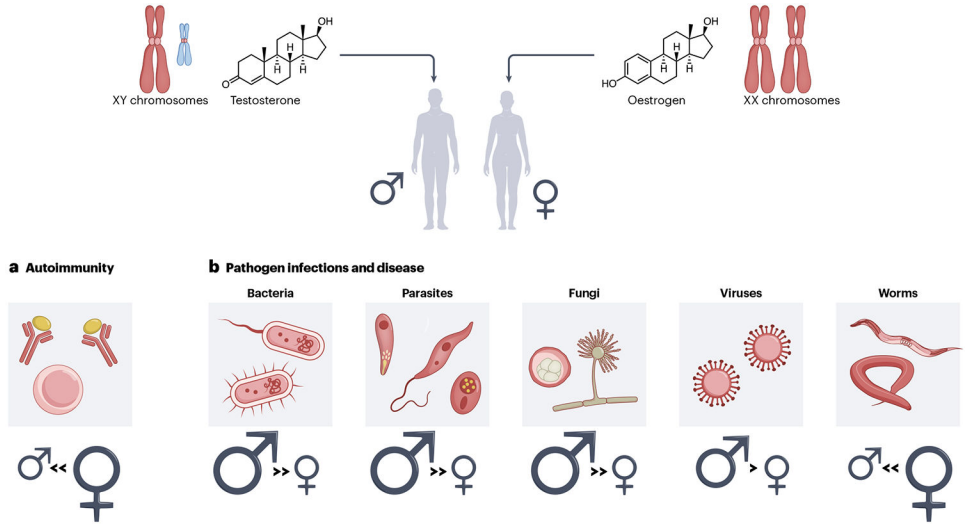

Figure 1. Sex differences with pathogen infections and autoimmune disease.

The sex chromosomes and the sex hormones in biological males (XY) and females (XX) are responsible for the observed sex differences with responses to various pathogens (a) and in autoimmune disease (b). (a) The overall sex bias associated with a particular class of pathogen infection (and associated disease) is shown. Size of the symbol reflects amount of sex bias. (b) Autoimmune diseases are strongly female-biased.

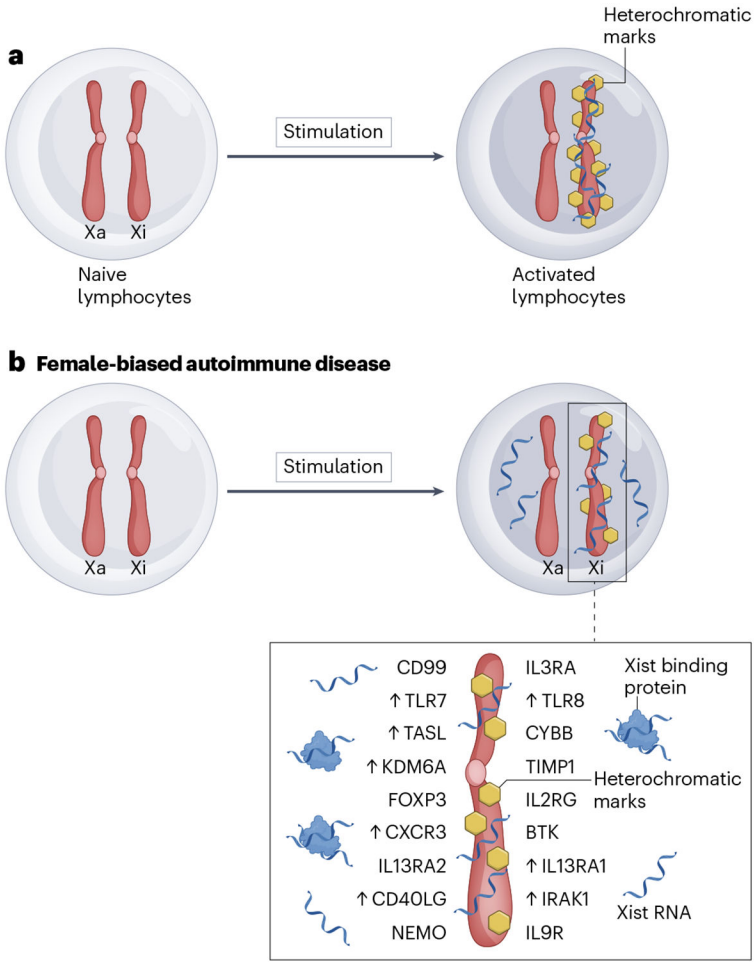

Figure 2. Number of X chromosomes and risk for autoimmune disease.

Increased numbers of X chromosomes is associated with higher risk for the female-biased autoimmune diseases SLE, SS, scleroderma, polymyositis, and dermatomyositis.

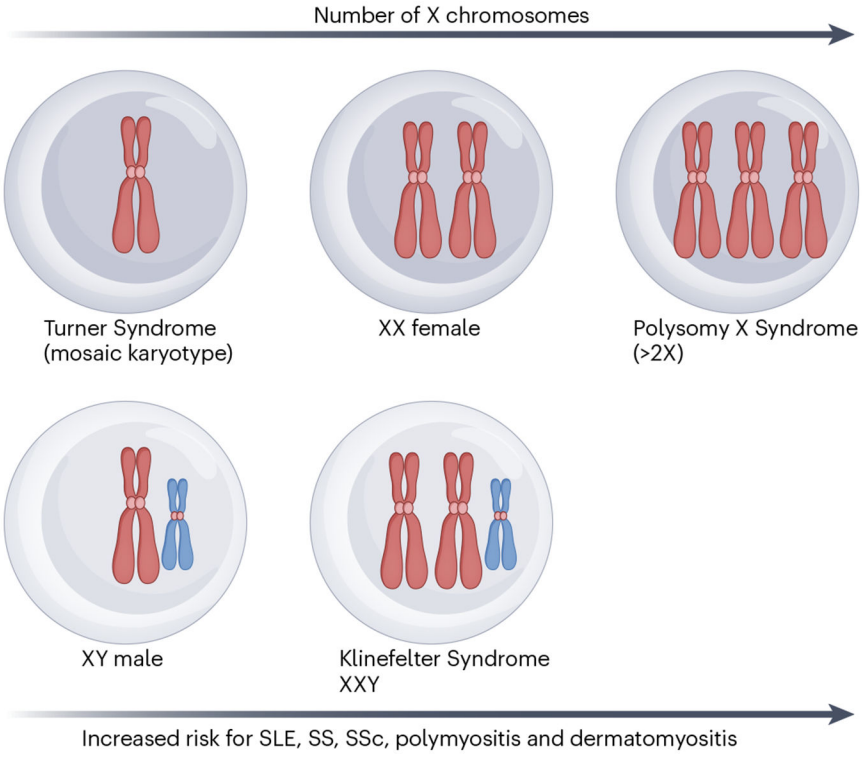

Figure 3. Impairments with dynamic XCI maintenance result in aberrant overexpression of X-linked genes in female-biased autoimmune disease.

(a) The Xi in naïve lymphocytes lack cytological enrichment of Xist RNA (pink curvey lines) and heterochromatic marks (colored circles), and these modifications return to the Xi in activated cells. (b) Activated lymphocytes from patients with autoimmune disease have dispersed Xist RNA and heterochromatic marks from the Xi, and increased expression of some X-linked genes (denoted with red arrows). Prevention of Xist RNA tethering to the Xi reduces enrichment of histone heterochromatic marks on this chromosome, and persistent absence of these epigenetic modifications across multiple cell divisions may increase abnormal overexpression across the Xi.

Table 1.

Prevalence, incidence, and sex bias for the female-biased autoimmune diseases SLE, SS, scleroderma, inflammatory myopathies, and RA.

Autoimmune Disease	Prevalence (per 100,000 people in United States)	Incidence (per 100,000 person-years in United States)	Sex Bias (% of Affected Individuals who are Women)
Systemic lupus erythematosus (SLE)	5-241[1]	1.0 – 23.2[1]	66%-93%[1] 83.71%[2]
Sjogren's syndrome (SS)	22-103[3]	3.9[4]	90.54%[2] 96.2%[4]
Systemic sclerosis/scleroderma (SSc)	27.6[5]	1.93[5]	83.7%[5] 75%-93.5%[6] 83.80%[2]
Inflammatory myopathies: dermatomyositis and polymyositis (DM/PM)	6.3[7]	0.116-0.6[7]	65.08%[2] 60%-75%[7]
Rheumatoid arthritis (RA)	1070[8] 1000[9]	75.3[8]	73.4%[8]

Table 2.

Immunity-related X-linked genes that are dosage-sensitive for autoimmune diseases.

Examples of X-linked genes that function in the adaptive and innate immune systems are shown.

Dosage sensitive X-linked gene	Function	Evidence for XCI escape	Gain/loss of function mouse models & phenotypes	Aberrant expression in autoimmune patients
Adaptive Immune System				
CD40LG	• Type II membrane protein expressed primarily on $CD4^+$ T cells • Binds to $CD40^+$ on B cells, ultimately leading to B cell activation, differentiation, and antibody production[1]	• Exhibits variable XCI escape in human fibroblasts[2] • *CD40LG* locus is regulated by DNA methylation, and CD4+ T cells treated with DNA methylation inhibitors increases *CD40LG* expression, suggesting reactivation from the Xi (direct evidence lacking)[1,3]	• *Cd40lg* overexpression in mice results in chronic inflammation, apoptosis-mediated thymic atrophy, glomerulonephritis, increased IgG antibodies, and increased lethality[4,5]	• Aberrantly overexpressed in SLE patient $CD4^+$ T cells, $CD8^+$ T cells, and B cells with active disease compared to healthy controls and patients in remission[1,6] • Female SLE patient CD4+ T cells have increased CD40LG expression compared to male SLE CD4+ T cells [1,6] • Patient with *CD40LG* duplication had autoimmune disease (splenomegaly, autoantibodies) [7]
CXCR3	• Chemokine receptor expressed on effector T cells that plays an important role in T cell trafficking to sites of infection[8] • During inflammation, *Cxcr3* is overexpressed in infiltrating CD4+ and CD8+ T cells[9]	• Silenced by XCI in human fibroblasts[2] • *CXCR3* regulated by DNA methylation, and CD4+ T cells treated with DNA methylation inhibitors may reactivate CXCR3 on Xi (only indirect evidence)[10] • Biallelic Cxcr3 expression in CD3+ T cells from mice infected with *Leishmania mexicana*[11]		• *CXCR3* is overexpressed in CD4+ T cells in urine and kidneys from patients with active lupus nephritis [12] • Female SLE CD4+ T cells have increased CXCR3 mRNA and protein levels[13] • Elevated infiltrating CXCR3+ CD3+ T cells in salivary gland tissue of SS patients[14]

Dosage sensitive X-linked gene	Function	Evidence for XCI escape	Gain/loss of function mouse models & phenotypes	Aberrant expression in autoimmune patients
BTK	• Essential signaling component of BCR, where Btk activation initiates signaling cascade for cell proliferation, activation, and survival	• Silenced by XCI in human fibroblasts[2]	• Btk inhibition in NZB/W F1 mice or inducible mouse model of lupus eliminates lupus-like disease symptoms: lower anti-dsDNA antibodies, reduced germinal center and plasma B cells, reduced complement deposition in kidneys, and reduced inflammatory cytokines[15,16] • *Btk* overexpression in mice increases numbers of germinal center B cells, plasma cells, increases ANAs, and immune complexes in kidneys[17,18]	• BTK is overexpressed in PBMCs from patients with active lupus nephritis[19]
FOXP3	• Expression required for establishment and maintenance of Tregs, for Treg function and identity	• Silenced by XCI in human fibroblasts[2]	• *Foxp3* overexpression is protective again renal dysfunction[20]	• SLE patients with increased disease severity exhibit greater numbers of CD4+ FOXP3+ T cells, possibly due to increased T cell activation [21] • SLE and SSc patient Tregs express lower mRNA and protein levels of FOXP3, which may compromise Treg function[22,23] • SSc patients have reduced numbers of Tregs[23]
OGT	• Glycosyltransferase enzyme that catalyzes the addition of O-GlcNAc modification to proteins Required for T and B cell activation		• *Ogt* overexpression in B cells results in enhanced activation, through increased O-GlcNAcylation of BCR dependent transcription factors[24] *Ogt* deletion in B cells impaired B cell homeostasis, activation, and antibody production[25]	• Elevated OGT mRNA and protein levels (and hypomethylation of OGT promoter) in female SLE patient CD4+ T cells compared to male SLE T cells [13]

Dosage sensitive X-linked gene	Function	Evidence for XCI escape	Gain/loss of function mouse models & phenotypes	Aberrant expression in autoimmune patients
Innate Immune System				
TASL (*Cxorf21*)	• IFN response gene that is part of the endolysosomal TLR machinery[26,27]	Variable XCI escape in human lymphoblastoid cells[2]		• Female biased increased expression in lymphoblastoid cell lines and thyroid tissue [26] • TASL is risk variant for SLE[28] • Positive correlation between TASL protein abundance and SLEDAI score in SLE patients >35 years of age[26]
TLR7	• Endosomal pattern recognition receptor that binds guanosine- and uridine-rich single-stranded RNA and induces MyD88-dependent activation of type I Interferon (IFN)[29,30]	• Variable escape (40-55%) in healthy human B cells, monocytes, plasmacytoid dendritic cells (DCs)[31] • Biallelic expression in SLE patient B cells[32] • Variable escape in human pDCs; biallelic TLR7 cells also had elevated expression of IFN -beta and IFN-alpha family members [33,34] • Variable escape in mouse plasmacytoid DCs; increased biallelic expression in disease NZB/W F1 mice[35]	• Male BXSB-Yaa mice have two copies of Tlr7, and exhibit accelerated lupus-like disease, with antinuclear antibodies (ANAs), glomerulonephritis, and splenomegaly[36,37] • *Tlr7* overexpressing mice develop spontaneous autoimmunity, with increased autoantibody production, autoreactive lymphocytes, splenomegaly and lethality.[38] • Tlr7 gain-of-function mice ($TLR7^{Y264H}$) have increased responsiveness to guanosine and 2',3'-cGMP, enhanced TLR7 signaling, increased survival of activated B cells, and cell-intrinsic expansion of age-associated B cells and germinal center B cells [39]	• Biallelic expression of *TLR7* enhances cell responsiveness to TLR7 ligands and leads to an increase in class switching events (human B cells)[31] • Increased *TLR7 expression* in female SLE patients relative to controls[40] • SLE patients with a TLR7 gain-of-function mutation (Y264H) exhibit elevated ANAs, and features of autoimmune disease including refractory autoimmune thrombocytopenia, neuromyelilits optica, and inflammataory arthralgias[41]

Table 3.

Sex differences across various classes of pathogens (virus, bacteria, worms, parasites, fungi) for humans and mouse/rodent models.

Pathogen prevalence and incidence, pathogen loads and disease severity, and mouse models exhibiting sex bias with infection or disease are shown in each column. Information regarding hormonal or genetic influences on the sex bias is provided (when available) for each pathogen.

	Pathogen	Pathogen Prevalence and Incidence	Pathogen Intensity/Load; Resulting Disease Severity	Mouse Models & Sex Biased Mechanisms/Pathways
VIRUS	Coronaviruses; SARS-CoV; SARS-CoV-2	Males have higher incidence[1-10]	Adult males (45-79yrs) have higher mortality[5,6 9] Females more likely to be diagnosed with Long Covid syndrome[11,12]	Male mice are more susceptible to SARS-CoV infection[13-15] Male mice have increased accumulation of inflammatory macrophages and neutrophils in lung (SARS-CoV)[3,13] Estrogen receptor signaling is protective after SARS-CoV-infection[13,16] SARS-CoV-2 entry receptor Ace2 is biallelically expressed in females, which might reflect its dual role in mediating viral replication vs renin-angiotensin-aldosterone system [4,17]
	Influenza	Infant males and older adult males have increased incidence[18-23]	Males (pre-pubescent, elderly) have high mortality.[19,23] Females (pre-menopausal; pregnancy) also have high mortality[18,24-26]	Male mice have greater disease severity and this increases with age[27] Female mice have greater mortality[28] Female mice are more protected following influenza vaccination[29,30] Low levels of testosterone in male mice correlate with poorer protection[27,31-33] but estriol protects female mice from severe disease and decreases influenza replication[34,35]
	Hepatitis A	Males have more hospitalizations[36]	Males have higher mortality[36]	n/a
	Hepatitis C	Similar incidence rates between males and females[37]	Males have greater disease severity (HCV-associated cirrhosis) [37] Females more likely to clear virus[37]	n/a
	West Nile Virus	Higher percentage of affected males in this case study[38]	Similar initial viremia[38] Females have more symptoms[38] Males have longer lived cytokine response[38] Males have increased mortality[38] Males more likely to develop neuroinvasive disease[38]	n/a

	Pathogen	Pathogen Prevalence and Incidence	Pathogen Intensity/Load; Resulting Disease Severity	Mouse Models & Sex Biased Mechanisms/Pathways
	Human Immunodeficiency Virus (HIV)	Females have higher incidence [39] Females have higher levels of immune activation and interferon signature gene expression[40]	Females have lower viral loads in early stages of infection (but comparable in advanced stage)[40,41] No sex difference with disease progression or clinical outcomes	Male-to-female transmission appears more efficient than female-to-male transmission[42]
	HCMV	Females (post-puberty pre-menopausal) have higher incidence of HCMV seroprevalence[43]		n/a
	Herpes Simplex Virus (HSV)	Females have higher prevalence[44,45]		Female mice more susceptible to infection[28] Female mice have higher HSV titers in brain tissue[28] Higher mortality in male mice[46] Ovariectomy of female mice or estrogen treatment of male mice eliminated sex differences after infection[28] Sex-biased survival differences depend on type I IFN signaling and DAP12 signaling[28]
	Coxsackievirus			Male mice have increased mortality[28,47] Males develop more severe cardiac inflammation due to Th1 response[47] Females are more resistant; exhibit predominantly Th2 responses[47]
	Ebola		Males have higher mortality[48]	n/a
	Measles	Females (age 45-64) have higher incidence[49]; Males (age 0-45) have higher incidence[50]	Females (ages 0-49) have higher mortality, particularly post-puberty pre-menopausal[49].	n/a
	Respiratory Syncytial Virus (RSV)	Males have higher incidence[51,52], but a metanalysis of acute respiratory infections in Africa did not identify sex as a factor in RSV prevalence[53]	Males have higher rates of hospitalizations[51]	Male neonatal mice have higher viral gene expression after RSV infection, and delayed viral resolution[54] After early-life RSV infection, male mice exposed to allergen have severe allergic exacerbation (female mice are protected). TSLP pathway (which impacts IFN-beta production) alters male immune environment after neonatal infection[54]
BACTERIA	*Heliobactor pylori*	Males have greater *H. Pylori* sero-prevalence[55,56] Infection has a male bias[55]	Males have more severe inflammation, atrophy, and intestinal metaplasia[57]	Male mice are more susceptible Males have higher colonization levels for *babA* virulence factor of H. pylori[58] Male mice treated with estradiol produce less IFN-gamma and IL-1-beta, and increased IL-10 and Th2 associated IgG1 levels[58]

	Pathogen	Pathogen Prevalence and Incidence	Pathogen Intensity/Load; Resulting Disease Severity	Mouse Models & Sex Biased Mechanisms/Pathways
				Estrogen is protective against gastric lesions; ovarectomy increases severity of gastritis and gastric cancer[58]
	Pseudomonas aeruginosa	Males have higher prevalence	Female CF patients have worse disease prognosis[59]	Female mice more susceptible to infection[60] Females mount strong inflammatory response in lungs[60] Estradiol upregulates expression of secretory leucoprotease which inhibits Tlr-dependent IL-8 release in bronchial epithelial cells during *P.aeruginosa* infection
	Salmonella	Higher incidence rates in male children for salmonellosis (up to age 15) [61] Females have higher incidence rates (ages 15–44 and 45–64)		n/a
	Chlamydia trachomatis;Chlamydia pneumoniae	Males have greater prevalence (C. pneumoniae)[62] Females have higher prevalence (C. trachomatis)[63]	Males have higher levels of *C. pneumoniae*[64] Females have higher infection rates because they are more likely to be screened (*C.trachomatis*)[65] Estrogen levels correlate with chlamydial load[64] Chlamydia-induced arthritis more common in men[66]	n/a
	Brucella spp.	Males have higher incidence[67] No sex bias with prevalence	Males more likely to develop Brucellosis[68]	n/a
	Borrelia burgdorferi (Lyme disease)	Males have higher incidence (USA 1992-1998)[69] Females >45 greater incidence (Sweden 1992-1993)[70,71] Females more likely to be re-infected after 5 years.	Males have more hospitalizations and likelihood for disseminated disease[72] Lyme neuroborreliosis is more common in female patients[73] Females have increased production of IFN-gamma, IL-4, IL6, IL-10, TNF-alpha[70]	Male mice have more infected tissues and higher spirochete loads[74]
	Mycobacterium tuberculosis	Males have higher incidence (male/female 1.7)[75]	Males exhibit higher mortality rates (global)[76] Pregnancy increases risk of disease complications[77] Females usually have less symptoms[64]	Male mice have accelerated disease progression, increased morbidity and mortality[78] Males have higher *M. tuberculosis* loads[78]

	Pathogen	Pathogen Prevalence and Incidence	Pathogen Intensity/Load; Resulting Disease Severity	Mouse Models & Sex Biased Mechanisms/Pathways
				Testosterone treatment increases susceptibility to infection
	Mycoplasma pulmonis			Male mice more susceptible[79] Male mice develop more severe disease in lung parenchyma[79] Removal of reproductive organs reduced disease severity[79]
	Coxiella burnettii	Males have higher incidence[80]	Human males more likely to become sympotomatic with Q fever (symptoms include fever, granulomatous hepatitis, myocarditis, pericarditis, pneumonia)[64,80] Pregnancy increases risk for persistent infections, and impaired immunity negatively impacts pregnancy[64]	Male mice have higher bacterial loads[64] Estrogen treatment of ovariectomized mice reduces bacterial loads and granulomas[81] C. burnetti infection results in sex-specific gene expression profiles: males upregulate *IL-10* and interferon-gamma production; females exhibt altered expression of circadian rhythm genes.[82]
	Campylobacter spp.	Males have higher incidence[64]		Males are more susceptible to infection and colonization[83] Males have higher shedding rates
	Clostridiodes difficile	Females have higher incidence[84] Females have increased risk of recurrent infection[57]	Increased disease severity in pregnant and peripartum females[84]	Progesterone and estrogen intermediates can inhibit spore germination in mice[57]
	Listeria monocytogenes	Females have higher incidence rates of invasive listeriosis[85] Pregnant females have higher incidence[64] Among older individuals, males have 2-4 higher incidence rates[85]	Pregnant females and older males have greater incidences of invasive disease[85] Older males have increased fatality rates[85]	Female mice more susceptible to infection and exhibit greater lethality[86] Females have higher bacterial load; Infected females have increased IL-10, which inhibits Th1 differentiation and Th1-derived cytokines[86] Estrogen treatment reduced IL-12, IFN-gamma, TNF-alpha; increased IL-4 and IL-10; reduced monocytes and lymphocyte accumulation at infection[87]
	Legionella pneumophila	Males have higher incidence	Males more likely to develop legionellosis and males more likely to have poor prognosis[64]	n/a
	Leptospira spp.	Males have higher incidence[64]		n/a
	Francisella tularensis	Males have higher incidence[65]		No sex difference with susceptibility Vaccinated female mice are more resistant to infection, with lower bacterial burdens, less tissue inflammation, and less proinflammatory cytokine production, and more Ft-specific antibodies in serum and lung[85]

	Pathogen	Pathogen Prevalence and Incidence	Pathogen Intensity/Load; Resulting Disease Severity	Mouse Models & Sex Biased Mechanisms/Pathways
	Escherichia coli	Females have higher incidence[64]		No sex difference with enterohemorrhagic *E.coli* disease in mice
	Treponema pallidum (syphilis)	Males have higher incidence[88,89]		n/a
	Neisseria gonorrhea	Males have higher incidence[64] Infected males may also have increased expression of gonococcal antimicrobial resistance genes[90]	Most females lack symptoms[64] Complications in males include epididymitis, infertility, prostatitis, seminal vesiculitis[91] Elevated progesterone promotes gonococcal infection (human cervical epithelial cells)	Estrogen treated mice have increased susceptibility to gonococcal infection[92]
	Streptococcus pneumoniae	Males have higher incidence for all types of pneumonia[64] Males (pre-puberty) have higher incidence	Males have greater hospitalization rates and increased mortality[64] Males more frequently diagnosed with Legionellosis (1.7:5 male to female)[93]	Male mice are more susceptible & have more severe disease[94] Males exhibit increased pro-inflammatory cytokines (IL-6, IL-17A, IFN-gamma)[94] Estrogen is protective, regulating macrophage activity (for pneumococcal pneumonia)[95]
	Yersinia enterocolitica	Males have higher incidence for Yersiniosis[96]	Males have higher levels of IgG4 antibodies for Yersinia outer membrane proteins, which is associated with anti-inflammatory response that is resistant to treatment[57]	n/a
	Sepsis: *Staphylococcus, Escherichia coli, Pseduomonas, etc*	Males have higher rates of sepsis and septic shock[65] Males more likely to develop sepsis after trauma or surgery[65]	Conflicting results for a sex bias with mortality[97]	Male mice develop greater inflammatory response, producing more pro-inflammatory cytokines[64] Males have more severe sepsis-induced cardiac dysfunction[85] Estrogen is protective, and female mice produced protective antibodies in response to estrogen; estrogen-driven antibodies were maternally transferrable to offspring[98]
WORMS	Pork tapeworm (Taenia solium) Neurocysticercosis	Females have higher incidence in some countries (Nigeria, Tanzania, Guatemala)[99] Females have more transitional cysts in brain (Ecuador)[100] No sex difference with incidence in Vietnam[99]	Female patients have greater number of transitional cysts[100]	Estrogen increases parasite loads and androgens decrease loads in mice, either acting directly on the worm's reproduction or by altering host's immune response to favor Th2 or Th1 pathways (*Taenia crassiceps*)[101]
	A. Lumbricoides	Females have higher incidence[102]		n/a

	Pathogen	Pathogen Prevalence and Incidence	Pathogen Intensity/Load; Resulting Disease Severity	Mouse Models & Sex Biased Mechanisms/Pathways
	Schistosoma masoni	Males have higher prevalence for infection[103]		Female and castrated male mice have greater morbidity after Schistosoma infection[104] Female mice have higher worm loads[104] Testosterone is protective for Schistosoma mansoni infections; female mice treated with testosterone had reduced worm burdens (if treated before infection)[104]
PARASITES	*Plasmodium falciparum* (malaria)		Male patients have greater disease severity[105]	n/a
	Cryptosporidium	Males have higher incidence[106]	Male patients have greater incidence of hospitalizations[107]	n/a
	Entamoeba histolytica (amoebiasis)	Asymtopmatic infection rates are the same across sexes[108]	Invasive amebiasis predominantly affects males; males have higher rates of invasive disease[108] Males have higher incidence of hepatic amebiasis[109]	Testosterone treatment induces proinflammatory responses in mouse (& human) classical monocytes, with increased production of CXCL1 and TNF[109]
	Leishmania	Males have higher incidence even when accounting for exposure[110] Adult males have higher incidence of cutaneous leishmaniasis[111] Childhood cutaneous leishmaniasis does not exhibit a sex bias[112] Males have higher incidence and greater risk ratio of visceral leishmaniasis[113] No sex bias for childhood cutaneous leishmaniasis[114]	Male patients exhibit higher rates of treatment failure and adverse effects[110]	Male mice have higher parasite burdens following infection (L.infantum)[115] Male mice express higher levels of IL-10 and TNF after infection and exhibit greater disease severity[115] Male mice (BALB/c congenic strains) are more susceptible to subcutanteous L.major, and exhibit more severe disease[110,116] Female mice heal small lesions following L. Mexicana infection, yet male mice exhibit persistent lesions, dependent on IL-4 levels[117] Male hamsters have increased disease severity and parasite burden with L. viannia infection. Testosterone-treated female animals had larger lesions than untreated females. Disease severity correlated with increased expression of IL-4, IL-10, and TGF-beta[118] X-linked *Cxcr3* is biallelically expressed in T cells of female mice and contributes to increased cytokine production[119]
	Toxoplasma gondii		Sex differences with infection-induced behavioral changes and personality shifts[120]	Female mice are more susceptible to infection and have higher cyst burdens[121] Female mice exhibit higher mortality after acute infection[121] Male mice produce higher TNF-

	Pathogen	Pathogen Prevalence and Incidence	Pathogen Intensity/Load; Resulting Disease Severity	Mouse Models & Sex Biased Mechanisms/Pathways
				alpha after day 10 of infection; female mice mortality did not correlate with lower TNF-alpha levels. Male mice produce higher IFN-gamma and IL-10 early during infection[121]
FUNGI	*Aspergillus fumigatus*	Males have higher incidence (invasive pulmonary aspergillosis)[122] Male bias with prevalence, incidence and severity[123] Males more susceptible to infection[123]		Female mice have higher levels of immune components (antibody titers, neutrophil eosinophil, and lymphocyte cells) after infection[124]
	Cryptococcus neoformans	Males have higher incidence[125] Males more affected than females[125]		Female mice express more cytokines in plasma and increased expression of TNF-alpha, interferon-gamma in spleen[126] Increased lethality for young male mice[126] Survival and fungal loads are similar between male and female mice[126]
	Paracoccidioides brasiliensis	Males have greater incidence (10:1 male to female, Latin America)[127]	Male patients have faster disease progression[128]	Male mice are more susceptible[129] Macrophages from infected female mice exhibit greater fungicidal activity, with higher nitric oxide production[129] Estrogen is protective following P. brasiliensis infection, as castrated male treated with estradiol have higher levels of IFN-gamma and lower levels of IL-10 compared to normal males. Ovariectomized female mice treated with testosterone produce less IFN-gamma and more IL-10 compared to normal female mice after infection[129]
	Microsporum, Trichophyton, epigermophyton (Tinea or Dermatophytosi)	Males have higher incidence [130]		n/a
	Candida albicans	Females have higher incidence (oral candidiasis)[131] Females have higher incidence (candida onychomycosis), with 3/4 females (childbearing age) infected at least once in their life; and 1/10 females having a recurring event[131]	Male patients with seropositivity for *C.albicans* have increased odds for schizopherenia[132] Female patients with seropositivity for *C.albicans* have increased odds for lower cognitive scores[132]	n/a