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Sex drives dimorphic immune responses to viral infections

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Abstract

New attention to sexual dimorphism in normal mammalian physiology and disease has uncovered a previously unappreciated breadth of mechanisms by which females and males differentially exhibit quantitative phenotypes. Thus, in addition to the established modifying effects of hormones, which prenatally and post-pubertally pattern cells and tissues in a sexually dimorphic fashion, sex differences are caused by extra-gonadal and dosage effects of genes encoded on sex chromosomes. Sex differences in immune responses, especially during autoimmunity, have been studied predominantly within the context of sex hormone effects. More recently, immune response genes have been localized to sex chromosomes themselves or found to be regulated by sex chromosome genes. Thus, understanding how sex impacts immunity requires the elucidation of complex interactions between sex hormones, sex chromosomes and immune response genes. In this brief review, we discuss current knowledge and new insights into these intricate relationships in the context of viral infections.

Introduction

Age, sex and immune state of the host are considered salient biological factors that determine the extent and strength of pathogen clearance during infectious diseases (1–3). With regard to viral infections, epidemiological studies have revealed that males have a higher mortality rate compared to females, who reportedly display stronger antiviral cellular and humoral immune responses (4). Although stronger immune responses may provide better protection against certain pathogens, in some chronic viral infections, it can lead to aberrant antigenic responses with immunopathology (5, 6). Net sex differences or the degree of sexual dimorphism in biological responses derive from genetic differences in chromosome complement and induce their effects via acute activational or prenatal organizational/epigenetic effects of gonadal sex hormones (estrogen, progesterone and androgens), extra-gonadal effects of sex chromosome encoded genes and compensatory mechanisms, such as reduction in gene dosage differences through X-chromosome

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inactivation. These processes underlie sex differences in most tissue responses during normal and diseases states including immunological responses to infectious diseases (Figure 1).

Differences in susceptibility and response to viral pathogens observed in male and females have been mostly attributed to activational effects of sex hormones and dosages of genes on X and Y chromosomes (4). The onset of puberty is associated with the numbers and functions of circulating granulocytes and monocytes, which are decreased but activated in females due to rising levels of progesterone in the setting of ovulation or pregnancy (7, 8). In addition, myeloid cells and lymphocytes express receptors for estrogen, progesterone and androgens, which orchestrate transcriptional pathways, ligand dependent or ligand independent signaling cascades that influence innate and adaptive immune responses to viruses (9–12). With regard to gene dosage on sex chromosomes, X-linked genes such as *IL-13, IL-4, IL-10, Xist, Tlr7, FoxP3* on X chromosome and *Sry* (testis-determining factor), *Sox9* (SRY-box 9) on Y chromosome may underlie sexually dimorphic responses that contribute to stronger innate, cellular and humoral immune responses and susceptibility to autoimmune diseases in females compared with males (13–15). Studies in humans and animal models indicate sexually dimorphic mechanisms that contribute to virologic control during infections with human immunodeficiency virus (HIV)-1, vesicular stomatitis virus (VSV), hantavirus (Seoul virus), influenza virus (H1N1), hepatitis C virus, Theiler's murine encephalomyelitis virus (TMEV), herpes simplex virus (HSV-1) and coxsackievirus B3 (CVB3) (5, 16–20). In this review, we will introduce the various mechanisms that impose sexual dimorphism in immune function in males and females. We will then discuss the impact of sexually dimorphic immune responses on pathogenesis during viral infections.

Organizational Effects of Sex Hormones on Immune Function

The initiation of sexual dimorphism occurs through early embryonic development due to effects of genes on sex chromosomes (21, 22). The sex determining region Y (SRY) gene on the Y chromosome induces male supporting cell precursors to differentiate into testosterone-expressing Sertoli cells, leading to masculinization of all tissues within the developing embryo (23–25). During embryonic development, the increased expression of multiple genes maintain the XX sex phenotype and inhibit the expression of genes, such as SOX9, a transcription factor which favor XY male phenotype (15). In males, expression of Sex Determining Region Y-Box 9 (SOX9) protein downstream of *Sry* is crucial in inducing male sex phenotype. SOX9 can independently induce male to female sex reversal in male embryos through deletion from chromosome 17 (23, 26, 27). Gonadal R-spondin1 (RSPO1) is a secreted protein that is highly expressed in female blastocysts and interacts with Wnt4, which promotes ovarian development and estrogen production via the Wnt4/β-catenin signaling pathway (28, 29). Losses of function mutational studies in RSPO1 and RSPO−/− XX mice have confirmed this observation. (27–30). FOXL2, a forkhead transcriptional regulator, also contributes to ovarian differentiation and maintaininace during embryonic development in females via suppression of testis specific or male sex determining genes such as SRY target gene Sox9 and fibroblast growth factor (Fgf) 9, the latter of which represses Wnt4 (31–34). Although SOX9 deletion is embryonic lethal, homozygous conditional inactivation and mutational studies of SOX9 have confirmed that SOX9 induces

suppression of Wnt-4, Foxl2 and β-catenin to prevent feminization of the male embryo (15). In addition, SOX9 also increases expression of genes required for male phenotype development in mammals including steroidogenic factor1 (Sf1), doublesex and mab-3 related transcription factor 1(Dmrt1), and GATA4 binding protein (23, 31, 35, 36).

Studies in rodents show that sexual dimorphism in immune function occurs through embryonic development and is maintained post-natally via the actions of gonadal hormones such as estrogen and testosterone (37–39). Prenatal castration of male mice results in post-pubertal thymic involution and aberrant T cell subset differentiation (40). Females exposed to higher concentration of androgen prenatally due to congenital adrenal hyperplasia, exhibit less modeling of behavior shown to them by other females, suggesting gender-related behavior change is due to prenatal hormonal exposure (41). Surprisingly, immune response to heterologous mixed lymphocyte reaction (MLR-A) is unaffected by perinatal masculinization in both sexes and is strongest in unmanipulated females (42, 43). Consistent with this, loss of feminization at prenatal stages, leads to decreased T-cell/ B-cell ratios compared with normally feminized mice that mirror ratios observed in male animals (44). Several studies also report the role of gonadotropin releasing hormone (GnRH), which maintains early levels of gonadal hormones in both sexes, in the prenatal patterning of the immune system. Postnatal GnRH antagonism, which inhibits expression of gonadal hormones, results in lower number of circulating CD8+ T and B cells in male rodents and primates (45). Similar studies in female rats showed reduced number of CD4+ T cells and reduced immune response of thymocytes and splenocytes to T cell mediated antigen (46, 47). The effects of estrogen and testosterone on B-cell development and differentiation also directly influence the production of IgG (48, 49). Prenatal secretion of testosterone limits the ability of males to produce immunoglobulins compared to females, who maintain much higher default plasma anti DNA immunoglobulin levels compared to males (2, 50). Additional studies in sea gull chicks depicts a reduced T cell and plasma immunoglobulin mediated immunity in prenatal testosterone treated chicks compared to control chicks (51). Activational effects of hormones at puberty further enhance sex differences in antibody production that are present at birth (see below), leading to persistently higher humoral immune response in females throughout their lifetime.

Activational effects of hormones on Immune Function

Post-pubertal expression of gonadal hormones leads to acute and reversible effects in adulthood that maintain physical and behavioral sex differences (52). Estrogen and progesterone in females and testosterone in males are the prime gonadal hormones secreted during the activational period. The effect of hormonal secretion during this period is not limited to reproductive system, but extends to multiple tissues, including those of the immune system (53). The androgen testosterone is synthesized in gonadal and adrenal tissues of both males and females, but is predominantly converted to estrogens via aromatization in the latter (54). Endogenous estrogens produced in female mammals include estrone (E1), 17β-estradiol (E2), and estriol (E3). E2 is the predominant form in females, produced by theca and granulosa cells of the ovaries in premenopausal women. The level of hormones secreted in post-pubertal female mammals varies in a cyclic fashion to facilitate ovulation and subsequent pregnancy.

Estrogen receptors (ER) exist in two forms ERα and ERβ, which bind ligands E1–3 to mediate gene expression. B and T lymphocytes, mast cells, macrophages, dendritic cells and natural killer cells predominantly express ERα (55). Hematopoietic progenitor cells express both ERα and ERβ (56). Based on studies in ERα- and ERβ-deficient mice, ERα appears to be the key regulator in differentiation of hematopoietic progenitor cells (57). Females produce higher levels of estrogen and regulate ER activation on their immune cells, which helps them to exert a stronger humoral and cellular immune response (37, 58).

ERs play vital roles in several signaling pathways, acting as a signal transduction molecule in calcium regulation across cell membrane, and inducing activation of G coupled and other surface receptors, such as receptors that drive expression of insulin growth factor (IGF) 1, and activation of ERK/MAPK, protein kinase C, PI3K and cAMP signaling (59, 60). ERα is also required for proper dendritic cell differentiation and CD40 mediated cytokine production (61). Although ERs can impact signaling pathways in ligand dependent and independent manners (62), signaling in immune cells is ligand dependent whereas signaling through coactivator-associated arginine methyltransferase (CARM)1 is ligand independent. E2 receptor (specifically ERα46 (63)), mediates anti-inflammatory signaling in monocytes and macrophages through suppression of CXC-motif ligand 8 (CXCL8) (63, 64). ERs activate STAT-signaling pathways during T and B cell proliferation, maintenance and activation. Under inflammatory conditions, ER activation also induces nitric oxide synthase and IFN-γ expression in T cells. ER ligands also mediate phosphorylation, nuclear localization and transcriptional activation of STAT1, STAT3 and STAT5 in B cells and circulating monocytes (65, 66). E2 additionally regulates STAT activity by increasing expression of cytokine inhibitor proteins such as Suppressor of Cytokine Signaling 1 and 5 in T cells and macrophages (67–70). In macrophages, ER signaling mediates inhibitory response towards pro-inflammatory genes regulated by NF-κB such as IL-6. On the other hand, E2 directly suppresses the expression of CC-motif ligand 2 (CCL2) in leukocytes, leading to reduction in migration (71, 72).

It is well established that ERs play an important role in promoting sexual dimorphism in the neonatal brain through chromatin remodeling, particularly through promoter methylation and acetylation. This process is mediated by ERα activation and dimerization, followed by nuclear translocation, DNA binding through estrogen response elements (ERE), recruitment of receptor coactivators and corepressors such as nuclear receptor corepressors (NCoR), leading to epigenetic modifications and regulation of downstream transcriptional factors (73–75). Current studies on epigenetics also indicate that methylation of ERα promoter not only contributes to sex differences in the brain, but also maintains sexual dimorphism throughout the life by creating methyl marks on the DNA of the individual (76). However, direct evidence of ER- or AR-mediated epigenetic modifications that contribute to immune cell differentiation and function has not yet been shown.

In addition to endogenous ER ligands, ligands that effect ER signaling are found in environmental sources including food, such as phytoestrogens, and pharmaceuticals, such as tamoxifen, toremifene and raloxifene, which are selective ER modulators (SERM). SERM have been used as therapeutics in multiple sclerosis, ovarian cancer, breast cancer and Ebolavirus infection to suppress the activity of Th1 cells and induce Th2 cytokine

expression (77–81). Further studies are required to understand the impact of environmental and exogenous estrogens, either independently or in combination with other factors, on immune function during exposure to pathogens.

Progesterone also mediates both stimulatory and suppressive roles in immune responses. The progesterone receptors are mainly expressed by T and NK cells but recent studies have detected them on dendritic and mesenchymal stem cells, where they suppresses Th1 and increases Th2 cytokine secretion (82, 83). Suppression of T cell cytotoxicity as well as Treg proliferation is also mediated by progesterone (84). Progesterone also inhibits the activity of NK cells via down-regulation of IFN-γ secretion (85). In macrophages, progesterone suppresses nitric oxide levels, inhibits FcγR expression and microparticle release, thereby dampening the initial immune response at initial stages of infection. During pregnancy, progesterone enhances immunomodulatory functions of mesenchymal stem cells through upregulation of PGE-2 and IL-6. This is essential in females to maintain the fetal-maternal interface (83).

Most testosterone (98%) is irreversibly converted to an active metabolite dihydrotestosterone (DHT) (86). DHT binds with higher affinity than testosterone to ARs, which are expressed in varying levels by leukocytes (87). In innate immune cells, such as neutrophils, AR signaling maintains cellular differentiation via induction of granulocyte colony-stimulating factor signaling through activation of ERK1/2 and STAT3 (88). In wound healing studies, AR regulates chemotactic ability of macrophages through upregulation of CCL2, TNF-α and CCR2 (89). AR signaling also regulates T and B cell function and development. $CD4^+$ thymocytes express lower levels of inducible AR (iAR), while $CD4^-$ $CD8^-$ and $CD8^+$ thymocytes express the highest levels (90). While AR signaling promotes Th1 mediated T-cell immune response, it also acts as an antagonist to NF-κB and interferon type I signalling pathways (91). Specifically, splenic $CD4^+$ and $CD8^+$ T cells both express iAR that binds to testosterone in males (92). Castration studies have revealed that in absence of testosterone, AR signaling suppresses the activation of CD4 and CD8+ T cells via by over production of IL-2 and IL-2R (47, 93). Moreover, absence of testosterone leads to dampening of Th1 differentiation from naïve CD4 T cells in autoimmune disease conditions through suppression of IFN-γ and IL-2 expression in males (94, 95).

Sex Chromosome Complement and Immune Function

Sex chromosome complement arises from fundamental genetic differences in XX and XY cells that are mediated by several processes such as X chromosome inactivation, X gene dosage and epigenetic modifications (96). In order to maintain X gene dosage in the female blastocyst, one of the X chromosomes is inactivated by formation of Barr bodies in individual cells (97). Barr bodies are formed as a result of Xist gene expression and histone modification making one of the X chromosomes inactive in every cell (98). This process, which is exclusive to XX somatic cells, is random, leading to cells with active maternal or paternal X, and compensates X gene dosages in all somatic cells (14). The gene products of X or Y gene also facilitate epigenetic modifications on the DNA of an individual. SRY interacts with Kruppel-associated box (KRAB) domain transcriptional factor through the high mobility box (HMG) box on SRY to recruit histone-modifying enzymes such as histone

deacetylase (HDAC) and heterochromatin protein 1, which remodels chromatin (99, 100). Few studies have evaluated sexual dimorphism in chromatin remodeling irrespective of hormonal influence and those that have, focused on the central nervous system. Thus, H3 methylation is more prevalent in males compared to females in cortical regions of the brain (101), HDAC 2 and 4 more prevalently bound to promoters of Esr1 and Cyp19a during brain differentiation in males compared to females. This increased interaction leads to stronger deacetylation and higher gene expression (102).

MiRNAs are also sexually dimorphic in nature and are observed to regulate SRY related genes. For example, in prenatal stage miR-124 is highly expressed in female supporting cells and suppresses Sox9 gene expression. MiR-202-5p/3p on the other hand is highly expressed in males through SOX9, which is generated by male supporting cells, and necessary for male sex determination. Data also suggests that miR-202-5p is a direct transcriptional target of SOX9 during testis differentiation (103). Interestingly, miR-124 has also been shown to inhibit STAT3 signaling, which suppresses T cell proliferation and leads to Foxp3+ regulatory T cell induction, including upregulation of interleukin-2, IFN-γ and TNF-α (104, 105). Another study using a murine model of multiple sclerosis found that peripheral administration of miR-124 leads to systemic deactivation of macrophages, reduced activation of myelin-specific T cells and suppression of disease progression (106). Since research regarding the role of sex chromosome complement in many physiologic and disease processes is still in early stages, less is known about their contributions to antiviral immunity. However, studies using four core genotype mice, in which role of XX versus XY genes can be separated from those of gonadal hormonal effects, are providing new insights into the impact of sex chromosome complement on immune responses, particularly during autoimmune diseases.

Female bias in disease expression of autoimmunity is well established with female to male ratios in systemic lupus erythematosis (SLE) and multiple sclerosis approaching 4:1 and 9:1, respectively. A study of sex chromosome aneuploidy in male subjects expressing an excess X chromosome found they were at a higher risk for SLE (107). Thus X chromosome likely plays a crucial role in disease incidence independently of hormonal effects (107, 108). The four-core genotype (FCG) mouse model is a novel tool for examining the effect of sex chromosome complement XX and XY on phenotypic sex differences induced in male and female mice without the confounding effects of hormonal patterning. In the FCG model, the testis-determining gene Sry is deleted from Y chromosome on male B6 or SJL mice (XY^-) and a transgenic Sry is inserted at multiple sites on an autosome (109). The model generates four genotypes of mice wherein Sry transgene is present in XX and XY^- mice, which develop testis in contrast to the XY^- mice, which instead develop ovaries similar to XX mice (109). Gonadectomy of FCG allows further examination of genetic contributions of sex chromosomes in adult animals that do not express sex steroids.

Using FCG mice, XXSry mice were found to display increased susceptibility for systemic lupus erythematosus (SLE) and experimental autoimmune encephalomyelitis (EAE) compared to XY^-Sry mice. Since, both XXSry and XY^-Sry had testis during development and the only difference between the two groups is the presence of Y chromosome complement, this study confirmed that sex complement alone could promote susceptibility

to diseases irrespective of the hormonal secretions (52, 108). Further comparison between XX and XY^{-} mice reported higher levels of IL-13Rα2 and reduced levels of Th2 cytokines in spleen cells isolated from XX mouse. These results suggest that subdued Th2 cytokine levels due to increase in X linked gene IL-13Rα2 expression could be due to X chromosome complement (108).

Sexually Dimorphic Immunity to Viral infections

Differences in susceptibility to viral infections are likely due to inherent differences in the immune system of females and males. Female mount a stronger immune response to viral infections compared to males due to more robust humoral and cellular immune responses (Figure 2). Clinical studies of humans in viral infections are complicated by the impact of non-biological factors, such as exposure rates, social behavior, habitat and diet, on viral pathogenesis in a sex-specific fashion. However, studies in a controlled setting have suggested that levels of estrogen and testosterone differentially alter expression of genes involved in innate immunity, such as those encoding TLRs and interferons (IFN), in females and males thereby contributing to sexual dimorphism in viral infections.

Immune response to viral infections

Innate immune response is the first line of defense against any viral infection. Males and females depict a different pattern of response to viral infections. Innate response is primarily mediated by three classes of pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs), retinoic acid-inducible gene I (RIG-I)-like receptors (RLRs), and nucleotide oligomerization domain (NOD)-like receptors (NLRs) (110, 111). These PRRs detect viral components, such as genomic DNA, double-stranded RNA (dsRNA), single-stranded RNA (ssRNA), RNA with 5'-triphosphate ends and viral proteins. The TLRs and RLRs specifically regulate the production of type 1 interferon (IFN) and other cytokines. NLRs on the other hand regulate interleukin (IL)-1β through caspase-1 activation (110, 112, 113). Sexual dimorphism is observed during antiviral responses mediated by TLR and IFN pathway (114, 115). Immune cells in females exhibit a 10-fold higher expression of TLR compared to males (116). In mammals, the number and activity of innate immune cells such as monocytes, macrophages and dendritic cells are higher in females than males. As a result, response to antigens, vaccines and infections is also higher in females compared to males (3, 117). Adaptive immune response also depicts a great share of sexual differences in response to viral infections. Depending on the stage of the infection, females exhibit higher inflammatory Th1, anti-inflammatory Th2 compared to males (3). Additionally, upregulation of anti-inflammatory genes and higher cytotoxic T cell activity is observed in females. Some studies have also shown higher number of regulatory T cells in females compared to males. Clinical investigations in humans have also reported lower CD3+, CD4+, and CD4+: CD8+ ratios, T helper cells in males compared to females (44, 118).

DNA virus members of the Herpesviridae Family

Herpes Simplex viruses (HSV-1 and HSV-2)

Infection with HSVs, DNA viruses that cause oral and genital herpes, and rare encephalitis in immunocompetent individuals, can lead to devastating disease in neonates and immunocompromised patients, via extensive dissemination to visceral organs and the CNS (119). In males, the T cell suppressive effects of androgens appear to protect against inflammatory-mediated demyelination infected with HSV-1 (120). Studies in mice have shown that E2 treatment increases chances of survival, decreases vaginal pathology and inflammation in HSV-1 infected females (121). Consistent with this, females infected with HSV generate higher levels of HSV specific IgG and IgM compared to males (122). Similarly, females infected with HSV-2 are protected against neurological damage and viral reactivation via virus specific CD8+ T cell activation (123, 124). Studies in ovariectomized mouse models have indicated that progesterone treatment increases the susceptibility of females to genital HSV-2 infection whereas estrogen treatment helps clear the infection rapidly. Interestingly, combined treatment of estrogen and progesterone in ovariectomized mice depicted increases the infection spread accompanied by persistent inflammation and neutrophil infiltration (125, 126). Although studies do not directly indicate the organizational effect but effect of estrogen and progesterone in ovariectomized animals suggests effect of sex hormones in HSV-2 infection.

Cytomegalovirus (CMV/MCMV)

CMV, a member of the Herpesviridae family with a large genome, causes systemic viral infections in immunocompetent individuals, which may be devastating and life-threatening in the immunocompromised (127). Knowledge of sexual dimorphism in CMV infection stems from experiments in murine CMV (MCMV), which is genetically similar to CMV and has been used to study the pathogenesis of CMV using mouse models. In MCMV-infected female mice, IFNα/β production by splenic plasmacytoid dendritic cells (pDCs) controls viral replication and is required to prevent viral reactivation (128). Studies in $MyD88^{-/-}$ mice infected with MCMV showed suppression of TLR9 signaling in neutrophils of female mice, which was associated with increased viral replication (129). Additionally, CD4+ T cell mediated responses, including expression of TNF-α, IL-12, IL-6 and IFN-γ, which are required for clearance of CMV, is also mainly mediated by TLR9 signaling, which is decreased in females (130, 131).

RNA Viruses

Hantavirus

Hantavirus is a negative-sense RNA virus member of the Bunyviridae family that predominantly infects rodents. Airborne transmission of virus occurs in humans by exposure to rodent urine, feces and saliva and leads to Hantavirus Pulmonary Syndrome (HPV), a severe respiratory disease that may be fatal (132). Male rats infected with the Seoul virus (SEOV) strain exhibit higher viral burdens in target organs and shed virus for a longer duration than similarly infected female animals (16, 133, 134). Accordingly, antiviral and proinflammatory factors such as *Tlr7, MyD88, Ifnβ, TNF-α and Ccl5* are more highly

expressed in female rodents (16, 135). Consistent with this, acute infection with Puumala virus (PUUV) strain in humans is associated with higher concentrations of IL-9 and GM-CSF in females compared to males (136, 137).

Coxsackievirus (CV) B3

Coxsackie viruses belong to the Picornaviridae family of positive-sense strand RNA viruses, of the genus Enterovirus. CVB3 infection leads to myocarditis during acute and chronic phase, which affects more males than females with double the mortality rate in infected individuals under the age of 40 (138). Cardiomyoctes are directly infected by CVB3 during the acute phase, which is followed by a chronic phase with prolonged T cell mediated immune response and persistence of CVB3 virus within the heart (139). Coxsackievirus-adenovirus receptor (CAR), is required for CVB3 entry into cardiomyoctes (140). The chronic phase CVB3 myocarditis is an autoimmune disease that requires Th17 cells, whose differentiation and expression of IL-17 is suppressed by estrogen, making females less susceptible to autoimmune myocarditis (138, 141). In contrast, lack of estrogen and presence of testosterone induces Th17 cell differentiation in CVB3 infected males, enhancing autoimmune-mediated cardiac damage. In females, Th2 and Treg mediated immune responses, which are increased through ERα signaling in T cells and macrophages in heart tissues suppresses CVB3-mediated immunopathology while clearing infection (139, 142). A recent study also indicates that sex chromosome complement plays a significant role in survival from CVB3 infection. Survival of CVB3-infected B6-ChrY consomic male mice was exclusively dependent on Y^{CVB3} loci on chromosome Y and independent of prenatal or adult testosterone (24). In summary, the immune make up of the males and presence of male sex steroid testosterone promotes the spread of CVB3 virus leading to myocarditis. Sex complement as well as activational effect of hormone contributes towards CVB3 viral pathogenesis.

Influenza

H5N1 avian influenza, H1N1 and H2N2 pandemic influenza, RNA viruses that cause severe, inflammatory-induced respiratory diseases, all demonstrate significant sexual dimorphism in their incidences, affecting more females than males (143, 144). Reports on H1N1 pandemic influenza indicated higher mortality in females of reproductive age (20–49 years), implicating roles for female gonadal hormones, especially during pregnancy (145). In murine studies, H1N1 infection in female mice prolongs the diestrus cycle, leading to lower serum levels of E2 (5, 145, 146). This reduction in E2 significantly increases the expression of inflammatory cytokines and chemokines, including TNF-α, IFN-γ, IL-6 and CCL2, that latter of which promoted the influx of mononuclear cells into virally infected lungs and exacerbated immune responses (5, 147). Under chronic infection, low levels of E2 binds to ER-α and modulates NF-κB transcriptional activity, further contributing to augmented inflammatory responses and immunopathology (114, 145). In contrast, lower levels of estrogen and higher level of androgen in influenza-infected males have been linked to immunosupression and reduced T cell counts, which may limit immunopathology in males (148). Clearly more studies emphasizing on the interplay between sex, hormones and genes are required to further understand sexual dimorphism behind influenza pathogenesis.

Human Immunodeficiency virus (HIV)-1

Untreated HIV-1 infection leads to acquired immune deficiency syndrome (AIDS), with near complete loss of CD4+ T cells. Meta-analysis data indicates 41% less HIV RNA in women compared to men following primary infection, which gradually increase to a higher viral load set point compared to males after chronic infection (149–151). In females, HIV-1 promotes type 1 IFN production by pDCs via TLR7 signaling, which itself is increased downstream of E3 signaling (115, 152). These effects lead to strong, initial cellular responses that limit HIV-1 replication (153). Continuous production of type 1 IFN by pDCs in females, however, leads to chronic T cell activation with CCR5 expression, providing more targets for HIV-1 (154). In HIV-1 infected women, plasmacytoid dendritic cells (pDCs) isolated from females produce more IFN-α through TLR7 ligand activation. This results in a secondary activation of CD8+ T cells (115). Follow up studies have shown that even with same viral load pDCs obtained from females showed higher CD8+ T cell activation compared to men (115). Additionally, females mount a stronger B and T cell activation following HIV-1 infection due to higher baseline count of $CD4^+$ T and $CD8^+$ T cells in women as compared to men (115, 151). The concentration of estrogen binding SHBG is increased in HIV infected male individuals. Though the mechanism is not very well understood, suppressing SHBG levels, subdues the severity of HIV infection in male HIV patients (155, 156). Another recent study in SCID mice showed that estrogen receptors ESR1 and ESR2 and X chromosome complement in females are necessary for IFN-α and TNF-α production under TLR7 activation in pDCs (157). This study confirmed that estrogen, female sex hormones and X chromosome dosage confers stronger innate and adaptive immune response in females compared to males in HIV infection. These studies together suggest that estradiol treatment could facilitate a stronger immune response to HIV infection.

Although, sexual dimorphism is observed in HIV pathogenesis, studies are needed to better understand the underlying mechanisms that contribute to sex based immune cell regulation in HIV-1-infected patients. These will assist in the design of experiments and the accuracy of clinical trials in HIV-1-infected populations.

Vaccine for viral infections

Sexually dimorphic response to viral vaccines is observed in males and females. Viral vaccines against Hepatitis A, Hepatitis B and HSV-2 all indicate a stronger side effect in young females following immunization. Additionally, higher IgA and IgG antibody response as well as higher transcriptional activation of genes important in immune cell signaling such as IFN and TLR7 are also observed in females compared to males (143, 158). These studies clearly demonstrate that development of vaccines against viral infection should carefully consider the effect of differential immune response in males and females.

Conclusions

This review highlights both early and recent findings regarding the impact of sex on immune cell numbers and function with a focus on sexually dimorphic phenotypes during viral infections. Although still an emerging field, it is clear that mechanisms by which mammals

achieve and maintain sex differences can directly and indirectly influence host-pathogen interactions at the cellular and molecular level. These findings support the notion that there are, in fact, “two normals” with regard to manifestations of infectious diseases, with sex-specific responses during acute virologic control and in immunopathologic manifestations of viral infections. Accordingly, the development of therapeutics to treat various phases of viral infections will require continued study and comparisons of viral pathogenesis in female and male animals and humans.

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References

1. Marriott I, Huet-Hudson YM. Sexual dimorphism in innate immune responses to infectious organisms. Immunologic Research. 2006; 34:177–192. [PubMed: 16891670]
2. Butterworth M, McClellan B, Allansmith M. Influence of sex in immunoglobulin levels. Nature. 1967; 214:1224–1225. [PubMed: 4169229]
3. Klein SL, Flanagan KL. Sex differences in immune responses. Nat Rev Immunol. 2016
4. Klein SL. Sex influences immune responses to viruses, and efficacy of prophylaxis and treatments for viral diseases. Bioessays. 2012; 34:1050–1059. [PubMed: 23012250]
5. Larcombe AN, Foong RE, Bozanich EM, Berry LJ, Garratt LW, Gualano RC, Jones JE, Dousha LF, Zosky GR, Sly PD. Sexual dimorphism in lung function responses to acute influenza A infection. Influenza Other Respir Viruses. 2011; 5:334–342. [PubMed: 21668688]
6. Molina V, Shoenfeld Y. Infection, vaccines and other environmental triggers of autoimmunity. Autoimmunity. 2005; 38:235–245. [PubMed: 16126512]
7. Lamason R, Zhao P, Rawat R, Davis A, Hall JC, Chae JJ, Agarwal R, Cohen P, Rosen A, Hoffman EP, Nagaraju K. Sexual dimorphism in immune response genes as a function of puberty. BMC Immunol. 2006; 7:2. [PubMed: 16504066]
8. Luppi P, Haluszczak C, Betters D, Richard CA, Trucco M, DeLoia JA. Monocytes are progressively activated in the circulation of pregnant women. J Leukoc Biol. 2002; 72:874–884. [PubMed: 12429709]
9. Kaushic C, Roth KL, Anipindi V, Xiu F. Increased prevalence of sexually transmitted viral infections in women: the role of female sex hormones in regulating susceptibility and immune responses. J Reprod Immunol. 2011; 88:204–209. [PubMed: 21296427]
10. Oertelt-Prigione S. The influence of sex and gender on the immune response. Autoimmun Rev. 2012; 11:A479–A485. [PubMed: 22155201]
11. Klein SL, Marriott I, Fish EN. Sex-based differences in immune function and responses to vaccination. Trans R Soc Trop Med Hyg. 2015; 109:9–15. [PubMed: 25573105]
12. Fischer J, Jung N, Robinson N, Lehmann C. Sex differences in immune responses to infectious diseases. Infection. 2015; 43:399–403. [PubMed: 25956991]
13. Wang J, Syrett CM, Kramer MC, Basu A, Atchison ML, Anguera MC. Unusual maintenance of X chromosome inactivation predisposes female lymphocytes for increased expression from the inactive X. Proc Natl Acad Sci U S A. 2016; 113:E2029–E2038. [PubMed: 27001848]
14. Dixon-McDougall T, Brown C. The making of a Barr body: the mosaic of factors that eXIST on the mammalian inactive X chromosome. Biochem Cell Biol. 2016; 94:56–70. [PubMed: 26283003]
15. Barrionuevo F, Bagheri-Fam S, Klattig J, Kist R, Taketo MM, Englert C, Scherer G. Homozygous inactivation of Sox9 causes complete XY sex reversal in mice. Biol Reprod. 2006; 74:195–201. [PubMed: 16207837]

16. Hannah MF, Bajic VB, Klein SL. Sex differences in the recognition of and innate antiviral responses to Seoul virus in Norway rats. Brain Behav Immun. 2008; 22:503–516. [PubMed: 18053684]
17. Geurs TL, Hill EB, Lippold DM, French AR. Sex differences in murine susceptibility to systemic viral infections. J Autoimmun. 2012; 38:J245–J253. [PubMed: 22209097]
18. Hagen S, Altfeld M. The X awakens: multifactorial ramifications of sex-specific differences in HIV-1 infection. J Virus Erad. 2016; 2:78–81. [PubMed: 27482439]
19. Fish EN. The X-files in immunity: sex-based differences predispose immune responses. Nat Rev Immunol. 2008; 8:737–744. [PubMed: 18728636]
20. 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. Am J Physiol Lung Cell Mol Physiol. 2016; 310:L415–L425. [PubMed: 26684252]
21. Bermejo-Alvarez P, Rizos D, Lonergan P, Gutierrez-Adan A. Transcriptional sexual dimorphism during preimplantation embryo development and its consequences for developmental competence and adult health and disease. Reproduction. 2011; 141:563–570. [PubMed: 21339284]
22. Lowe R, Gemma C, Rakyan VK, Holland ML. Sexually dimorphic gene expression emerges with embryonic genome activation and is dynamic throughout development. BMC Genomics. 2015; 16:295. [PubMed: 25888192]
23. Sekido R, Lovell-Badge R. Sex determination involves synergistic action of SRY and SF1 on a specific Sox9 enhancer. Nature. 2008; 453:930–934. [PubMed: 18454134]
24. Case LK, Toussaint L, Moussawi M, Roberts B, Saligrama N, Brossay L, Huber SA, Teuscher C. Chromosome y regulates survival following murine coxsackievirus b3 infection. G3 (Bethesda). 2012; 2:115–121. [PubMed: 22384388]
25. Makiyan Z. Studies of gonadal sex differentiation. Organogenesis. 2016; 12:42–51. [PubMed: 26950283]
26. Durando M, Cocito L, Rodriguez HA, Varayoud J, Ramos JG, Luque EH, Munoz-de-Toro M. Neonatal expression of amh, sox9 and sf-1 mRNA in Caiman latirostris and effects of in ovo exposure to endocrine disrupting chemicals. Gen Comp Endocrinol. 2013; 191:31–38. [PubMed: 23747749]
27. Lavery R, Chassot AA, Pauper E, Gregoire EP, Klopfenstein M, de Rooij DG, Mark M, Schedl A, Ghyselinck NB, Chaboissier MC. Testicular differentiation occurs in absence of R-spondin1 and Sox9 in mouse sex reversals. PLoS Genet. 2012; 8:e1003170. [PubMed: 23300469]
28. Tomizuka K, Horikoshi K, Kitada R, Sugawara Y, Iba Y, Kojima A, Yoshitome A, Yamawaki K, Amagai M, Inoue A, Oshima T, Kakitani M. R-spondin1 plays an essential role in ovarian development through positively regulating Wnt-4 signaling. Hum Mol Genet. 2008; 17:1278–1291. [PubMed: 18250097]
29. Chassot AA, Ranc F, Gregoire EP, Roepers-Gajadien HL, Taketo MM, Camerino G, de Rooij DG, Schedl A, Chaboissier MC. Activation of beta-catenin signaling by Rspo1 controls differentiation of the mammalian ovary. Hum Mol Genet. 2008; 17:1264–1277. [PubMed: 18250098]
30. Smith CA, Shoemaker CM, Roeszler KN, Queen J, Crews D, Sinclair AH. Cloning and expression of R-Spondin1 in different vertebrates suggests a conserved role in ovarian development. BMC Dev Biol. 2008; 8:72. [PubMed: 18651984]
31. Kim Y, Kobayashi A, Sekido R, DiNapoli L, Brennan J, Chaboissier MC, Poulat F, Behringer RR, Lovell-Badge R, Capel B. Fgf9 and Wnt4 act as antagonistic signals to regulate mammalian sex determination. PLoS Biol. 2006; 4:e187. [PubMed: 16700629]
32. Schmidt D, Ovitt CE, Anlag K, Fehsenfeld S, Gredsted L, Treier AC, Treier M. The murine winged-helix transcription factor Foxl2 is required for granulosa cell differentiation and ovary maintenance. Development. 2004; 131:933–942. [PubMed: 14736745]
33. Ottolenghi C, Omari S, Garcia-Ortiz JE, Uda M, Crisponi L, Forabosco A, Pilia G, Schlessinger D. Foxl2 is required for commitment to ovary differentiation. Hum Mol Genet. 2005; 14:2053–2062. [PubMed: 15944199]
34. Uhlenhaut NH, Jakob S, Anlag K, Eisenberger T, Sekido R, Kress J, Treier AC, Klugmann C, Klasen C, Holter NI, Riethmacher D, Schutz G, Cooney AJ, Lovell-Badge R, Treier M. Somatic

sex reprogramming of adult ovaries to testes by FOXL2 ablation. Cell. 2009; 139:1130–1142. [PubMed: 20005806]

35. Kashimada K, Svingen T, Feng CW, Pelosi E, Bagheri-Fam S, Harley VR, Schlessinger D, Bowles J, Koopman P. Antagonistic regulation of Cyp26b1 by transcription factors SOX9/SF1 and FOXL2 during gonadal development in mice. FASEB J. 2011; 25:3561–3569. [PubMed: 21757499]
36. Matson CK, Murphy MW, Sarver AL, Griswold MD, Bardwell VJ, Zarkower D. DMRT1 prevents female reprogramming in the postnatal mammalian testis. Nature. 2011; 476:101–104. [PubMed: 21775990]
37. Kovats S. Estrogen receptors regulate innate immune cells and signaling pathways. Cell Immunol. 2015; 294:63–69. [PubMed: 25682174]
38. Tejera-Alhambra M, Alonso B, Teijeiro R, Ramos-Medina R, Aristimuno C, Valor L, de Andres C, Sanchez-Ramon S. Perforin expression by CD4+ regulatory T cells increases at multiple sclerosis relapse: sex differences. Int J Mol Sci. 2012; 13:6698–6710. [PubMed: 22837658]
39. McCarthy MM, Arnold AP. Reframing sexual differentiation of the brain. Nat Neurosci. 2011; 14:677–683. [PubMed: 21613996]
40. Azad N, LaPaglia N, Agrawal L, Steiner J, Uddin S, Williams DW, Lawrence AM, Emanuele NV. The role of gonadectomy and testosterone replacement on thymic luteinizing hormone-releasing hormone production. J Endocrinol. 1998; 158:229–235. [PubMed: 9771467]
41. Hines M, Pasterski V, Spencer D, Neufeld S, Patalay P, Hindmarsh PC, Hughes IA, Acerini CL. Prenatal androgen exposure alters girls' responses to information indicating gender-appropriate behaviour. Philos Trans R Soc Lond B Biol Sci. 2016; 371:20150125. [PubMed: 26833843]
42. Konstadoulakis MM, Syrigos KN, Baxevanis CN, Syrigou EI, Papamichail M, Peveretos P, Anapliotou M, Golematis BC. Effect of testosterone administration, pre- and postnatally, on the immune system of rats. Horm Metab Res. 1995; 27:275–278. [PubMed: 7557838]
43. Weinstein Y, Ran S, Segal S. Sex-associated differences in the regulation of immune responses controlled by the MHC of the mouse. J Immunol. 1984; 132:656–661. [PubMed: 6228595]
44. Amadori A, Zamarchi R, De Silvestro G, Forza G, Cavatton G, Danieli GA, Clementi M, Chieco-Bianchi L. Genetic control of the CD4/CD8 T-cell ratio in humans. Nat Med. 1995; 1:1279–1283. [PubMed: 7489409]
45. Gould KG, Akinbami MA, Mann DR. Effect of neonatal treatment with a gonadotropin releasing hormone antagonist on developmental changes in circulating lymphocyte subsets: a longitudinal study in male rhesus monkeys. Dev Comp Immunol. 1998; 22:457–467. [PubMed: 9699491]
46. Mann DR, Fraser HM. The neonatal period: a critical interval in male primate development. J Endocrinol. 1996; 149:191–197. [PubMed: 8708529]
47. Page ST, Plymate SR, Bremner WJ, Matsumoto AM, Hess DL, Lin DW, Amory JK, Nelson PS, Wu JD. Effect of medical castration on CD4+ CD25+ T cells, CD8+ T cell IFN-gamma expression, and NK cells: a physiological role for testosterone and/or its metabolites. Am J Physiol Endocrinol Metab. 2006; 290:E856–E863. [PubMed: 16352669]
48. Paavonen T, Andersson LC, Adlercreutz H. Sex hormone regulation of in vitro immune response. Estradiol enhances human B cell maturation via inhibition of suppressor T cells in pokeweed mitogen-stimulated cultures. J Exp Med. 1981; 154:1935–1945. [PubMed: 6459399]
49. Sthoeger ZM, Chiorazzi N, Lahita RG. Regulation of the immune response by sex hormones. I. In vitro effects of estradiol and testosterone on pokeweed mitogen-induced human B cell differentiation. J Immunol. 1988; 141:91–98. [PubMed: 3288699]
50. Ainbender E, Weisinger RB, Hevizy M, Hodes HL. Difference in the immunoglobulin class of polioantibody in the serum of men and women. J Immunol. 1968; 101:92–98. [PubMed: 4173940]
51. Muller W, Groothuis TG, Kasprzik A, Dijkstra C, Alatalo RV, Siitari H. Prenatal androgen exposure modulates cellular and humoral immune function of black-headed gull chicks. Proc Biol Sci. 2005; 272:1971–1977. [PubMed: 16191605]
52. Arnold AP. The organizational-activational hypothesis as the foundation for a unified theory of sexual differentiation of all mammalian tissues. Horm Behav. 2009; 55:570–578. [PubMed: 19446073]
53. Gaumond I, Arsenault P, Marchand S. The role of sex hormones on formalin-induced nociceptive responses. Brain Res. 2002; 958:139–145. [PubMed: 12468038]

54. Lai JJ, Lai KP, Zeng W, Chuang KH, Altuwaijri S, Chang C. Androgen receptor influences on body defense system via modulation of innate and adaptive immune systems: lessons from conditional AR knockout mice. Am J Pathol. 2012; 181:1504–1512. [PubMed: 22959669]
55. Nilsson S, Makela S, Treuter E, Tujague M, Thomsen J, Andersson G, Enmark E, Pettersson K, Warner M, Gustafsson JA. Mechanisms of estrogen action. Physiol Rev. 2001; 81:1535–1565. [PubMed: 11581496]
56. Phiel KL, Henderson RA, Adelman SJ, Elloso MM. Differential estrogen receptor gene expression in human peripheral blood mononuclear cell populations. Immunol Lett. 2005; 97:107–113. [PubMed: 15626482]
57. Nakada D, Oguro H, Levi BP, Ryan N, Kitano A, Saitoh Y, Takeichi M, Wendt GR, Morrison SJ. Oestrogen increases haematopoietic stem-cell self-renewal in females and during pregnancy. Nature. 2014; 505:555–558. [PubMed: 24451543]
58. Bird MD, Karavitis J, Kovacs EJ. Sex differences and estrogen modulation of the cellular immune response after injury. Cell Immunol. 2008; 252:57–67. [PubMed: 18294625]
59. Zhou T, Yang Z, Chen Y, Huang Z, You B, Peng Y, Chen J. Estrogen Accelerates Cutaneous Wound Healing by Promoting Proliferation of Epidermal Keratinocytes via Erk/Akt Signaling Pathway. Cell Physiol Biochem. 2016; 38:959–968. [PubMed: 26938432]
60. Xie H, Hua C, Sun L, Zhao X, Fan H, Dou H, Hou Y. 17beta-estradiol induces CD40 expression in dendritic cells via MAPK signaling pathways in a minichromosome maintenance protein 6-dependent manner. Arthritis Rheum. 2011; 63:2425–2435. [PubMed: 21538324]
61. Douin-Echinard V, Laffont S, Seillet C, Delpy L, Krust A, Chambon P, Gourdy P, Arnal JF, Guery JC. Estrogen receptor alpha, but not beta, is required for optimal dendritic cell differentiation and [corrected] CD40-induced cytokine production. J Immunol. 2008; 180:3661–3669. [PubMed: 18322171]
62. Carascossa S, Dudek P, Cenni B, Briand PA, Picard D. CARM1 mediates the ligand-independent and tamoxifen-resistant activation of the estrogen receptor alpha by cAMP. Genes Dev. 2010; 24:708–719. [PubMed: 20360387]
63. Murphy AJ, Guyre PM, Wira CR, Pioli PA. Estradiol regulates expression of estrogen receptor ERalpha46 in human macrophages. PLoS One. 2009; 4:e5539. [PubMed: 19440537]
64. Lasarte S, Elsner D, Sanchez-Elsner T, Fernandez-Pineda A, Lopez-Fernandez LA, Corbi AL, Munoz-Fernandez MA, Relloso M. Estradiol downregulates NF-kappab translocation by Ikbkg transcriptional repression in dendritic cells. Genes Immun. 2013; 14:462–469. [PubMed: 23883819]
65. Ho HH, Ivashkiv LB. Role of STAT3 in type I interferon responses. Negative regulation of STAT1-dependent inflammatory gene activation. J Biol Chem. 2006; 281:14111–14118. [PubMed: 16571725]
66. Kuchipudi SV. The Complex Role of STAT3 in Viral Infections. J Immunol Res. 2015; 2015:272359. [PubMed: 26199948]
67. Alexander WS, Starr R, Fenner JE, Scott CL, Handman E, Sprigg NS, Corbin JE, Cornish AL, Darwiche R, Owczarek CM, Kay TW, Nicola NA, Hertzog PJ, Metcalf D, Hilton DJ. SOCS1 is a critical inhibitor of interferon gamma signaling and prevents the potentially fatal neonatal actions of this cytokine. Cell. 1999; 98:597–608. [PubMed: 10490099]
68. Kinjyo I, Hanada T, Inagaki-Ohara K, Mori H, Aki D, Ohishi M, Yoshida H, Kubo M, Yoshimura A. SOCS1/JAB is a negative regulator of LPS-induced macrophage activation. Immunity. 2002; 17:583–591. [PubMed: 12433365]
69. Cornish AL, Davey GM, Metcalf D, Purton JF, Corbin JE, Greenhalgh CJ, Darwiche R, Wu L, Nicola NA, Godfrey DI, Heath WR, Hilton DJ, Alexander WS, Starr R. Suppressor of cytokine signaling-1 has IFN-gamma-independent actions in T cell homeostasis. J Immunol. 2003; 170:878–886. [PubMed: 12517953]
70. Brender C, Columbus R, Metcalf D, Handman E, Starr R, Huntington N, Tarlinton D, Odum N, Nicholson SE, Nicola NA, Hilton DJ, Alexander WS. SOCS5 is expressed in primary B and T lymphoid cells but is dispensable for lymphocyte production and function. Mol Cell Biol. 2004; 24:6094–6103. [PubMed: 15199163]

71. Pan T, Zhong L, Wu S, Cao Y, Yang Q, Cai Z, Cai X, Zhao W, Ma N, Zhang W, Zhang H, Zhou J. 17beta-estradiol enhances the expansion and activation of myeloid-derived suppressor cells via STAT3 signaling in human pregnancy. Clin Exp Immunol. 2016

72. Kawana K, Kawana Y, Schust DJ. Female steroid hormones use signal transducers and activators of transcription protein-mediated pathways to modulate the expression of T-bet in epithelial cells: a mechanism for local immune regulation in the human reproductive tract. Mol Endocrinol. 2005; 19:2047–2059. [PubMed: 15860546]

73. Schwarz JM, Nugent BM, McCarthy MM. Developmental and hormone-induced epigenetic changes to estrogen and progesterone receptor genes in brain are dynamic across the life span. Endocrinology. 2010; 151:4871–4881. [PubMed: 20702577]

74. Pedram A, Razandi M, Lewis M, Hammes S, Levin ER. Membrane-localized estrogen receptor alpha is required for normal organ development and function. Dev Cell. 2014; 29:482–490. [PubMed: 24871949]

75. Zhang X, Tanaka K, Yan J, Li J, Peng D, Jiang Y, Yang Z, Barton MC, Wen H, Shi X. Regulation of estrogen receptor alpha by histone methyltransferase SMYD2-mediated protein methylation. Proc Natl Acad Sci U S A. 2013; 110:17284–17289. [PubMed: 24101509]

76. Edelmann MN, Auger AP. Epigenetic impact of simulated maternal grooming on estrogen receptor alpha within the developing amygdala. Brain Behav Immun. 2011; 25:1299–1304. [PubMed: 21352906]

77. Banchs HL, Gonzalez V, Gonzalez Cancel I, Quintana C, Calderon R, Altieri PI. Heart transplantation in females: the experience in Puerto Rico. Bol Asoc Med P R. 2005; 97:248–256. [PubMed: 16599066]

78. Nalbandian G, Paharkova-Vatchkova V, Mao A, Nale S, Kovats S. The selective estrogen receptor modulators, tamoxifen and raloxifene, impair dendritic cell differentiation and activation. J Immunol. 2005; 175:2666–2675. [PubMed: 16081843]

79. Marino M, Galluzzo P, Ascenzi P. Estrogen signaling multiple pathways to impact gene transcription. Curr Genomics. 2006; 7:497–508. [PubMed: 18369406]

80. Johansen LM, Brannan JM, Delos SE, Shoemaker CJ, Stossel A, Lear C, Hoffstrom BG, Dewald LE, Schornberg KL, Scully C, Lehar J, Hensley LE, White JM, Olinger GG. FDA-approved selective estrogen receptor modulators inhibit Ebola virus infection. Sci Transl Med. 2013; 5:190ra179.

81. Wisdom AJ, Cao Y, Itoh N, Spence RD, Voskuhl RR. Estrogen receptor-beta ligand treatment after disease onset is neuroprotective in the multiple sclerosis model. J Neurosci Res. 2013; 91:901–908. [PubMed: 23633287]

82. Butts CL, Shukair SA, Duncan KM, Bowers E, Horn C, Belyavskaya E, Tonelli L, Sternberg EM. Progesterone inhibits mature rat dendritic cells in a receptor-mediated fashion. Int Immunol. 2007; 19:287–296. [PubMed: 17289656]

83. Zhao X, Liu L, Liu D, Fan H, Wang Y, Hu Y, Hou Y. Progesterone enhances immunoregulatory activity of human mesenchymal stem cells via PGE2 and IL-6. Am J Reprod Immunol. 2012; 68:290–300. [PubMed: 22747921]

84. Enninga EA, Holtan SG, Creedon DJ, Dronca RS, Nevala WK, Ognjanovic S, Markovic SN. Immunomodulatory effects of sex hormones: requirements for pregnancy and relevance in melanoma. Mayo Clin Proc. 2014; 89:520–535. [PubMed: 24684874]

85. Arruvito L, Giulianelli S, Flores AC, Paladino N, Barboza M, Lanari C, Fainboim L. NK cells expressing a progesterone receptor are susceptible to progesterone-induced apoptosis. J Immunol. 2008; 180:5746–5753. [PubMed: 18390760]

86. Llewelyn DE, Read GF, Hillier SG. Proceedings: Novel procedure for the simultaneous determination of testosterone and 5alpha-dihydrotestosterone concentrations in unpurified plasma extracts by radioimmunoassay. J Endocrinol. 1975; 67:7P–8P.

87. Penning TM, Bauman DR, Jin Y, Rizner TL. Identification of the molecular switch that regulates access of 5alpha-DHT to the androgen receptor. Mol Cell Endocrinol. 2007; 265–266:77–82.

88. Chuang KH, Altuwaijri S, Li G, Lai JJ, Chu CY, Lai KP, Lin HY, Hsu JW, Keng P, Wu MC, Chang C. Neutropenia with impaired host defense against microbial infection in mice lacking androgen receptor. J Exp Med. 2009; 206:1181–1199. [PubMed: 19414555]

89. Lai JJ, Lai KP, Chuang KH, Chang P, Yu IC, Lin WJ, Chang C. Monocyte/macrophage androgen receptor suppresses cutaneous wound healing in mice by enhancing local TNF-alpha expression. J Clin Invest. 2009; 119:3739–3751. [PubMed: 19907077]

90. Olsen NJ, Kovacs WJ. Effects of androgens on T and B lymphocyte development. Immunol Res. 2001; 23:281–288. [PubMed: 11444393]

91. Kissick HT, Sanda MG, Dunn LK, Pellegrini KL, On ST, Noel JK, Arredouani MS. Androgens alter T-cell immunity by inhibiting T-helper 1 differentiation. Proc Natl Acad Sci U S A. 2014; 111:9887–9892. [PubMed: 24958858]

92. Benten WP, Becker A, Schmitt-Wrede HP, Wunderlich F. Developmental regulation of intracellular and surface androgen receptors in T cells. Steroids. 2002; 67:925–931. [PubMed: 12234628]

93. Lanini S, Nanni Costa A, Grossi PA, Procaccio F, Ricci A, Capobianchi MR, Terrault NA, Ippolito G. Liver transplant recipients and prioritization of anti-HCV therapy: an Italian cohort analysis. Liver Int. 2016; 36:410–417. [PubMed: 26264452]

94. Bao M, Yang Y, Jun HS, Yoon JW. Molecular mechanisms for gender differences in susceptibility to T cell-mediated autoimmune diabetes in nonobese diabetic mice. J Immunol. 2002; 168:5369–5375. [PubMed: 11994496]

95. Bebo BF Jr, Schuster JC, Vandenbark AA, Offner H. Androgens alter the cytokine profile and reduce encephalitogenicity of myelin-reactive T cells. J Immunol. 1999; 162:35–40. [PubMed: 9886367]

96. Arnold AP, Chen X, Itoh Y. What a difference an X or Y makes: sex chromosomes, gene dose, and epigenetics in sexual differentiation. Handb Exp Pharmacol. 2012:67–88.

97. Ercan S. Mechanisms of x chromosome dosage compensation. J Genomics. 2015; 3:1–19. [PubMed: 25628761]

98. Simon MD, Pinter SF, Fang R, Sarma K, Rutenberg-Schoenberg M, Bowman SK, Kesner BA, Maier VK, Kingston RE, Lee JT. High-resolution Xist binding maps reveal two-step spreading during X-chromosome inactivation. Nature. 2013; 504:465–469. [PubMed: 24162848]

99. Prokop JW, Rauscher FJ 3rd, Peng H, Liu Y, Araujo FC, Watanabe I, Reis FM, Milsted A. MAS promoter regulation: a role for Sry and tyrosine nitration of the KRAB domain of ZNF274 as a feedback mechanism. Clin Sci (Lond). 2014; 126:727–738. [PubMed: 24128372]

100. Oh HJ, Li Y, Lau YF. Sry associates with the heterochromatin protein 1 complex by interacting with a KRAB domain protein. Biol Reprod. 2005; 72:407–415. [PubMed: 15469996]

101. Tsai HW, Grant PA, Rissman EF. Sex differences in histone modifications in the neonatal mouse brain. Epigenetics. 2009; 4:47–53. [PubMed: 19029819]

102. Matsuda KI, Mori H, Nugent BM, Pfaff DW, McCarthy MM, Kawata M. Histone deacetylation during brain development is essential for permanent masculinization of sexual behavior. Endocrinology. 2011; 152:2760–2767. [PubMed: 21586557]

103. Wainwright EN, Jorgensen JS, Kim Y, Truong V, Bagheri-Fam S, Davidson T, Svingen T, Fernandez-Valverde SL, McClelland KS, Taft RJ, Harley VR, Koopman P, Wilhelm D. SOX9 regulates microRNA miR-202-5p/3p expression during mouse testis differentiation. Biol Reprod. 2013; 89:34. [PubMed: 23843232]

104. Wei J, Wang F, Kong LY, Xu S, Doucette T, Ferguson SD, Yang Y, McEnery K, Jethwa K, Gjyshi O, Qiao W, Levine NB, Lang FF, Rao G, Fuller GN, Calin GA, Heimberger AB. miR-124 inhibits STAT3 signaling to enhance T cell-mediated immune clearance of glioma. Cancer Res. 2013; 73:3913–3926. [PubMed: 23636127]

105. Jiang S, Li C, McRae G, Lykken E, Sevilla J, Liu SQ, Wan Y, Li QJ. MeCP2 reinforces STAT3 signaling and the generation of effector CD4+ T cells by promoting miR-124-mediated suppression of SOCS5. Sci Signal. 2014; 7:ra25. [PubMed: 24619648]

106. Ponomarev ED, Veremeyko T, Barteneva N, Krichevsky AM, Weiner HL. MicroRNA-124 promotes microglia quiescence and suppresses EAE by deactivating macrophages via the C/EBP-alpha-PU.1 pathway. Nat Med. 2011; 17:64–70. [PubMed: 21131957]

107. Dillon SP, Kurien BT, Li S, Bruner GR, Kaufman KM, Harley JB, Gaffney PM, Wallace DJ, Weisman MH, Scofield RH. Sex chromosome aneuploidies among men with systemic lupus erythematosus. J Autoimmun. 2012; 38:J129–J134. [PubMed: 22154021]

108. Smith-Bouvier DL, Divekar AA, Sasidhar M, Du S, Tiwari-Woodruff SK, King JK, Arnold AP, Singh RR, Voskuhl RR. A role for sex chromosome complement in the female bias in autoimmune disease. J Exp Med. 2008; 205:1099–1108. [PubMed: 18443225]
109. Itoh Y, Mackie R, Kampf K, Domadia S, Brown JD, O'Neill R, Arnold AP. Four core genotypes mouse model: localization of the Sry transgene and bioassay for testicular hormone levels. BMC Res Notes. 2015; 8:69. [PubMed: 25870930]
110. Medzhitov R. Recognition of microorganisms and activation of the immune response. Nature. 2007; 449:819–826. [PubMed: 17943118]
111. Kanneganti TD, Lamkanfi M, Nunez G. Intracellular NOD-like receptors in host defense and disease. Immunity. 2007; 27:549–559. [PubMed: 17967410]
112. Akira S, Uematsu S, Takeuchi O. Pathogen recognition and innate immunity. Cell. 2006; 124:783–801. [PubMed: 16497588]
113. Cao X. Self-regulation and cross-regulation of pattern-recognition receptor signalling in health and disease. Nat Rev Immunol. 2016; 16:35–50. [PubMed: 26711677]
114. Robinson DP, Lorenzo ME, Jian W, Klein SL. Elevated 17beta-estradiol protects females from influenza A virus pathogenesis by suppressing inflammatory responses. PLoS Pathog. 2011; 7:e1002149. [PubMed: 21829352]
115. Meier A, Chang JJ, Chan ES, Pollard RB, Sidhu HK, Kulkarni S, Wen TF, Lindsay RJ, Orellana L, Mildvan D, Bazner S, Streeck H, Alter G, Lifson JD, Carrington M, Bosch RJ, Robbins GK, Altfeld M. Sex differences in the Toll-like receptor-mediated response of plasmacytoid dendritic cells to HIV-1. Nat Med. 2009; 15:955–959. [PubMed: 19597505]
116. 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. 2011; 118:5918–5927. [PubMed: 21911834]
117. vom Steeg LG, Klein SL. SeXX Matters in Infectious Disease Pathogenesis. PLoS Pathog. 2016; 12:e1005374. [PubMed: 26891052]
118. 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. 2008; 9:299–308. [PubMed: 18369735]
119. Kollias CM, Huneke RB, Wigdahl B, Jennings SR. Animal models of herpes simplex virus immunity and pathogenesis. J Neurovirol. 2015; 21:8–23. [PubMed: 25388226]
120. Yirrell DL, Blyth WA, Hill TJ. The influence of androgens on paralysis in mice following intravenous inoculation of herpes simplex virus. J Gen Virol. 1987; 68(Pt 9):2461–2464. [PubMed: 2821183]
121. MacDonald EM, Savoy A, Gillgrass A, Fernandez S, Smieja M, Rosenthal KL, Ashkar AA, Kaushic C. Susceptibility of human female primary genital epithelial cells to herpes simplex virus, type-2 and the effect of TLR3 ligand and sex hormones on infection. Biol Reprod. 2007; 77:1049–1059. [PubMed: 17881767]
122. Han X, Lundberg P, Tanamachi B, Openshaw H, Longmate J, Cantin E. Gender influences herpes simplex virus type 1 infection in normal and gamma interferon-mutant mice. J Virol. 2001; 75:3048–3052. [PubMed: 11222734]
123. Mueller SN, Mackay LK. Tissue-resident memory T cells: local specialists in immune defence. Nat Rev Immunol. 2016; 16:79–89. [PubMed: 26688350]
124. van Lint A, Ayers M, Brooks AG, Coles RM, Heath WR, Carbone FR. Herpes simplex virus-specific CD8+ T cells can clear established lytic infections from skin and nerves and can partially limit the early spread of virus after cutaneous inoculation. J Immunol. 2004; 172:392–397. [PubMed: 14688347]
125. Gillgrass AE, Fernandez SA, Rosenthal KL, Kaushic C. Estradiol regulates susceptibility following primary exposure to genital herpes simplex virus type 2, while progesterone induces inflammation. J Virol. 2005; 79:3107–3116. [PubMed: 15709030]
126. Ragupathy V, Xue W, Tan J, Devadas K, Gao Y, Hewlett I. Progesterone augments cell susceptibility to HIV-1 and HIV-1/HSV-2 co-infections. J Mol Endocrinol. 2016; 57:185–199. [PubMed: 27538988]

127. Vancikova Z, Dvorak P. Cytomegalovirus infection in immunocompetent and immunocompromised individuals--a review. Curr Drug Targets Immune Endocr Metabol Disord. 2001; 1:179–187. [PubMed: 12476798]

128. Chang WL, Barry PA, Szubin R, Wang D, Baumgarth N. Human cytomegalovirus suppresses type I interferon secretion by plasmacytoid dendritic cells through its interleukin 10 homolog. Virology. 2009; 390:330–337. [PubMed: 19524994]

129. Delale T, Paquin A, Asselin-Paturel C, Dalod M, Brizard G, Bates EE, Kastner P, Chan S, Akira S, Vicari A, Biron CA, Trinchieri G, Briere F. MyD88-dependent and -independent murine cytomegalovirus sensing for IFN-alpha release and initiation of immune responses in vivo. J Immunol. 2005; 175:6723–6732. [PubMed: 16272328]

130. Traub S, Demaria O, Chasson L, Serra F, Desnues B, Alexopoulou L. Sex bias in susceptibility to MCMV infection: implication of TLR9. PLoS One. 2012; 7:e45171. [PubMed: 23028824]

131. Lester SN, Li K. Toll-like receptors in antiviral innate immunity. J Mol Biol. 2014; 426:1246–1264. [PubMed: 24316048]

132. Jonsson CB, Figueiredo LT, Vapalahti O. A global perspective on hantavirus ecology, epidemiology, and disease. Clin Microbiol Rev. 2010; 23:412–441. [PubMed: 20375360]

133. Klein SL, Bird BH, Glass GE. Sex differences in immune responses and viral shedding following Seoul virus infection in Norway rats. Am J Trop Med Hyg. 2001; 65:57–63. [PubMed: 11504409]

134. Easterbrook JD, Klein SL. Corticosteroids modulate Seoul virus infection, regulatory T-cell responses and matrix metalloprotease 9 expression in male, but not female, Norway rats. J Gen Virol. 2008; 89:2723–2730. [PubMed: 18931068]

135. Klein SL, Cernetich A, Hilmer S, Hoffman EP, Scott AL, Glass GE. Differential expression of immunoregulatory genes in male and female Norway rats following infection with Seoul virus. J Med Virol. 2004; 74:180–190. [PubMed: 15258986]

136. Vapalahti O, Mustonen J, Lundkvist A, Henttonen H, Plyusnin A, Vaheri A. Hantavirus infections in Europe. Lancet Infect Dis. 2003; 3:653–661. [PubMed: 14522264]

137. Ahlm C, Linderholm M, Juto P, Stegmayr B, Settergren B. Prevalence of serum IgG antibodies to Puumala virus (haemorrhagic fever with renal syndrome) in northern Sweden. Epidemiol Infect. 1994; 113:129–136. [PubMed: 7914872]

138. Robinson DP, Huber SA, Moussawi M, Roberts B, Teuscher C, Watkins R, Arnold AP, Klein SL. Sex chromosome complement contributes to sex differences in coxsackievirus B3 but not influenza A virus pathogenesis. Biol Sex Differ. 2011; 2:8. [PubMed: 21806829]

139. 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. 1994; 68:5126–5132. [PubMed: 8035512]

140. Kallewaard NL, Zhang L, Chen JW, Guttenberg M, Sanchez MD, Bergelson JM. Tissue-specific deletion of the coxsackievirus and adenovirus receptor protects mice from virus-induced pancreatitis and myocarditis. Cell Host Microbe. 2009; 6:91–98. [PubMed: 19616768]

141. Li Z, Yue Y, Xiong S. Distinct Th17 inductions contribute to the gender bias in CVB3-induced myocarditis. Cardiovasc Pathol. 2013; 22:373–382. [PubMed: 23523188]

142. Frisancho-Kiss S, Nyland JF, Davis SE, Frisancho JA, Barrett MA, Rose NR, Fairweather D. Sex differences in coxsackievirus B3-induced myocarditis: IL-12Rbeta1 signaling and IFN-gamma increase inflammation in males independent from STAT4. Brain Res. 2006; 1126:139–147. [PubMed: 16949558]

143. Klein SL, Pekosz A. Sex-based biology and the rational design of influenza vaccination strategies. J Infect Dis. 2014; 209(Suppl 3):S114–S119. [PubMed: 24966191]

144. Klein SL, Passaretti C, Anker M, Olukoya P, Pekosz A. The impact of sex, gender and pregnancy on 2009 H1N1 disease. Biol Sex Differ. 2010; 1:5. [PubMed: 21208468]

145. Klein SL, Hodgson A, Robinson DP. Mechanisms of sex disparities in influenza pathogenesis. J Leukoc Biol. 2012; 92:67–73. [PubMed: 22131346]

146. Torcia MG, Nencioni L, Clemente AM, Civitelli L, Celestino I, Limongi D, Fadigati G, Perissi E, Cozzolino F, Garaci E, Palamara AT. Sex differences in the response to viral infections: TLR8 and TLR9 ligand stimulation induce higher IL10 production in males. PLoS One. 2012; 7:e39853. [PubMed: 22768144]

147. Gilliver SC. Sex steroids as inflammatory regulators. J Steroid Biochem Mol Biol. 2010; 120:105–115. [PubMed: 20045727]

148. Hoffmann J, Otte A, Thiele S, Lotter H, Shu Y, Gabriel G. Sex differences in H7N9 influenza A virus pathogenesis. Vaccine. 2015; 33:6949–6954. [PubMed: 26319064]

149. Sterling TR, Vlahov D, Astemborski J, Hoover DR, Margolick JB, Quinn TC. Initial plasma HIV-1 RNA levels and progression to AIDS in women and men. N Engl J Med. 2001; 344:720–725. [PubMed: 11236775]

150. Sterling TR, Lyles CM, Vlahov D, Astemborski J, Margolick JB, Quinn TC. Sex differences in longitudinal human immunodeficiency virus type 1 RNA levels among seroconverters. J Infect Dis. 1999; 180:666–672. [PubMed: 10438353]

151. Ziegler S, Altfeld M. Sex differences in HIV-1-mediated immunopathology. Curr Opin HIV AIDS. 2016; 11:209–215. [PubMed: 26845674]

152. Sterling TR, Pisell-Noland T, Perez JL, Astemborski J, McGriff JR, Nutting L, Hoover DR, Vlahov D, Bollinger RC. Sex-based differences in T lymphocyte responses in HIV-1-seropositive individuals. J Infect Dis. 2005; 191:881–885. [PubMed: 15717262]

153. Li G, Cheng M, Nunoya J, Cheng L, Guo H, Yu H, Liu YJ, Su L, Zhang L. Plasmacytoid dendritic cells suppress HIV-1 replication but contribute to HIV-1 induced immunopathogenesis in humanized mice. PLoS Pathog. 2014; 10:e1004291. [PubMed: 25077616]

154. Tsao LC, Guo H, Jeffrey J, Hoxie JA, Su L. CCR5 interaction with HIV-1 Env contributes to Env-induced depletion of CD4 T cells in vitro and in vivo. Retrovirology. 2016; 13:22. [PubMed: 27026376]

155. Monroe AK, Dobs AS, Xu X, Palella FJ, Kingsley LA, Witt MD, Brown TT. Sex hormones, insulin resistance, and diabetes mellitus among men with or at risk for HIV infection. J Acquir Immune Defic Syndr. 2011; 58:173–180. [PubMed: 21705912]

156. Martin ME, Benassayag C, Amiel C, Canton P, Nunez EA. Alterations in the concentrations and binding properties of sex steroid binding protein and corticosteroid-binding globulin in HIV +patients. J Endocrinol Invest. 1992; 15:597–603. [PubMed: 1430842]

157. Laffont S, Rouquie N, Azar P, Seillet C, Plumas J, Aspord C, Guery JC. X-Chromosome complement and estrogen receptor signaling independently contribute to the enhanced TLR7-mediated IFN-alpha production of plasmacytoid dendritic cells from women. J Immunol. 2014; 193:5444–5452. [PubMed: 25339659]

158. Lindsey NP, Schroeder BA, Miller ER, Braun MM, Hinckley AF, Marano N, Slade BA, Barnett ED, Brunette GW, Horan K, Staples JE, Kozarsky PE, Hayes EB. Adverse event reports following yellow fever vaccination. Vaccine. 2008; 26:6077–6082. [PubMed: 18809449]

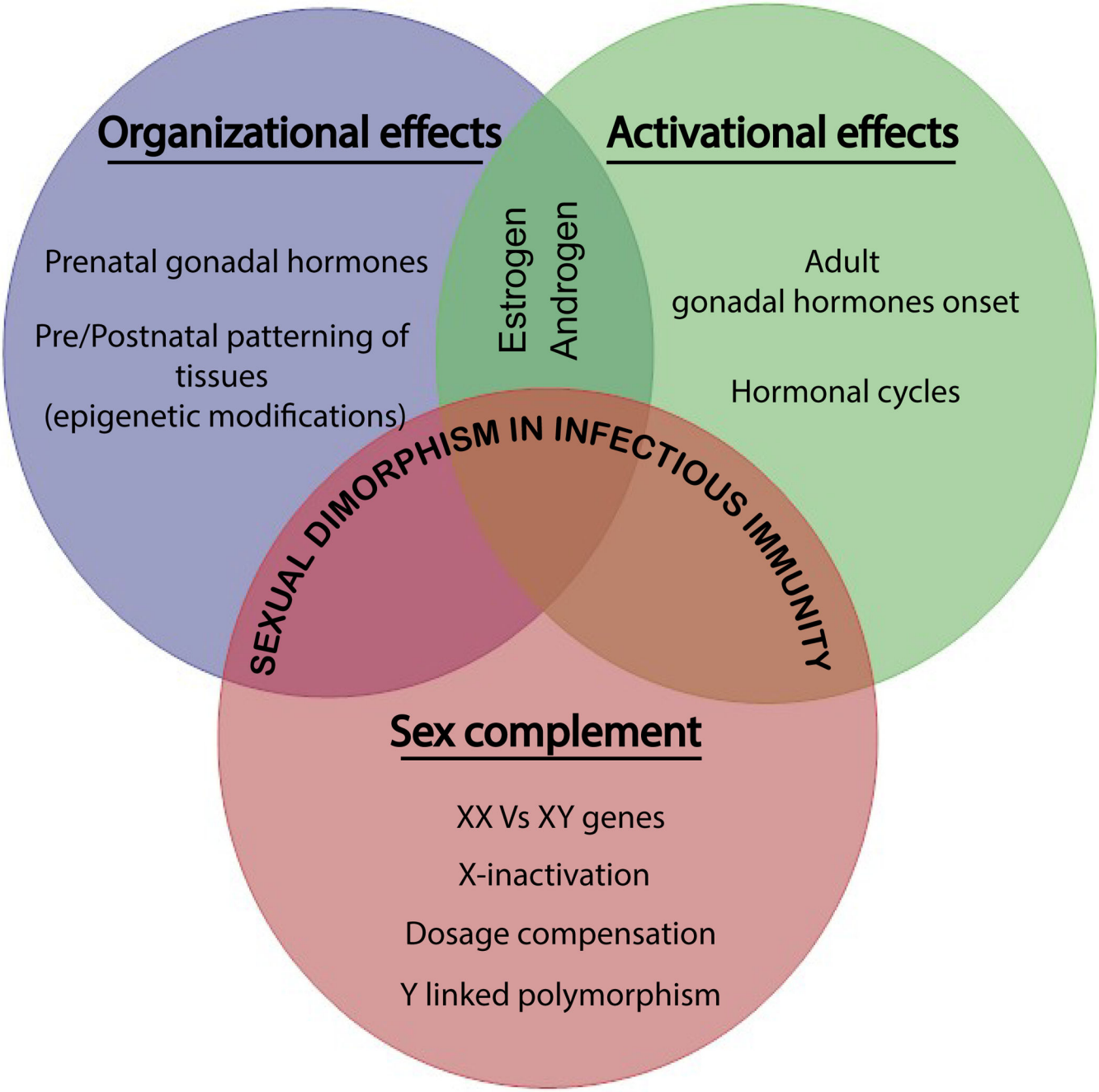

Figure 1.

Mechanisms of tissue sexual dimorphism that underlie sex differences in immune responses. Sex hormones, such as estrogens and androgens, contribute to both organizational and activational effects via gene effects that include both promoter activation and chromatin remodeling (epigenetic modifications). Sex chromosome complement exerts its effect in promoting sexual dimorphism independent of sex hormones. X-dosage compensation and escape from X-inactivation influence differential gene expression of innate immune molecules. Y chromosome contributions include Y gene-associated polymorphisms. Studies

evaluating sexual dimorphism in immune responses focus on the interdependence of these factors as well as their independent contributions.

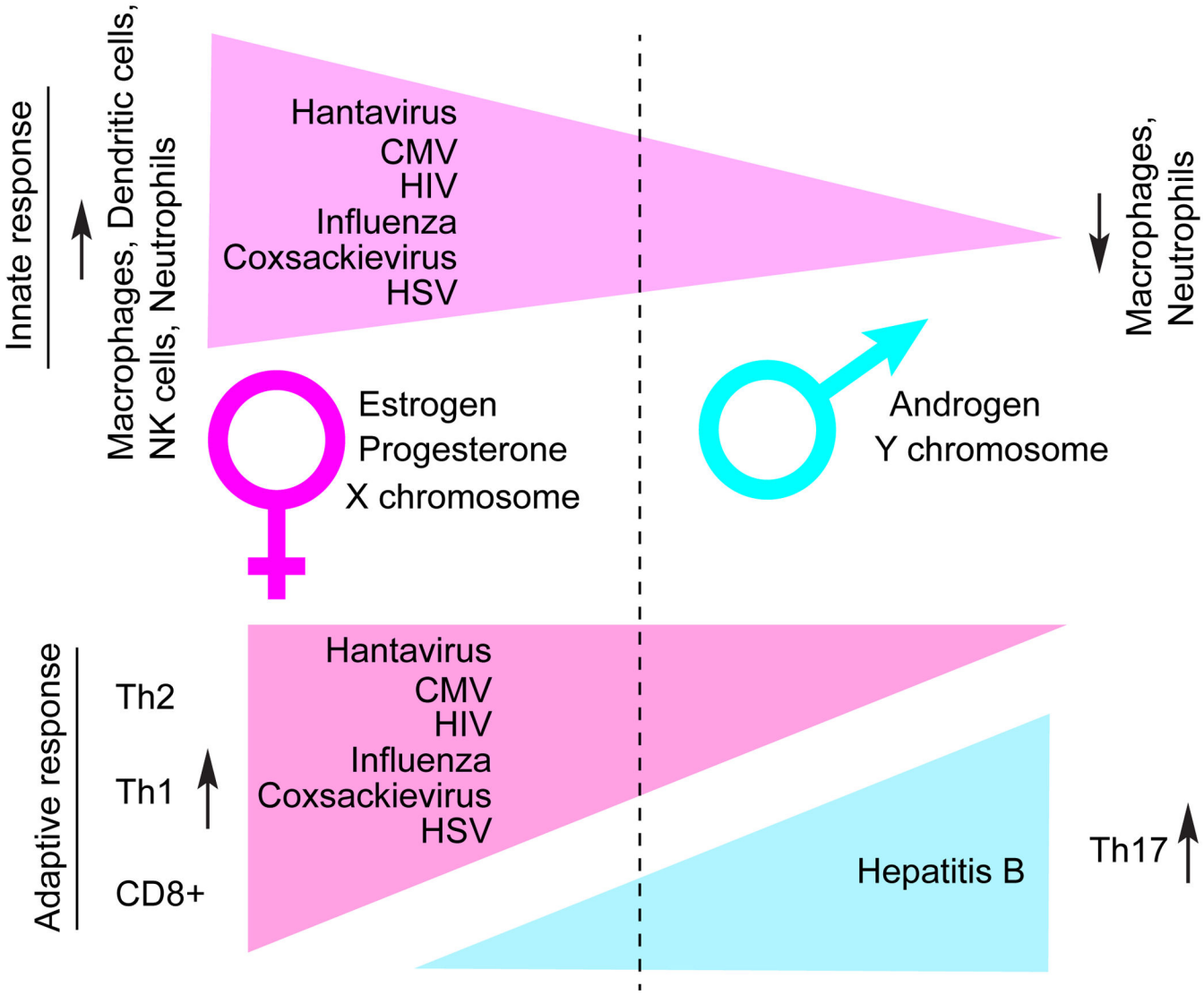

Figure 2.

The interplay of sex chromosomes, sex hormones and immune responses influence sex differences in virologic control. Females display increased innate and adaptive immune responses to most viral infections compared to males, due to difference in effects of sex hormones (estrogen, progesterone and androgen). X and Y chromosome complement also contributes to sexually dimorphic immune responses to viruses in females and males. The relative increase in immune responses in females may contribute to differential levels of virologic control during acute infections and/or immunopathologic effects of anti-viral T cells that may lead to chronic inflammation.