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Sex Differences in Mast Cell–Associated Disorders: A Life Span Perspective

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Mast cells are critical innate immune effectors located throughout the body that are crucial for host defense mechanisms via orchestrating immune responses to a variety of host and environmental stimuli necessary for survival. The role of mast cells in brain development and behavior, meningeal function, and stress-related disorders has also been increasingly recognized. While critical for survival and development, excessive mast cell activation has been linked with an increasing number of inflammatory, stress-associated, and neuroimmune disorders including allergy/anaphylaxis, autoimmune diseases, migraine headache, and chronic pain disorders. Further, a strong sex bias exists for mast cell–associated diseases with females often at increased risk. Here we review sex differences in human mast cell–associated diseases and animal models, and the underlying biological mechanisms driving these sex differences, which include adult gonadal sex hormones as well the emerging organizational role of perinatal gonadal hormones on mast cell activity and development.

Mast cells are hematopoietic-derived innate immune cells ubiquitously located in the body and are potent orchestrators and effector cells in the immune response. Moreover, many mast cell–associated disorders including irritable bowel syndrome, migraine, chronic pain, allergy/anaphylaxis, and autoimmune disease, exhibit a strong sex bias in which females are more susceptible. Adult sex hormones may explain some of the causes of sex-biased disease responses; however, this idea is challenged by the fact that sex biases in many mast cell–associated disorders are evident in prepubertal children. In this review, we will discuss sex biases in mast cell disease susceptibility with a focus on factors of sex that may be at play. We highlight the diverse roles of mast cells in health and disease in context with the interaction of sex. Further, we call attention to early life as a critical period in shaping mast cell function and discuss early life environmental and host interactions that may influence mast cell disease susceptibility across the life span. The findings in this review provide insights for therapeutic targets for mast cell disorders with a potential for identifying sex-specific therapies in pediatric and adult disease.

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MAST CELL BIOLOGICAL ROLES IN HEALTH AND DISEASE

Mast cells are important effector cells of the immune system and play critical roles in inflammatory disease. Mast cells arise from hematopoietic $CD34^+/CD117^+$ stem cells that circulate as committed progenitors in blood, and populate all tissues, especially at host–environment interfaces such as the skin, the lung, and the gut (Abraham and Malaviya 1997). Mast cells are long-lived, able to survive months or years, and can proliferate in tissues in response to certain stimuli (Abraham and Malaviya 1997; Galli et al. 2005). The most distinguishable characteristic of mast cells are the 50- to 200-electron dense granules that occupy the majority of the cytoplasm of mature mast cells (Krystel-Whittemore et al. 2015). Stored within these granules are large amounts of preformed proinflammatory mediators (e.g., histamine, serotonin, proteases, etc.), which when released initiate rapid and robust physiologic effects on the vasculature, epithelium, and nervous systems (Krystel-Whittemore et al. 2015).

The strategic location of mast cells next to vessels and nerves and at host–environment interfaces, as well as the plethora of immune mediators they contain and synthesize, positions them to be involved in a variety of pathologic conditions.

Mast cells are best known for their association with pathologic conditions such as allergy and anaphylaxis where aberrant mast cell activation leads to damage of host tissues. However, mast cells are indispensable to the host and no humans lacking mast cells have ever been described (Wong et al. 2014). Further, mast cell–like cells have been described in an early ancestor of vertebrates, *Ciona intestinalis*, pointing to an ancient origin of mast cells (>500 million years ago), well before the development of adaptive immunity and therefore IgE-mediated allergy (Wong et al. 2014). The fact that mast cells have persisted throughout vertebrate evolution reinforces their importance in immune responses against infectious diseases, including those by parasites, bacteria, and viruses.

Mast cells are positioned at host–environment interfaces with a repertoire of receptors ready to react to pathogen-associated molecular patterns and other signals of infection (Gilfillan et al. 2009). Further, mast cells have a kinetic advantage over other sentinel immune cells through their ability to release a multitude of preformed immune mediators instantaneously at a site of infection. Mast cells promote clearance of bacteria and prevent dissemination of infections in the peritoneum, bladder, lung, gut, and skin (Malaviya et al. 1996; Wei et al. 2005; Siebenhaar et al. 2007; Sutherland et al. 2008; Shelburne et al. 2009). Mast cells release mediators in response to parasite infection, including histamine to increase vascular permeability, and smooth muscle contraction to expel parasites, and proteases that are directly toxic to parasites (Vermillion et al. 1988; McKean and Pritchard 1989; McDermott et al. 2003). During viral infections, mast cells are involved in recruitment of immune cells, but further questions remain with regard to other functions of mast cells during viral infections (Orinska et al. 2005).

EPIDEMIOLOGY OF SEX DIFFERENCES IN MAST CELL–ASSOCIATED DISEASE

An increasing number of clinical and epidemiologic studies demonstrate sex biases in mast cell–associated disorders, often with females exhibiting increased prevalence and severity of disease. Diseases classically associated with mast cells including allergy, anaphylaxis, and asthma (Webb and Lieberman 2006; Osman et al. 2007a; Poulos et al. 2007; Kool et al. 2016; Acker et al. 2017). Further, evidence has mounted supporting important roles of mast cells in other immune-related disorders. Clinical and preclinical animal research have linked mast cells with autoimmune diseases such as multiple sclerosis (MS) (Orton et al. 2006) and rheumatoid arthritis (Alamanos and Drosos 2005), which also exhibit a female sex bias, occurring in women at 4 times the rate of men (Chiaroni-Clarke et al. 2016). Heightened mast cell activation near sensory neurons has been linked with symptom severity of chronic pain disorders such as irritable bowel syndrome (Sperber et al. 2017), migraine (Stovner et al. 2007), interstitial cystitis (Berry et al. 2011), and fibromyalgia (Walitt et al. 2015), which all occur

much more frequently in women (Mogil 2012). Further, mast cells degranulation has been implicated in sex-specific pain disorders in women such as vulvodynia and endometriosis (Bornstein et al. 2004; Anaf et al. 2006).

Research into the mechanisms underlying sex differences in mast cell–mediated disease has largely focused on adult gonadal sex hormones as the main drivers of sex differences. This focus is likely due in part to the sex reversal in prevalence of allergic rhinitis, food allergy, and asthma from a male predominance prior to puberty to a female predominance in adulthood (Kelly and Gangur 2009; Fröhlich et al. 2017; Pinart et al. 2017; Hohmann et al. 2019). However, childhood prevalence of a number of mast cell–associated diseases still exhibit a female predominance such as eczema (Ballardini et al. 2013), autoimmune disease (Chiaroni-Clarke et al. 2016), irritable bowel syndrome (Korterink et al. 2015), migraine (Victor et al. 2010), fibromyalgia (Kashikar-Zuck and Ting 2014), interstitial cystitis (Vaz et al. 2012), and general chronic pain (King et al. 2011). With regard to asthma, sex-specific childhood prevalence rates of asthma have shifted between 1989 and 2004 moving from male-biased prevalence to no sex difference, while eczema and allergic rhinitis prevalence changed from a male bias to a female bias (Osman et al. 2007b). Similarly, the prevalence of childhood food allergies, which have previously been reported to be more common in males, have now shifted toward a female predominance (Branum and Lukacs 2008; McGowan and Keet 2013). This shift toward a female bias in asthma and atopy (heightened immune responses to common skin, airway, and food allergens) could be attributed to several factors including enhanced sensitivity in the evaluation of clinical symptoms and diagnosis of atopy, or a decrease in the bias of health professionals to more readily diagnose boys with atopy (Osman et al. 2007b). Together, sex differences in susceptibility to mast cell–associated disease exist throughout life, and therefore early life and adult sex-based factors in pathogenesis of these disorders are likely involved and covered later in this review.

ROLE OF MAST CELLS IN SEX DIFFERENCES IN IgE-MEDIATED ALLERGY/ANAPHYLAXIS AND EXPERIMENTAL AUTOIMMUNE ENCEPHALOMYELITIS

As described above, a female sex bias is evident in mast cell–associated disorders, but the specific contribution of mast cells to this sex bias is poorly understood. Here, we focus on studies that have demonstrated sex differences in mast cells activation in animal models of passive systemic anaphylaxis and experimental autoimmune encephalomyelitis (EAE), and how sex differences in mast cells may drive sex-biased mast cell disease risk and severity.

Sex Differences in IgE-Mediated Passive Systemic Anaphylaxis and the Role of Mast Cells

As discussed above, a distinguishing feature of mast cells is the capacity to store and release preformed granule mediators (e.g., histamine, serotonin, proteases), which allows them to respond rapidly to threats in the microenvironment. However, aberrant or excessive activation of mast cells, such as in allergy and anaphylaxis, can have potentially life-threatening consequences. Allergy is the most recognized negative consequence of mast cell activation and afflicts 30%–40% of people worldwide (Pawankar et al. 2012). Mast cells are the main effector cell in IgE-mediated allergic reactions. Infusing IgE antibodies into wild-type mice, mast cell–deficient mice, and mast cell knockin mice demonstrates that many of the allergen-induced biologic responses are entirely dependent upon mast cell degranulation, including cardiopulmonary collapse in anaphylaxis, tissue swelling, fibrin deposition, airway hyperreactivity, and immune cell recruitment (Galli et al. 2005). Allergies develop when innocuous environmental antigens elicit type 2 immune responses through activation of $CD4^+$ T helper type 2 cells that engage B cells to produce allergen-specific IgE antibodies (Hofmann and Abraham 2009). IgE binds to FcεRI receptors on tissue mast cells and basophils, which mainly circulate in low numbers in the blood (Voehringer 2013). Mast cells are activated upon reexposure to the

allergen, which cross-links IgE antibodies bound to FcεRI receptors, causing degranulation and release of multiple preformed mediators (e.g., histamine, serotonin, proteases, etc.), referred to as an immediate hypersensitivity reaction (Hofmann and Abraham 2009). These mediators are responsible for increasing vascular permeability, smooth muscle contraction, and mucus secretion as well as signaling nerves and recruiting other immune cells, which contribute to allergic symptoms like redness, swelling, itching, runny nose, and diarrhea (Hofmann and Abraham 2009). In allergic asthma, mast cell mediators cause bronchoconstriction, mucus secretion, and respiratory mucosal edema leading to reduced air flow and wheeze (Hofmann and Abraham 2009). Other allergic disorders including allergic rhinitis, eczema, urticaria, and food allergy also manifest through IgE-mediated mast cell activation (Galli and Tsai 2012). Further, systemic IgE-mediated mast cell activation can result in anaphylaxis, a catastrophic immune response that can rapidly lead to death if untreated (Galli and Tsai 2012).

In line with the female sex bias in humans, IgE-mediated induction of clinical scores of anaphylaxes and pathophysiologic outcomes (e.g., blood histamine levels, tissue mast cell activation, airway hyperreactivity, and hypothermia) in mouse models are more severe in female animals (Mackey et al. 2016, 2020; Hox et al. 2015). Despite several studies reporting heightened severity of mast cell–mediated anaphylaxis in females, the factors responsible for these sex differences have been conflicting. Ovariectomy reduced allergic airway inflammation in female rats (Ligeiro de Oliveira et al. 2004) and the hypothermia and airway inflammation in C57Bl6 mice (Hox et al. 2015), while estrogen replacement in ovariectomized mice reversed the effects of ovariectomy. Further, Hox et al. (2015) reported that females express higher levels of endothelial nitric oxide synthase (eNOS) and phosphorylated eNOS, compared with males and ovariectomized females, and that administration of the NOS inhibitor, L-NAME, reduced hypothermia responses in female mice but not males. Overall, these finding imply that gonadal estrogens enhance the severity of IgE-mediated hypothermia and airway inflammation via enhanced eNOS, thus contributing to heightened anaphylactic responses in females. In contrast, we found that ovariectomy of adult C57Bl6 females and castration of males had no significant effect on IgE-mediated histamine release or hypothermia (Mackey et al. 2020). Instead, Mackey et al. (2020) concluded that these sex differences were a result of organizational effects of perinatal androgens, rather than adult androgens, shaping sex differences in mast cell histamine release and hypothermia, as discussed in more detail below.

Role of Mast Cells in Autoimmune Disease and Their Contribution to Sex Differences in Disease Severity

Autoimmune diseases are a result of the immune system failing to recognize self from non-self molecules, resulting in activation of self-reactive lymphocytes by innate immune cells to respond to self-antigens (Brown and Hatfield 2012). As mentioned previously, mast cells are associated with several autoimmune diseases in humans, including Sjogren's syndrome (Konttinen et al. 2000), chronic idiopathic urticaria (Saini et al. 2009), experimental vasculitis (Ishii et al. 2009), rheumatoid and idiopathic arthritis (Nigrovic et al. 2007; Sullivan 2007), bullous pemphigoid (Wintroub et al. 1978), and systemic lupus erythematosus (Kaczmarczyk-Sekula et al. 2015). But the mast cell's role in MS, a chronic inflammatory disorder of the central nervous system (CNS) characterized by mononuclear cell infiltration of the brain and demyelination of neurons, has received the most attention. Mast cells are observed within the demyelinated plaques in the brains of humans with MS and elevated levels of tryptase are found in the cerebrospinal fluid of MS patients (Krüger et al. 1990; Rozniecki et al. 1995). In the rodent model of MS, EAE, mast cell–deficient mice (Wsh mice) exhibited less severe EAE-type lesions, including less severe demyelination (Brown et al. 2002; Desbiens et al. 2016). Perivascular mast cells are a source of vasoactive and proinflammatory mediators that increase the permeability of the blood–brain barrier and can recruit immune cells to the brain (Sayed

et al. 2010), which is important for MS pathogenesis. Further, administration of a mast cell stabilizer drug reduced severity of EAE (Brown and Hatfield 2012), supporting a critical role of mast cells in the MS-associated pathology and in general autoimmunity as reviewed previously (Brown and Hatfield 2012).

The biological mechanisms underlying the female sex bias in autoimmune diseases has received considerable attention. Sex differences in autoimmune disease are thought to be mediated through various mechanisms, including sex hormone and genetic factors and a complex interplay between innate and adaptive immune cells. Mast cells have been proposed as potentially critical players mediating sex differences in autoimmune diseases. It was also demonstrated that IL-33 is a critical protective factor in the EAE model, through a mechanism involving IL-33-mediated activation of ILC2 cells and generation of a Th2 response to confer protection against inflammation-induced CNS lesions in males. In vitro experiments with bone marrow–derived mast cells (BMMCs) showed that testosterone, through binding to androgen receptors (ARs) expressed on mast cells, induces IL-33 production and release from male, but not female mast cells, which the authors speculated could be a mast cell–dependent mechanism driving sex differences in the EAE model. The authors also showed that cultured female mast cells release greater amounts of inflammatory IL-1β and TNF-α, which was speculated as a potential driver of a Th-17-dominated anti-myelin response contributing to heightened disease severity in females (Russi et al. 2018). Together, these studies support a critical role of mast cells in the pathogenesis of EAE lesions and that mechanism involving sex-dependent effects of testosterone on male mast cells could protect males from autoimmune-associated CNS lesions.

ADDRESSING SEX BIASES IN MAST CELL–ASSOCIATED DISEASES IN CHILDREN: ROLE OF PERINATAL ANDROGENS

While much attention has been directed toward adult gonadal sex hormones as a mechanism mediating sex differences in mast cell–associated disease, epidemiological evidence demonstrates these same sex biases in prepubertal children, as noted above. Therefore, sex-based factors independent of adult gonadal sex hormones are likely playing a significant role. A defining mechanism of sexual differentiation in the fetus and newborn is the perinatal androgen surge in males. During this organizational period, testes secrete gonadal androgens (testosterone and dihydrotestosterone) in both prenatal and early postnatal life, which is known to induce permanent masculinizing effects on many body systems. Testosterone can also be converted to estradiol via the aromatase enzyme to drive defeminizing effects via estrogen receptors. Androgens and estrogens with their respective receptors bind to hormone-responsive elements on target DNA sequences, which attracts cofactors that form transcriptional complexes to regulate gene transcription (Hiort 2013). Many coregulators have inherent histone acetyltransferase and methyltransferase activity, which can alter the epigenetic state of the genome and change gene expression (Arnold et al. 2012). These epigenetic marks to histones or DNA can have long-lasting impacts on gene expression, permanently influencing the function and phenotype of cells (Arnold et al. 2012). In contrast to males, sexual differentiation in females during the organizational period occurs in the absence of the androgen surge and is thought to be largely independent of gonadal hormones as the ovaries are relatively quiescent until puberty. The actions of the perinatal testicular androgen surge on many tissues during this critical period organize many body systems to respond to pubertal gonadal hormones or the "activational" phase in adulthood. In other words, the perinatal androgen surge leads to a fixed program of gene expression in target cells throughout life, which controls the function and phenotype of that cell, including future responsiveness to hormones.

Perinatal Androgens in Males as Major Drivers of Sex Differences in IgE-Mediated Anaphylaxis through Alterations in Mast Cell Development

As mentioned above, studies by Mackey et al. (2016, 2020) demonstrated that female mice exhibit greater concentrations of serum histamine

levels, which coincided with more severe hypothermia, compared with male mice. Similar sex differences were also observed in mice exposed to psychological restraint stress (Mackey et al. 2016; D'Costa et al. 2019). Moreover, sex differences in IgE-mediated passive systemic anaphylaxis were also demonstrated in 14-day-old mice, which suggested that factors other than adult gonadal sex hormones could play a significant role in the sex differences. Administration of testosterone propionate (TP) to pregnant dams resulted in "masculinized" mast cell–mediated responses, with reduced blood histamine concentrations and reduced severity of hypothermia response in female offspring at neonatal and adult stages. On the other hand, inhibition of the perinatal androgens surge in males by administration of the anti-androgen di-(2-ethylhexyl) phthalate (DEHP) to pregnant dams, resulted in heightened severity or "feminized" IgE-mediated anaphylaxis responses in male offspring. Together, these studies established the perinatal androgen surge as a critical event driving long-term attenuated mast cell responses in males. This work further introduced the concept that host, genetic, and environmental-associated alterations in androgens during the critical perinatal period can have lasting developmental consequences on mast cell–associated disease severity.

Developmental Effects of Perinatal Androgens on Mast Cell Granule Mediator Storage and Its Role in Sex Differences in Mast Cell–Mediated Anaphylaxis

Studies by Mackey et al. (2016, 2020) showed that heightened anaphylaxis in female mice was associated with higher levels of blood histamine. Examination of tissue mast cells revealed no significant differences in mast cell number or degranulation between the sexes. Isolation of peritoneal mast cells from female and male mice and rats demonstrated that female mast cells contain higher levels of preformed granule-associated mediators (e.g., histamine, serotonin, tryptase, etc.). Electron microscopy also revealed more electron-dense granules in female mast cells compared with male mast cells, further indicating that females have an increased capacity to store granule mediators. Furthermore, infusion of female mast cells into mast cell–deficient male mice recipients, and vice versa, showed that sex differences in IgE-mediated passive systemic anaphylaxis were determined by the sex of the donor mast cells and not the recipient. Additionally, Mackey et al. (2020) showed that mast cells derived in vitro from bone marrow hematopoietic stem cell precursors (BMMCs) obtained from female, male, and perinatally androgenized females exhibit sex differences in mast cell granule mediator content, with male and androgenized female-derived BMMCs exhibiting significantly reduced levels of histamine, serotonin, and proteases compared with female BMMCs. Together, these findings demonstrate that biological sex and high perinatal androgen levels alter the developmental programming of mast cells toward reduced granule mediators' storage and release, contributing to reduced clinical severity of mast cell–mediated anaphylaxis.

Perinatal Androgens as Modulators of Early Brain Mast Cell Activity, Brain Development, and Sex-Related Behavior

While best known for their pathophysiological role in inflammatory diseases, mast cells have been implicated in normal development of organ systems, specifically the nervous system. Mast cells are abundant in the brain and meninges and have been shown to modulate neuronal physiology and behavior. With regard to early developmental programming, an interplay between sex hormone levels during the perinatal organizational period, mast cells and sexual dimorphism of the preoptic area (POA), and sex-specific behaviors has been demonstrated. In a study by Lenz et al. (2018), male rat fetuses exhibited significantly greater numbers of mast cells in the POA compared with females. Administration of masculinizing doses of estradiol (metabolite of testosterone via aromatase enzyme) during the perinatal period increased POA mast cell numbers and degranulation in females to the level of males, and was associated with "male-typical" synaptic patterning in the brain and masculinization of adult sex behavior (Lenz et al. 2018).

Similarly, activation of fetal brain mast cells by allergen challenge in pregnant dams resulted in sex-specific changes in dendritic spine patterning of POA neurons, and lifelong alterations in adult behavior, such that female offspring exhibited male-typical sexual behavior, while male offspring exhibited decreased male-typical behaviors (Lenz et al. 2019). Together, these studies highlighted not only the important developmental role of mast cells in brain development and adult sexual behavior but demonstrated that perinatal estrogen organizes sex differences in POA neurons and lasting developmental changes in adult sexual behavior via modulation of mast cell number and activation.

IMPACT OF ESTROUS CYCLE AND SEX HORMONE LEVELS ON TISSUE MAST CELL NUMBERS

Tissue mast cell numbers can change dramatically throughout the estrous cycle and correspond with changing concentrations of sex hormones. In rodents, the density of mast cells fluctuates with the estrous cycle in the dura mater, mammary gland, ovary, and uterus, but not in the jejunum or colon (Aydın et al. 1998; Bradesi et al. 2001; Boes and Levy 2012; Jing et al. 2012). Similarly, mast cell numbers in the ovary and uterus change during the estrous cycle in dogs, cats, cows, and goats, with highest numbers of mast cells in reproductive organs during the follicular phase when estrogen levels are high (Özen et al. 2007; Karaca et al. 2008; Hamouzova et al. 2017, 2020). Exogenous estrogen treatment of rodents increased the numbers of mast cells in the dura mater, uterus, and mammary gland, but not in the jejunum or colon (Bradesi et al. 2001; Jensen et al. 2010; Boes and Levy 2012; Jing et al. 2012). In contrast to mast cell numbers, mast cell degranulation was not influenced by the estrous cycle or exogenous estrogen in the dura mater; however, mast cell degranulation was reduced in the ovary and uterus during estrus, when estrogen levels were high (Aydın et al. 1998; Boes and Levy 2012). Ovariectomy reduced mast cell degranulation in response to substance P in the jejunum, but increased mast cell degranulation in response to substance P in the colon (Bradesi et al. 2001). In addition, G protein estrogen receptor agonist treatment in rats induced mast cell degranulation in colonic tissues (Xu et al. 2020). Taken together, estrogen increases mast cell numbers in a tissue-specific manner during fetal development, adulthood, and during the estrous cycle, but does not appear to have clear role in mast cell degranulation. The mechanisms by which estrogen modulates mast cell number remains poorly understood and represents a critical gap in knowledge that has implications for development and mast cell–associated disease, particularly those in which disease severity or clinical flares are more common during specific stages of the estrous cycle. For example, estrogen and progesterone have been suggested to enhance mast cell–associated disease in females. Further, symptoms of asthma and irritable bowel syndrome fluctuate with the menstrual cycle, suggesting involvement of estrogen and progesterone (Vrieze et al. 2003; Meleine and Matricon 2014). Visceral pain sensitivity to colorectal distension increased in rats during estrus and proestrus, when estrogen levels are high (Moloney et al. 2016). While collectively these studies present an interesting association between sex hormone levels, mast cell number, and disease severity, a definitive mechanistic link between these factors remains unknown.

SEX HORMONE INTERACTIONS WITH MAST CELLS

The above studies demonstrate a link between sex hormones levels and mast cell number and activity; however, precisely how sex hormones influence mast cell activity remains to be elucidated. Several studies in human and rodent mast cells have shown that mast cells express receptors for estrogen, progesterone, and testosterone (AR) (Pang et al. 1995; Zaitsu et al. 2007; Jensen et al. 2010), which implies that sex hormones could be acting directly on mast cells to alter their function. In support of this, several in vitro mast cell experiments have examined the effects of sex hormones on mast cell activation. Exogenous estrogen administration induces relatively minor degranulation responses (~5%) across several mast cell lines and sources including RBL-2H3

rodent mast cell line, HMC-1 human mast cell line, primary BMMCs, and rat peritoneal mast cells (Narita et al. 2007; Zaitsu et al. 2007; Zhu et al. 2018). Mast cell degranulation responses to estrogens was shown to be through a membrane-associated form of estrogen receptor α, and not the nuclear receptor (Zaitsu et al. 2007). However, a more recent study showed no effect of exogenous estrogen on mast cell degranulation in HMC-1 cells (Chen et al. 2010), but estrogen reduced the secretion of TNF-α, IL-6, and IL-1β after ionophore stimulus (Kim et al. 2001). High doses of progesterone also induce a minor mast cell degranulation response in HMC-1 cells (Jensen et al. 2010). In contrast, progesterone inhibited degranulation of rat peritoneal mast cells stimulated with substance P (Vasiadi et al. 2006). Interestingly, low doses of estradiol and progesterone increased histamine release (~5%) in female rat peritoneal mast cells but had no effect on male rat peritoneal mast cells (Munoz-Cruz et al. 2015). Together, these studies suggest that estrogen and progesterone have modest effects on in vitro mast cell degranulation responses.

The influence of testosterone on mast cell activity has been evaluated to a lesser extent. However, a recent meta-analysis analyzing immune function outcomes in experimental models after manipulation of sex hormones (122 studies) found testosterone had a moderate immunosuppressive effect on immune function, while estrogen had no effect on immune function overall (Foo et al. 2017). In line with this conclusion, animal models of parasitism found orchidectomy increases clearance of helminths, while ovariectomy had no effect (Tiuria et al. 1994). However, testosterone administration in female rodents decreased the ability to expel intestinal parasites (Tiuria et al. 1995). Conversely, testosterone has been shown to be protective in models of asthma and autoimmune disease. Castrated male mice exhibited enhanced IL-33-mediated lung inflammation, which was attributed to the effects of testosterone in reducing the innate lymphoid cell 2 (ILC2) populations (Laffont et al. 2017), but the specific role of mast cells in this study was not evaluated. Human and rodent mast cells express ARs (Chen et al. 2010; Russi et al. 2018; Mackey et al. 2020). Of note, BMMCs derived from female mice have higher AR (*Ar*) gene expression compared to male-derived BMMCs (Mackey et al. 2016); however, Russi et al. 2018 did not detect sex differences in IL-33 protein expression in BMMCs via flow cytometry. Several studies have shown that response to testosterone and other mast cell stimuli may be sex dependent. Low doses of testosterone and dihydrotestosterone induced degranulation in female, but not male, rat peritoneal mast cells (Chen et al. 2010; Munoz-Cruz et al. 2015). As mentioned previously, testosterone induced IL-33 gene and protein expression in male but not female BMMCs (Russi et al. 2018). Overall, these studies show that both male and female mast cells express functional ARs, but testosterone effects on mast cell gene and protein expression can be sex specific.

INFLUENCE OF THE SEX CHROMOSOME COMPLEMENT ON THE MAST CELL

Sex hormones have been shown to be a major player in determining sex differences in body plan and function, but sex chromosome complement also plays an important role in sex-specific development of the body. Mammalian sex determination begins in the zygote where an inherent imbalance of genes encoded by heteromorphic sex chromosomes (XX vs. XY) influences gonadal development. Most notably, in the male zygote, the Y-linked gene *Sry* induces a series of cellular and molecular events that lead to the formation of testes. In the absence of *Sry*, ovaries develop in the XX female through an active, albeit less understood series of events. Sex determination of the gonads based on sex chromosomes leads to lifelong sex differences in the secretion of sex steroid hormones.

Beyond the role of sex chromosome complement on gonadal differentiation and steroid hormone production, there is potential for direct sex chromosome effects driving sex differences in mast cells. Females inherit two X chromosomes, whereas males carry one X chromosome and one Y chromosome. To avoid duplicate gene expression in females, one X chromosome is randomly silenced during X chromosome inactivation in females. Previous studies showed up to 7% of

genes escape silencing from the inactive X chromosome in mouse tissues (Berletch et al. 2015) and 15% in human cells (Carrel and Willard 2005). Considering the X chromosome contains approximately 1100 genes, of which many are involved in immunity, the effect of gene escape from X chromosome inactivation in mast cells may have consequences for the development and activity of the cells (Libert et al. 2010). Further, gene expression from the Y chromosome in male cells may create variances that impact cell phenotype and function (Cortez et al. 2014). The complement of sex chromosomes in a cell can also influence genome-wide DNA methylation in a hormone-independent fashion (Wijchers and Festenstein 2011). Mast cells derived from adult male and female mice exhibit markedly different transcriptomes (Mackey et al. 2016), but to our knowledge, the direct effects of the sex chromosome complement in mast cells has not been elucidated. Exploration of sex differences in fetal-derived mast cells prior to the perinatal androgen surge would provide insight into the effects of the sex chromosome complement. Moreover, use of the "four core genotypes" mouse model, which allows for dissociation of sex hormones and sex chromosomes, would be valuable to determine possible sex chromosome complement effects on mast cell phenotype and function (Arnold and Chen 2009).

EVOLUTIONARY PERSPECTIVE OF MAST CELL SEX DIFFERENCES: DO FEMALES OR MALES HOLD THE ADVANTAGE?

As mentioned above, mast cells are critical effector cells of the innate immune system with a primary role in protection from infection through their ability to rapidly orchestrate innate and adaptive immune responses. In general, males are more susceptible to pathogenic infections and exhibit higher mortality rates than females (vom Steeg and Klein 2016). For example, males have increased prevalence of viral infections from HIV, influenza, and hepatitis B and bacterial infections including tuberculosis, legionellosis, and campylobacter (vom Steeg and Klein 2016). Sex differences exist in the SARS-CoV-2 pandemic with men developing more severe manifestations of disease (M:F relative ratio of hospitalization 1.5:1), which results in higher death rates (M:F relative ratio of case fatalities 1.7:1) compared with women (Gebhard et al. 2020). In parallel, antibody responses to bacterial and viral vaccines, including influenza and hepatitis B, are higher in females than males (Klein and Flanagan 2016). A comprehensive review of parasitic infections in relation to sex demonstrated that 46 out of 53 (86.8%) parasite species (protozoa, nematodes, trematodes, and cestodes) had higher infection rates in males for a variety of species (Klein 2004). Sex differences in infection rates and vaccine responses have been largely demonstrated in adults, but this trend is also evident in children, as newborn male children are more vulnerable to infections and are more likely to die than female children (Sawyer 2012). Further, boys under the age of 5 have higher rates of protozoan, trematode, and nematode infections than girls (Flanagan et al. 2015). Female children before the onset of puberty also have greater antibody responses to many vaccines (hepatitis B, diphtheria, pertussis, pneumococcal, rabies, measles, and RTS,S against malaria) (Klein and Flanagan 2016). While the specific contributions of mast cells to sex differences in infectious disease remains to be elucidated, the well-established role of mast cells in host defense, pathogen clearance, and host survival suggests that heightened mast responses in females may confer an important survival advantage. However, in conditions where pathogen disease pressures are lower, such as in developed countries, the heightened mast cell responses in females may underlie the increased risk for chronic mast cell–associated diseases.

CONCLUDING REMARKS

Biological sex can be a protective factor against disease, sometimes to a greater extent than offered by drugs or therapies. Discovering the sex-biasing factors that can protect from disease may lead to the development of novel targets of therapy. Here, we discussed the sometimes complex and multifactorial nature of sex differences in mast cells and how this might underlie the sex bias in mast cell–associated diseases throughout life (Fig. 1). While adult sex hormones clearly

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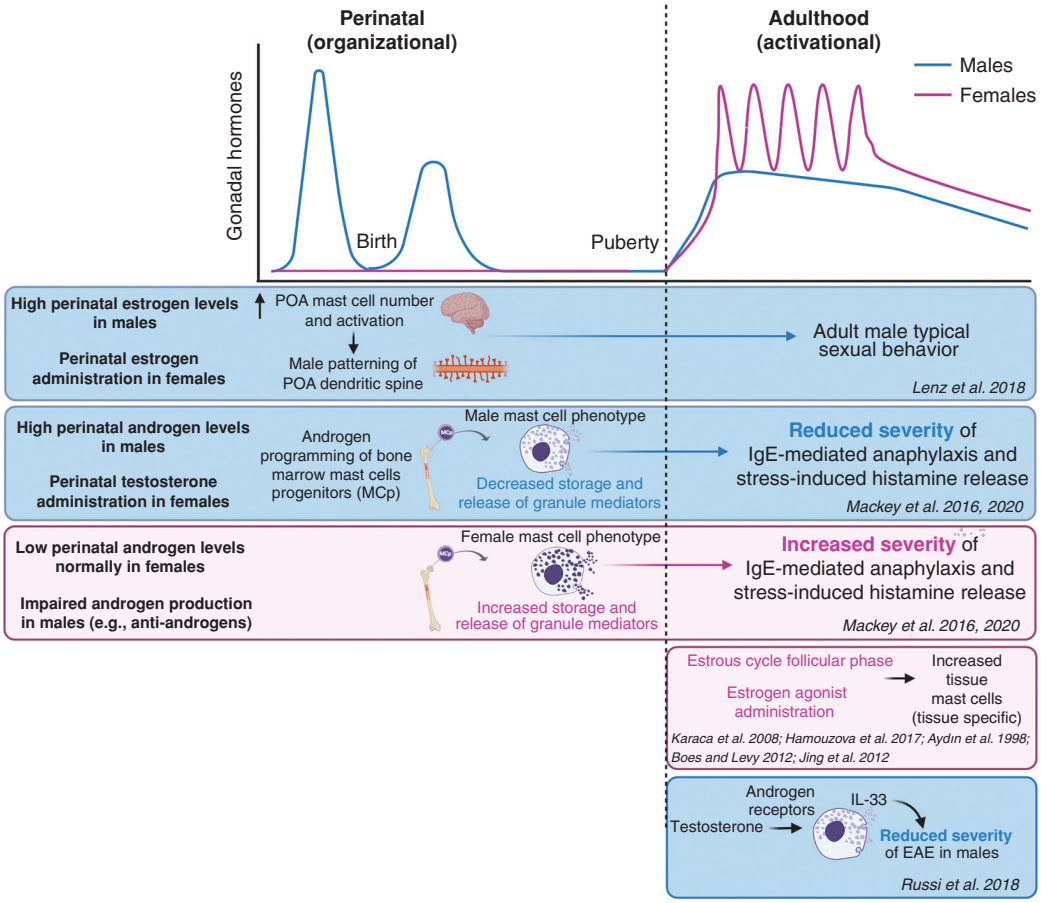

Figure 1. Sex hormones during perinatal organizational and adult activational periods influence mast cell development and activity, shaping neurobehavioral development and mast cell–associated disease across the life span. During the sensitive perinatal period, exposure to sex hormones, either naturally (e.g., male perinatal androgen surge) or potentially a result of endocrine, genetic, and environmental factors, can impact early mast cell activity and subsequent neurobehavioral development, and shape the development and long-term functional response potential of the mast cells that contribute to sex differences in mast cell function and disease risk. Changing sex hormone levels in adulthood (e.g., estrous cycle) alters tissue cell number and activity in various tissues that play a role in normal physiological functions and disease risk. (POA) Preoptic area, (EAE) experimental autoimmune encephalomyelitis.

influence mast cell number and activity, and likely explain some of the sex disparities in mast cell responses, sex biases in mast cell–related disorders are often evident in children prior to puberty, and therefore the study of early life mechanisms driving lifelong changes in development and disease risk is critically important. In addition, understanding how adult sex hormones modulate mast cell function and how perinatal androgens alter the developmental programming of mast cells and their role in development, host defense, and inflammatory disease risk could offer new insights into host and environmental factors affecting disease risk across the life span and development of novel therapeutic targets to decrease mast cell disease susceptibility. Conversely, given the critical and beneficial role of mast cell activation in pathogen host defense and immunity, deciphering this mechanism may also provide useful targets

for enhancing immune responses when that would be beneficial.

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REFERENCES

Abraham SN, Malaviya R. 1997. Mast cells in infection and immunity. *Infect Immun* **65:** 3501–3508. doi:10.1128/iai.65.9.3501-3508.1997

Acker WW, Plasek JM, Blumenthal KG, Lai KH, Topaz M, Seger DL, Goss FR, Slight SP, Bates DW, Zhou L. 2017. Prevalence of food allergies and intolerances documented in electronic health records. *J Allergy Clin Immunol* **140:** 1587–1591.e1. doi:10.1016/j.jaci.2017.04.006

Alamanos Y, Drosos AA. 2005. Epidemiology of adult rheumatoid arthritis. *Autoimmun Rev* **4:** 130–136. doi:10.1016/j.autrev.2004.09.002

Anaf V, Chapron C, El Nakadi I, De Moor V, Simonart T, Noel JC. 2006. Pain, mast cells, and nerves in peritoneal, ovarian, and deep infiltrating endometriosis. *Fertil Steril* **86:** 1336–1343. doi:10.1016/j.fertnstert.2006.03.057

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

Arnold AP, Chen X, Itoh Y. 2012. What a difference an X or Y makes: sex chromosomes, gene dose, and epigenetics in sexual differentiation. *Handb Exp Pharmacol* **214:** 67–88. doi:10.1007/978-3-642-30726-3_4

Aydın Y, Tunçel N, Gürer F, Tunçel M, Koşar M, Oflaz G. 1998. Ovarian, uterine and brain mast cells in female rats: cyclic changes and contribution to tissue histamine. *Comp Biochem Physiol A Mol Integr Physiol* **120:** 255–262. doi:10.1016/S1095-6433(98)00027-0

Ballardini N, Kull I, Söderhäll C, Lilja G, Wickman M, Wahlgren CF. 2013. Eczema severity in preadolescent children and its relation to sex, filaggrin mutations, asthma, rhinitis, aggravating factors and topical treatment: a report from the BAMSE birth cohort. *Br J Dermatol* **168:** 588–594. doi:10.1111/bjd.12196

Berletch JB, Ma W, Yang F, Shendure J, Noble WS, Disteche CM, Deng X. 2015. Escape from X inactivation varies in mouse tissues. *PLoS Genet* **11:** e1005079. doi:10.1371/journal.pgen.1005079

Berry SH, Elliott MN, Suttorp M, Bogart LM, Stoto MA, Eggers P, Nyberg L, Clemens JQ. 2011. Prevalence of symptoms of bladder pain syndrome/interstitial cystitis among adult females in the United States. *J Urol* **186:** 540–544. doi:10.1016/j.juro.2011.03.132

Boes T, Levy D. 2012. Influence of sex, estrous cycle, and estrogen on intracranial dural mast cells. *Cephalalgia* **32:** 924–931. doi:10.1177/0333102412454947

Bornstein J, Goldschmid N, Sabo E. 2004. Hyperinnervation and mast cell activation may be used as histopathologic diagnostic criteria for vulvar vestibulitis. *Gynecol Obstet Invest* **58:** 171–178. doi:10.1159/000079663

Bradesi S, Eutamene H, Theodorou V, Fioramonti J, Bueno L. 2001. Effect of ovarian hormones on intestinal mast cell reactivity to substance P. *Life Sci* **68:** 1047–1056. doi:10.1016/S0024-3205(00)01008-0

Branum AM, Lukacs SL. 2008. Food allergy among U.S. children: trends in prevalence and hospitalizations. *NCHS Data Brief* **10:** 1–8.

Brown MA, Hatfield JK. 2012. Mast cells are important modifiers of autoimmune disease: with so much evidence, why is there still controversy? *Front Immunol* **3:** 147. doi:10.3389/fimmu.2012.00147

Brown MA, Tanzola MB, Robbie-Ryan M. 2002. Mechanisms underlying mast cell influence on EAE disease course. *Mol Immunol* **38:** 1373–1378. doi:10.1016/S0161-5890(02)00091-3

Carrel L, Willard HF. 2005. X-inactivation profile reveals extensive variability in X-linked gene expression in females. *Nature* **434:** 400–404. doi:10.1038/nature03479

Chen W, Beck I, Schober W, Brockow K, Effner R, Buters JT, Behrendt H, Ring J. 2010. Human mast cells express androgen receptors but treatment with testosterone exerts no influence on IgE-independent mast cell degranulation elicited by neuromuscular blocking agents. *Exp Dermatol* **19:** 302–304. doi:10.1111/j.1600-0625.2009.00969.x

Chiaroni-Clarke RC, Munro JE, Ellis JA. 2016. Sex bias in paediatric autoimmune disease—not just about sex hormones? *J Autoimmun* **69:** 12–23. doi:10.1016/j.jaut.2016.02.011

Cortez D, Marin R, Toledo-Flores D, Froidevaux L, Liechti A, Waters PD, Grützner F, Kaessmann H. 2014. Origins and functional evolution of Y chromosomes across mammals. *Nature* **508:** 488–493. doi:10.1038/nature13151

D'Costa S, Ayyadurai S, Gibson AJ, Mackey E, Rajput M, Sommerville LJ, Wilson N, Li Y, Kubat E, Kumar A, et al. 2019. Mast cell corticotropin-releasing factor subtype 2 suppresses mast cell degranulation and limits the severity of anaphylaxis and stress-induced intestinal permeability. *J Allergy Clin Immunol* **143:** 1865–1877.e4. doi:10.1016/j.jaci.2018.08.053

Desbiens L, Lapointe C, Gharagozloo M, Mahmoud S, Pejler G, Gris D, D'Orléans-Juste P. 2016. Significant contribution of mouse mast cell protease 4 in early phases of experimental autoimmune encephalomyelitis. *Mediators Inflamm* **2016:** 9797021. doi:10.1155/2016/9797021

Flanagan CE, Wise SK, DelGaudio JM, Patel ZM. 2015. Association of decreased rate of influenza vaccination with increased subjective olfactory dysfunction. *JAMA Otolaryngol Head Neck Surg* **141:** 225–228. doi:10.1001/jamaoto.2014.3399

Foo YZ, Nakagawa S, Rhodes G, Simmons LW. 2017. The effects of sex hormones on immune function: a meta-

analysis. *Biol Rev Camb Philos Soc* **92:** 551–571. doi:10.1111/brv.12243

Fröhlich M, Pinart Gilberga M, Keller T, Reich A, Cabieses B, Hohmann C, Postma DS, Bousquet J, Antó i Boqué JM, Keil T. 2017. Is there a sex-shift in prevalence of allergic rhinitis and comorbid asthma from childhood to adulthood? A meta-analysis. *Clin Transl Allergy* **7:** 44. doi:10.1186/s13601-017-0176-5

Galli SJ, Tsai M. 2012. IgE and mast cells in allergic disease. *Nat Med* **18:** 693–704. doi:10.1038/nm.2755

Galli SJ, Kalesnikoff J, Grimbaldeston MA, Piliponsky AM, Williams CM, Tsai M. 2005. Mast cells as "tunable" effector and immunoregulatory cells: recent advances. *Annu Rev Immunol* **23:** 749–786. doi:10.1146/annurev.immunol.21.120601.141025

Gebhard C, Regitz-Zagrosek V, Neuhauser HK, Morgan R, Klein SL. 2020. Impact of sex and gender on COVID-19 outcomes in Europe. *Biol Sex Differ* **11:** 1–13. doi:10.1186/s13293-020-00304-9

Gilfillan AM, Peavy RD, Metcalfe DD. 2009. Amplification mechanisms for the enhancement of antigen-mediated mast cell activation. *Immunol Res* **43:** 15–24. doi:10.1007/s12026-008-8046-9

Hamouzova P, Cizek P, Novotny R, Bartoskova A, Tichy F. 2017. Distribution of mast cells in the feline ovary in various phases of the oestrous cycle. *Reprod Domest Anim* **52:** 483–486. doi:10.1111/rda.12938

Hamouzova P, Cizek P, Bartoskova A, Vitasek R, Tichy F. 2020. Changes in the mast cell distribution in the canine ovary and uterus throughout the oestrous cycle. *Reprod Domest Anim* **55:** 479–485. doi:10.1111/rda.13641

Hiort O. 2013. The differential role of androgens in early human sex development. *BMC Med* **11:** 152. doi:10.1186/1741-7015-11-152

Hofmann AM, Abraham SN. 2009. New roles for mast cells in modulating allergic reactions and immunity against pathogens. *Curr Opin Immunol* **21:** 679–686. doi:10.1016/j.coi.2009.09.007

Hohmann C, Keller T, Gehring U, Wijga A, Standl M, Kull I, Bergstrom A, Lehmann I, von Berg A, Heinrich J, et al. 2019. Sex-specific incidence of asthma, rhinitis and respiratory multimorbidity before and after puberty onset: individual participant meta-analysis of five birth cohorts collaborating in MeDALL. *BMJ Open Respir Res* **6:** e000460. doi:10.1136/bmjresp-2019-000460

Hox V, Desai A, Bandara G, Gilfillan AM, Metcalfe DD, Olivera A. 2015. Estrogen increases the severity of anaphylaxis in female mice through enhanced endothelial nitric oxide synthase expression and nitric oxide production. *J Allergy Clin Immunol* **135:** 729–736.e5. doi:10.1016/j.jaci.2014.11.003

Ishii T, Fujita T, Matsushita T, Yanaba K, Hasegawa M, Nakashima H, Ogawa F, Shimizu K, Takehara K, Tedder TF, et al. 2009. Establishment of experimental eosinophilic vasculitis by IgE-mediated cutaneous reverse passive Arthus reaction. *Am J Pathol* **174:** 2225–2233. doi:10.2353/ajpath.2009.080223

Jensen F, Woudwyk M, Teles A, Woidacki K, Taran F, Costa S, Malfertheiner SF, Zenclussen AC. 2010. Estradiol and progesterone regulate the migration of mast cells from the periphery to the uterus and induce their maturation and degranulation. *PLoS ONE* **5:** e14409. doi:10.1371/journal.pone.0014409

Jing H, Wang Z, Chen Y. 2012. Effect of oestradiol on mast cell number and histamine level in the mammary glands of rat. *Anat Histol Embryol* **41:** 170–176. doi:10.1111/j.1439-0264.2011.01120.x

Kaczmarczyk-Sekuła K, Dyduch G, Kostański M, Wielowieyska-Szybińska D, Szpor J, Białas M, Okoń K. 2015. Mast cells in systemic and cutaneous lupus erythematosus. *Pol J Pathol* **66:** 397–402. doi:10.5114/pjp.2015.57253

Karaca T, Arikan S, Kalender H, Yoruk M. 2008. Distribution and heterogeneity of mast cells in female reproductive tract and ovary on different days of the oestrus cycle in Angora goats. *Reprod Domest Anim* **43:** 451–456. doi:10.1111/j.1439-0531.2007.00934.x

Kashikar-Zuck S, Ting TV. 2014. Juvenile fibromyalgia: current status of research and future developments. *Nat Rev Rheumatol* **10:** 89–96. doi:10.1038/nrrheum.2013.177

Kelly C, Gangur V. 2009. Sex disparity in food allergy: evidence from the PubMed database. *J Allergy (Cairo)* **2009:** 159845. doi:10.1155/2009/159845

Kim MS, Chae HJ, Shin TY, Kim HM, Kim HR. 2001. Estrogen regulates cytokine release in human mast cells. *Immunopharmacol Immunotoxicol* **23:** 495–504. doi:10.1081/IPH-100108596

King S, Chambers CT, Huguet A, MacNevin RC, McGrath PJ, Parker L, MacDonald AJ. 2011. The epidemiology of chronic pain in children and adolescents revisited: a systematic review. *Pain* **152:** 2729–2738. doi:10.1016/j.pain.2011.07.016

Klein SL. 2004. Hormonal and immunological mechanisms mediating sex differences in parasite infection. *Parasite Immunol* **26:** 247–264. doi:10.1111/j.0141-9838.2004.00710.x

Klein SL, Flanagan KL. 2016. Sex differences in immune responses. *Nat Rev Immunol* **16:** 626–638. doi:10.1038/nri.2016.90

Konttinen YT, Hietanen J, Virtanen I, Ma J, Sorsa T, Xu JW, Williams NP, Manthorpe R, Janin A. 2000. Mast cell derangement in salivary glands in patients with Sjögren's syndrome. *Rheumatol Int* **19:** 141–147. doi:10.1007/s002960050118

Kool B, Chandra D, Fitzharris P. 2016. Adult food-induced anaphylaxis hospital presentations in New Zealand. *Postgrad Med J* **92:** 640–644. doi:10.1136/postgradmedj-2015-133530

Korterink JJ, Diederen K, Benninga MA, Tabbers MM. 2015. Epidemiology of pediatric functional abdominal pain disorders: a meta-analysis. *PLoS ONE* **10:** e0126982. doi:10.1371/journal.pone.0126982

Krüger PG, Bø L, Myhr KM, Karlsen AE, Taule A, Nyland HI, Mørk S. 1990. Mast cells and multiple sclerosis: a light and electron microscopic study of mast cells in multiple sclerosis emphasizing staining procedures. *Acta Neurol Scand* **81:** 31–36. doi:10.1111/j.1600-0404.1990.tb00927.x

Krystel-Whittemore M, Dileepan KN, Wood JG. 2015. Mast cell: a multi-functional master cell. *Front Immunol* **6:** 620. doi:10.3389/fimmu.2015.00620

Laffont S, Blanquart E, Savignac M, Cénac C, Laverny G, Metzger D, Girard JP, Belz GT, Pelletier L, Seillet C, et

Cold Spring Harbor Perspectives in Biology
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al. 2017. Androgen signaling negatively controls group 2 innate lymphoid cells. *J Exp Med* **214:** 1581–1592. doi:10.1084/jem.20161807

Lenz KM, Pickett LA, Wright CL, Davis KT, Joshi A, McCarthy MM. 2018. Mast cells in the developing brain determine adult sexual behavior. *J Neurosci* **38:** 8044–8059. doi:10.1523/JNEUROSCI.1176-18.2018

Lenz KM, Pickett LA, Wright CL, Galan A, McCarthy MM. 2019. Prenatal allergen exposure perturbs sexual differentiation and programs lifelong changes in adult social and sexual behavior. *Sci Rep* **9:** 4837. doi:10.1038/s41598-019-41258-2

Libert C, Dejager L, Pinheiro I. 2010. The X chromosome in immune functions: when a chromosome makes the difference. *Nat Rev Immunol* **10:** 594–604. doi:10.1038/nri2815

Ligeiro de Oliveira AP, Oliveira-Filho RM, da Silva ZL, Borelli P, Tavares de Lima W. 2004. Regulation of allergic lung inflammation in rats: interaction between estradiol and corticosterone. *Neuroimmunomodulation.* **11:** 20–27. doi:10.1159/000072965

Mackey E, Ayyadurai S, Pohl CS, D'Costa S, Li Y, Moeser AJ. 2016. Sexual dimorphism in the mast cell transcriptome and the pathophysiological responses to immunological and psychological stress. *Biol Sex Differ* **7:** 60. doi:10.1186/s13293-016-0113-7

Mackey E, Thelen KM, Bali V, Fardisi M, Trowbridge M, Jordan CL, Moeser AJ. 2020. Perinatal androgens organize sex differences in mast cells and attenuate anaphylaxis severity into adulthood. *Proc Natl Acad Sci* **117:** 23751–23761. doi:10.1073/pnas.1915075117

Malaviya R, Ikeda T, Ross E, Abraham SN. 1996. Mast cell modulation of neutrophil influx and bacterial clearance at sites of infection through TNF-α. *Nature* **381:** 77–80. doi:10.1038/381077a0

McDermott JR, Bartram RE, Knight PA, Miller HR, Garrod DR, Grencis RK. 2003. Mast cells disrupt epithelial barrier function during enteric nematode infection. *Proc Natl Acad Sci* **100:** 7761–7766. doi:10.1073/pnas.1231488100

McGowan EC, Keet CA. 2013. Prevalence of self-reported food allergy in the National Health and Nutrition Examination Survey (NHANES) 2007–2010. *J Allergy Clin Immunol* **132:** 1216–1219.e5. doi:10.1016/j.jaci.2013.07.018

McKean PG, Pritchard DI. 1989. The action of a mast cell protease on the cuticular collagens of *Necator americanus*. *Parasite Immunol* **11:** 293–297. doi:10.1111/j.1365-3024.1989.tb00667.x

Meleine M, Matricon J. 2014. Gender-related differences in irritable bowel syndrome: potential mechanisms of sex hormones. *World J Gastroenterol* **20:** 6725–6743. doi:10.3748/wjg.v20.i22.6725

Mogil JS. 2012. Sex differences in pain and pain inhibition: multiple explanations of a controversial phenomenon. *Nat Rev Neurosci* **13:** 859–866. doi:10.1038/nrn3360

Moloney RD, Sajjad J, Foley T, Felice VD, Dinan TG, Cryan JF, O'Mahony SM. 2016. Estrous cycle influences excitatory amino acid transport and visceral pain sensitivity in the rat: effects of early-life stress. *Biol Sex Differ* **7:** 33. doi:10.1186/s13293-016-0086-6

Muñoz-Cruz S, Mendoza-Rodríguez Y, Nava-Castro KE, Yepez-Mulia L, Morales-Montor J. 2015. Gender-related effects of sex steroids on histamine release and FcεRI expression in rat peritoneal mast cells. *J Immunol Res* **2015:** 351829. doi:10.1155/2015/351829

Narita S, Goldblum RM, Watson CS, Brooks EG, Estes DM, Curran EM, Midoro-Horiuti T. 2007. Environmental estrogens induce mast cell degranulation and enhance IgE-mediated release of allergic mediators. *Environ Health Perspect* **115:** 48–52. doi:10.1289/ehp.9378

Nigrovic PA, Binstadt BA, Monach PA, Johnsen A, Gurish M, Iwakura Y, Benoist C, Mathis D, Lee DM. 2007. Mast cells contribute to initiation of autoantibody-mediated arthritis via IL-1. *Proc Natl Acad Sci* **104:** 2325–2330. doi:10.1073/pnas.0610852103

Orinska Z, Bulanova E, Budagian V, Metz M, Maurer M, Bulfone-Paus S. 2005. TLR3-induced activation of mast cells modulates $CD8^+$ T-cell recruitment. *Blood* **106:** 978–987. doi:10.1182/blood-2004-07-2656

Orton SM, Herrera BM, Yee IM, Valdar W, Ramagopalan SV, Sadovnick AD, Ebers GC; Canadian Collaborative Study Group. 2006. Sex ratio of multiple sclerosis in Canada: a longitudinal study. *Lancet Neurol* **5:** 932–936. doi:10.1016/S1474-4422(06)70581-6

Osman M, Hansell AL, Simpson CR, Hollowell J, Helms PJ. 2007a. Gender-specific presentations for asthma, allergic rhinitis and eczema in primary care. *Prim Care Respir J* **16:** 28–35. doi:10.3132/pcrj.2007.00006

Osman M, Tagiyeva N, Wassall HJ, Ninan TK, Devenny AM, McNeill G, Helms PJ, Russell G. 2007b. Changing trends in sex specific prevalence rates for childhood asthma, eczema, and hay fever. *Pediatr Pulmonol* **42:** 60–65. doi:10.1002/ppul.20545

Özen A, Ergün L, Ergün E, ŞimŞek N. 2007. Morphological studies on ovarian mast cells in the cow. *Turk J Vet Anim Sci* **31:** 131–136.

Pang X, Cotreau-Bibbo MM, Sant GR, Theoharides TC. 1995. Bladder mast cell expression of high affinity oestrogen receptors in patients with interstitial cystitis. *Br J Urol* **75:** 154–161. doi:10.1111/j.1464-410X.1995.tb07303.x

Pawankar R, Canonica GW, Holgate ST, Lockey RF. 2012. Allergic diseases and asthma: a major global health concern. *Curr Opin Allergy Clin Immunol* **12:** 39–41. doi:10.1097/ACI.0b013e32834ec13b

Pinart M, Keller T, Reich A, Fröhlich M, Cabieses B, Hohmann C, Postma DS, Bousquet J, Antó JM, Keil T. 2017. Sex-related allergic rhinitis prevalence switch from childhood to adulthood: a systematic review and meta-analysis. *Int Arch Allergy Immunol* **172:** 224–235. doi:10.1159/000464324

Poulos LM, Waters AM, Correll PK, Loblay RH, Marks GB. 2007. Trends in hospitalizations for anaphylaxis, angioedema, and urticaria in Australia, 1993–1994 to 2004–2005. *J Allergy Clin Immunol* **120:** 878–884. doi:10.1016/j.jaci.2007.07.040

Rozniecki JJ, Hauser SL, Stein M, Lincoln R, Theoharides TC. 1995. Elevated mast cell tryptase in cerebrospinal fluid of multiple sclerosis patients. *Ann Neurol* **37:** 63–66. doi:10.1002/ana.410370112

Russi AE, Ebel ME, Yang Y, Brown MA. 2018. Male-specific IL-33 expression regulates sex-dimorphic EAE susceptibility. *Proc Natl Acad Sci* **115:** E1520–E1529. doi:10.1073/pnas.1710401115

Saini SS, Paterniti M, Vasagar K, Gibbons SP Jr, Sterba PM, Vonakis BM. 2009. Cultured peripheral blood mast cells

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from chronic idiopathic urticaria patients spontaneously degranulate upon IgE sensitization: relationship to expression of Syk and SHIP-2. *Clin Immunol* **132:** 342–348. doi:10.1016/j.clim.2009.05.003

Sawyer CC. 2012. Child mortality estimation: estimating sex differences in childhood mortality since the 1970s. *PLoS Med* **9:** e1001287. doi:10.1371/journal.pmed.1001287

Sayed BA, Christy AL, Walker ME, Brown MA. 2010. Meningeal mast cells affect early T cell central nervous system infiltration and blood–brain barrier integrity through TNF: a role for neutrophil recruitment? *J Immunol* **184:** 6891–6900. doi:10.4049/jimmunol.1000126

Shelburne CP, Nakano H, St. John AL, Chan C, McLachlan JB, Gunn MD, Staats HF, Abraham SN. 2009. Mast cells augment adaptive immunity by orchestrating dendritic cell trafficking through infected tissues. *Cell Host Microbe* **6:** 331–342. doi:10.1016/j.chom.2009.09.004

Siebenhaar F, Syska W, Weller K, Magerl M, Zuberbier T, Metz M, Maurer M. 2007. Control of *Pseudomonas aeruginosa* skin infections in mice is mast cell-dependent. *Am J Pathol* **170:** 1910–1916. doi:10.2353/ajpath.2007.060770

Sperber AD, Dumitrascu D, Fukudo S, Gerson C, Ghoshal UC, Gwee KA, Hungin APS, Kang JY, Minhu C, Schmulson M, et al. 2017. The global prevalence of IBS in adults remains elusive due to the heterogeneity of studies: a Rome Foundation working team literature review. *Gut* **66:** 1075–1082. doi:10.1136/gutjnl-2015-311240

Stovner L, Hagen K, Jensen R, Katsarava Z, Lipton R, Scher A, Steiner T, Zwart JA. 2007. The global burden of headache: a documentation of headache prevalence and disability worldwide. *Cephalalgia* **27:** 193–210. doi:10.1111/j.1468-2982.2007.01288.x

Sullivan KE. 2007. Inflammation in juvenile idiopathic arthritis. *Rheum Dis Clin North Am* **33:** 365–388. doi:10.1016/j.rdc.2007.07.004

Sutherland RE, Olsen JS, McKinstry A, Villalta SA, Wolters PJ. 2008. Mast cell IL-6 improves survival from *Klebsiella* pneumonia and sepsis by enhancing neutrophil killing. *J Immunol* **181:** 5598–5605. doi:10.4049/jimmunol.181.8.5598

Tiuria R, Horii Y, Tateyama S, Tsuchiya K, Nawa Y. 1994. The Indian soft-furred rat, *Millardia meltada*, a new host for *Nippostrongylus brasiliensis*, showing androgen-dependent sex difference in intestinal mucosal defence. *Int J Parasitol* **24:** 1055–1057. doi:10.1016/0020-7519(94)90170-8

Tiuria R, Horii Y, Makimura S, Ishikawa N, Tsuchiya K, Nawa Y. 1995. Effect of testosterone on the mucosal defence against intestinal helminths in Indian soft-furred rats, *Millardia meltada* with reference to goblet and mast cell responses. *Parasite Immunol* **17:** 479–484. doi:10.1111/j.1365-3024.1995.tb00918.x

Vasiadi M, Kempuraj D, Boucher W, Kalogeromitros D, Theoharides TC. 2006. Progesterone inhibits mast cell secretion. *Int J Immunopathol Pharmacol* **19:** 787–794. doi:10.1177/039463200601900408

Vaz GT, Vasconcelos MM, Oliveira EA, Ferreira AL, Magalhães PG, Silva FM, Lima EM. 2012. Prevalence of lower urinary tract symptoms in school-age children. *Pediatr Nephrol* **27:** 597–603. doi:10.1007/s00467-011-2028-1

Vermillion DL, Ernst PB, Scicchitano R, Collins SM. 1988. Antigen-induced contraction of jejunal smooth muscle in the sensitized rat. *Am J Physiol* **255:** G701–G708. doi:10.1152/ajpgi.1988.255.6.G701

Victor TW, Hu X, Campbell JC, Buse DC, Lipton RB. 2010. Migraine prevalence by age and sex in the United States: a life-span study. *Cephalalgia* **30:** 1065–1072. doi:10.1177/0333102409355601

Voehringer D. 2013. Protective and pathological roles of mast cells and basophils. *Nat Rev Immunol* **13:** 362–375. doi:10.1038/nri3427

vom Steeg LG, Klein SL. 2016. SeXX matters in infectious disease pathogenesis. *PLoS Pathog* **12:** e1005374. doi:10.1371/journal.ppat.1005374

Vrieze A, Postma DS, Kerstjens HA. 2003. Perimenstrual asthma: a syndrome without known cause or cure. *J Allergy Clin Immunol* **112:** 271–282. doi:10.1067/mai.2003.1676

Walitt B, Nahin RL, Katz RS, Bergman MJ, Wolfe F. 2015. The prevalence and characteristics of fibromyalgia in the 2012 National Health Interview Survey. *PLoS ONE* **10:** e0138024. doi:10.1371/journal.pone.0138024

Webb LM, Lieberman P. 2006. Anaphylaxis: a review of 601 cases. *Ann Allergy Asthma Immunol* **97:** 39–43. doi:10.1016/S1081-1206(10)61367-1

Wei OL, Hilliard A, Kalman D, Sherman M. 2005. Mast cells limit systemic bacterial dissemination but not colitis in response to *Citrobacter rodentium*. *Infect Immun* **73:** 1978–1985. doi:10.1128/IAI.73.4.1978-1985.2005

Wijchers PJ, Festenstein RJ. 2011. Epigenetic regulation of autosomal gene expression by sex chromosomes. *Trends Genet* **27:** 132–140. doi:10.1016/j.tig.2011.01.004

Wintroub BU, Mihm MC Jr, Goetzl EJ, Soter NA, Austen KF. 1978. Morphologic and functional evidence for release of mast-cell products in bullous pemphigoid. *N Engl J Med* **298:** 417–421. doi:10.1056/NEJM197802232980803

Wong GW, Zhuo L, Kimata K, Lam BK, Satoh N, Stevens RL. 2014. Ancient origin of mast cells. *Biochem Biophys Res Commun* **451:** 314–318. doi:10.1016/j.bbrc.2014.07.124

Xu S, Wang X, Zhao J, Yang S, Dong L, Qin B. 2020. GPER-mediated, oestrogen-dependent visceral hypersensitivity in stressed rats is associated with mast cell tryptase and histamine expression. *Fundam Clin Pharmacol* **34:** 433–443. doi:10.1111/fcp.12537

Zaitsu M, Narita S, Lambert KC, Grady JJ, Estes DM, Curran EM, Brooks EG, Watson CS, Goldblum RM, Midoro-Horiuti T. 2007. Estradiol activates mast cells via a non-genomic estrogen receptor-α and calcium influx. *Mol Immunol* **44:** 1977–1985. doi:10.1016/j.molimm.2006.09.030

Zhu TH, Ding SJ, Li TT, Zhu LB, Huang XF, Zhang XM. 2018. Estrogen is an important mediator of mast cell activation in ovarian endometriomas. *Reproduction* **155:** 73–83. doi:10.1530/REP-17-0457

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