

Endocrine regulation of lung disease and inflammation

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Impact statement

Sex-differences in the incidence and severity of inflammatory lung diseases have been recognized for years. Women of reproductive age are more likely to suffer from chronic lung disease, with higher mortality rates than men. Physiological changes in hormone levels such as those occurring during the menstrual cycle, pregnancy, and menopause have been associated with lung function changes and asthma symptoms. Despite this, the roles of sex hormones in the mechanisms associated with lung diseases have not been fully elucidated. This review summarizes basic and clinical studies of sex hormones as potential modulators of lung function and inflammation. The information obtained from sex-specific research on lung physiology and pathology will potentially help in the development of sex-specific therapeutics for inflammatory lung disease that may account for the hormonal status of the patient.

Abstract

Sex-based disparities have been identified in respiratory physiology, and in many chronic lung diseases including asthma, chronic obstructive pulmonary disease, and cystic fibrosis. The observed sex differences in lung disease prevalence and incidence have been linked to changes in circulating levels of sex hormones that start after puberty and that have been shown to affect physiological and immunological functions. While the exact roles of male and female sex hormones in these processes have not been fully elucidated, it is now evident that these can target many lung cell types and affect several functions of the respiratory system. In this mini-review, we have summarized seminal studies aimed to understand the effects of the most relevant male and female sex hormones (estrogens, progesterone, and androgens) and their receptors on lung function. Moreover, we have reviewed the known influences of sex hormones and of the hypothalamic–pituitary–gonadal axis in lung disease and immunity. Understanding the roles of sex hormones in the regulation of lung function and inflammation is the first step for the potential development of more effective therapeutic options to prevent and treat lung disease in men and women.

Keywords: Sex differences, lung immunity, lung disease, asthma, hormone, inflammation

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Introduction

Inflammatory lung diseases affect a large proportion of the world's population, and are a substantial health problem and a significant economic burden. It is estimated that these diseases affect more than 510 million people worldwide, with worsening of symptoms reported markedly higher in women as compared to men.¹ A critical barrier in our ability to effectively treat women with lung disease and in preventing negative lung health effects is the gap of knowledge of sex-specific mechanisms of inflammation in the lung, and the contributions of sex hormones to these mechanisms. In the past decade,

several clinical and basic science studies have been conducted in order to elucidate the specific roles that male and female sex hormones play in lung inflammatory processes.^{2,3} Here, we discuss the most recent literature available describing sex differences in inflammatory lung disease prevalence and outcomes, with a particular emphasis on asthma and COPD, which show a clear sexual dimorphism in prevalence and incidence.^{4,5} We also summarize the results from multiple studies focused on understanding the roles of sex hormones as modulators of lung function and inflammation using different experimental models.

Sex differences in lung diseases

Various lung disorders and cancers display gender disparities in their prevalence, severity, and/or outcome. For example, cystic fibrosis (CF), a genetic disorder associated with frequent respiratory infections, has been shown to have poorer outcomes and higher mortality in females than males, particularly in response to *Pseudomonas aeruginosa* infection.⁶ Intriguingly, idiopathic pulmonary arterial hypertension is also more predominant in females than males, while idiopathic pulmonary fibrosis disproportionately affects males.^{7–9} With regard to lung cancer, the leading cause of cancer deaths worldwide, the most recent reports indicate that while the disease is still more likely to occur in men than in women in the United States (1 in 15 men vs. 1 in 17 women), the rates of lung cancer in women are rising faster, and have recently exceeded rates for men in the younger populations.^{10,11} In addition, specific types of cancers such as malignant mesothelioma and adenocarcinoma are more common in men and in women, respectively.¹² While studies continue to report statistical data on sex differences in the prevalence for these diseases, very few have explored the effects of sex hormones in their development and course. However, for inflammatory lung diseases such as asthma and chronic obstructive pulmonary disease (COPD), researchers have begun to explore in more detail the effects of male and female hormones in the mechanisms associated with their onset and progression.¹³

Asthma and COPD are the most prevalent inflammatory diseases of the lung, affecting a significant portion of the world's population. The most recent Global Burden and Disease Study reported that in 2015 more than 174 million people had COPD and more than 358 million people suffered from asthma, resulting in 3.2 million and 0.4 million deaths, respectively.¹⁴ While both diseases impose a substantial public health burden in terms of impaired quality of life and mortality in men and women, a clear sexual dimorphism exists in their risk, prevalence, and severity.^{15–17} While asthma symptoms in children are more prevalent in boys than in girls, studies in adult populations more frequently report negative lung health outcomes for women than men, suggesting an involvement of female sex hormones in mediating these effects.¹⁸ The severity of asthma in men also increases later in life when testosterone levels decrease, suggesting a potential role of androgens in mediating asthma pathophysiology.¹⁹

Asthma is a chronic inflammatory disease that displays a notorious sexual dimorphism across the lifespan. Many epidemiological studies of childhood asthma have shown that prepubertal boys have more asthma than girls, especially at younger ages.²⁰ In the United States, it is estimated that 9.2% of boys and 7.4% of girls under 18 years old currently suffer from asthma.²¹ Interestingly, these patterns are reversed after puberty, where asthma prevalence rates for women are almost twice as those for men (10.4% vs. 6.2% for women and men over 18 years of age, respectively).²¹ These statistics have led investigators to generate the hypothesis that hormonal changes starting in puberty contribute to asthma development. In this regard, studies

showing variations in asthma symptoms and hospitalization rates throughout the menstrual cycle in adult women, and a decline in asthma incidence in women after menopause also support this hypothesis.^{22,23} This notion is further supported by studies showing that girls who undergo menarche at an earlier age have a higher risk of developing asthma after puberty than girls in which menarche occurs later.²⁴

With regard to puberty, data on asthma prevalence indicated that in 2016 about 11.2% of the U.S. population ages 12–14 had asthma.²⁵ A recent study in children and adolescents reported that the prevalence of asthma in adolescents (aged 13–14 years) was significantly higher than that in schoolchildren aged 6–7 years.²⁶ This study also found that the severity of asthma in girls was higher than that in boys aged 13–14 years. In older adults, two phenotypes are usually observed: patients with longstanding asthma who develop additional airflow limitation, and those who develop late-onset asthma. In these patients, symptoms are frequently superimposed with age-related respiratory problems, making associations with hormonal factors difficult to isolate.²⁷

For many years, COPD was considered a disease that primarily affected men.²⁸ However, recently there has been a shocking increase in the number of women diagnosed with COPD, partially due to a rise in smoking rates in females over the past few decades.^{29,30} The most recent reports have also indicated that females have more severe disease with early onset and are more sensitive to tobacco exposure than men.³⁰ While females tend to smoke less than men, they have a faster annual decay in lung function than male smokers, making them more prone to develop COPD.³¹ Interestingly, it has been shown that cigarette smoke exposure alters estrogen signaling in airway smooth muscle, which could contribute to increased airway contractility in women.³² In addition, women smokers are about twice as likely as men smokers to develop COPD, suggesting a role of female hormones in the mechanisms leading to COPD development.³³ Despite these data, clinical studies conducted to date have not reported the effects of the menstrual cycle or hormone replacement therapy on COPD, nor sufficient evidence to support the effect of sex and gender in the overall response to COPD treatment.^{34,35} Overall, more research is needed to elucidate the mechanisms underlying the observed sex differences in COPD susceptibility and progression.

Sex hormones and lung disease

Both clinical studies and experimental evidence from mouse models have shown that female hormones such as estrogens and their metabolites (e.g. estradiol, estrone, estriol) can trigger lung inflammatory and allergic reactions, and male hormones such as testosterone usually play the opposite role.^{36,37} While most studies cited below have concentrated on the effects of estradiol, in this manuscript, we use the term “estrogen” to refer to all compounds. In the next few sections, we discuss recent work on the roles of hypothalamic, pituitary, and gonadal

hormones in lung function, with a particular emphasis on lung inflammatory cells.

The HPG axis and the lung: Is there a crosstalk?

The hypothalamic-pituitary-gonadal (HPG) axis includes the hypothalamus, the pituitary gland, and the gonads. To control functions such as reproduction, neurohormones such as gonadotropin-releasing hormone (GnRH) are released from the hypothalamus and target the pituitary gland, which releases hormones including luteinizing hormone (LH) and follicle-stimulating hormone (FSH), that stimulate the gonads to produce sex hormones such as estrogen, progesterone, testosterone, activin, inhibin, and follistatin. While pathological or environmentally induced changes in the function of this axis may produce hormonal alterations that affect reproduction, they can also cause local and systemic effects on different systems such as the respiratory or immune system. In addition, sex steroid hormone receptors, and GnRH, LH, and activin receptors have been identified in many tissues including the lung, suggesting that alterations in serum hormones would potentially affect normal lung function.³⁸ In this regard, clinical studies have shown that several lung function parameters actually vary throughout the women's menstrual cycle phases,³⁹ and during pregnancy.^{40,41} Studies conducted in mice have also hypothesized that estrogen usually acts as a pro-inflammatory agent, while androgens act as negative regulators of lung inflammation.^{42,43} While many studies have focused on sex steroid receptor-associated signaling pathways, the exact mechanisms underlying these effects remain unknown.⁴⁴⁻⁴⁹

With regard to lung disease and normal HPG axis function, an interesting fact is the observed reduction in asthma severity in menopausal women between ages 50 and 65.⁵⁰ During the post-menopausal period, GnRH levels rise due to a dramatic decrease in sex hormone synthesis.⁵¹ This loss of hypothalamic feedback inhibition causes the increase of GnRH and gonadotropins levels following ovarian senescence.⁵² However, in a research study, post-menopausal women with asthma exhibited lower serum FSH and LH levels when compared to non-asthmatic post-menopausal women.⁵³ This trend was also observed in women with preexisting lung disease.⁴⁰ Despite these data, additional studies need to be performed to unveil the relationships between the HPG axis and respiratory function in the healthy and asthmatic lung. Additionally, studies have shown that neuroendocrine hormones external to the HPG axis also regulate lung diseases such as asthma and its pathogenesis.⁵⁴ There is now evidence that the HPA (hypothalamic-pituitary-adrenal) axis, which largely controls glucocorticoid secretion, could be an important mediator of these effects, particularly due to the strong relationship between stress and immunity and the known roles of glucocorticoids in mediating the mechanisms of lung development and inflammation.⁵⁵ A study of long-term systemic administration of exogenous glucocorticoids in subjects with lung disease showed inhibition of the HPA axis and decreased lung function.⁵⁶ It has also been shown

that secretion dysfunction of cortical hormones can aggravate asthma severity and make patients become more dependent on exogenous glucocorticoids, creating a vicious cycle that manifests in repeated asthma attacks.⁵⁷

Little is known on the effects of lung disease on reproductive function in men and women, although a few studies have reported that asthma can actually affect pregnancy and fertility, mainly due to side effects of systemic inflammation.⁵⁸⁻⁶⁰ Overall, while the evidence on the physiological crosstalk between neuroendocrine and pulmonary systems has shown influences of hormones secreted by both the HPG and HPA on lung function, inflammatory processes, and lung disease, more research is needed to elucidate the mechanisms linking these processes.

Sex hormones and sex hormone receptors in the lung: Expression and function

Male and female sex hormones mainly exert their effects through interactions with their receptors, whose expression has been detected in murine and human lung immune cells (Figure 1). These are: the estrogen receptors (ERs), the androgen receptor (AR), and the progesterone receptors (PRs). Their actions involve either direct control of transcription through binding of hormone-receptor complexes to gene promoter regions (genomic effects), or indirect regulation through activation of intracellular signaling cascades mediated by G proteins (non-genomic effects) that also result in transcriptional regulation (Figure 2).⁶¹

A number of studies have suggested that sex hormones contribute to the overall lung inflammatory response to exogenous insults such as pollutants and infectious agents, as well as lung disease.⁶² Table 1 summarizes the known effects of sex hormones (estrogen, progesterone, and testosterone) on the expression of cytokines and inflammatory mediators in the lung. Table 2 summarizes the known influences of sex hormones on lung disease. While most of these effects have been attributed to gonadal hormones, it should be mentioned that the lung is able to synthesize sex hormones locally, and mediate local production of reactive oxygen species and/or undergo oxidative stress that can also contribute to inflammation, although more research in this subject needs to be conducted. This notion is supported by work in normal and cancerous lung cells indicating the expression of key enzymes in important metabolic pathways leading to estrogen synthesis, such as aromatase (CYP19A1), hydroxysteroid (17-beta) dehydrogenase type 1 (HSD17 β 1), steroid sulfatase (STS), and estrogen sulfotransferase (EST).⁶³

Estrogen

The literature on estrogen effects on lung function and disease remains inconclusive.⁹⁸ While some animal studies have shown that increases in circulating estrogen levels result in reduced innate immunity, others have reported pro-inflammatory effects.⁴⁶ This may be partially due to the pleiotropic expression of the ERs and the multiple genomic and non-genomic effects of estrogen in various cell

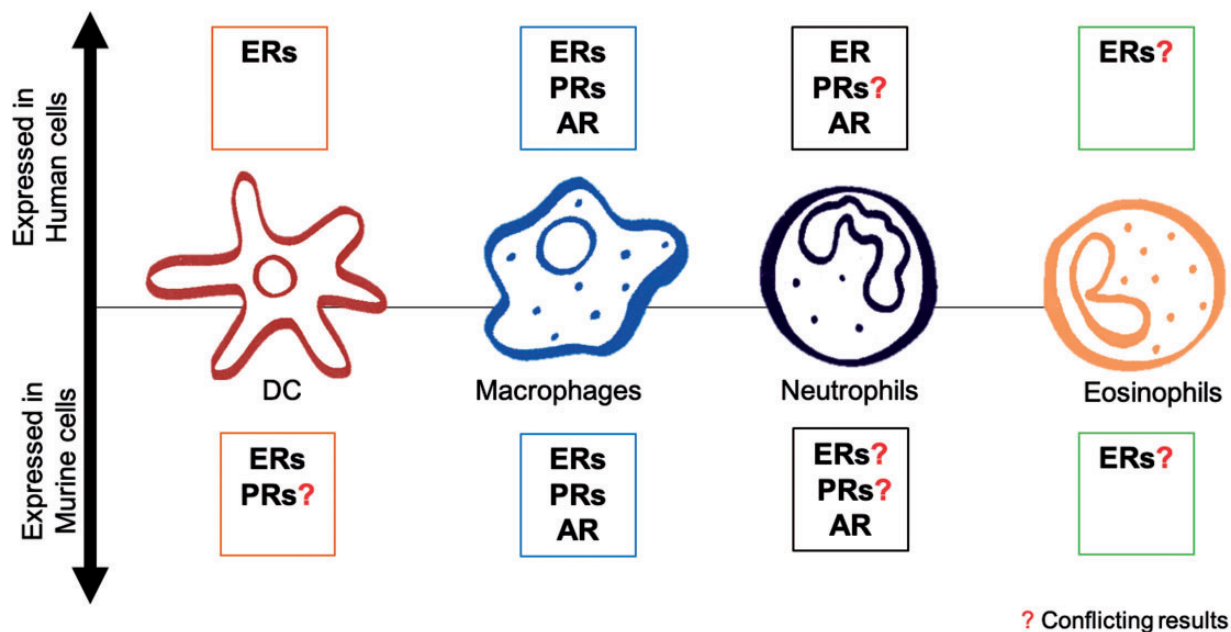


Figure 1. Expression of sex hormone receptors in lung immune cells. (A color version of this figure is available in the online journal.)

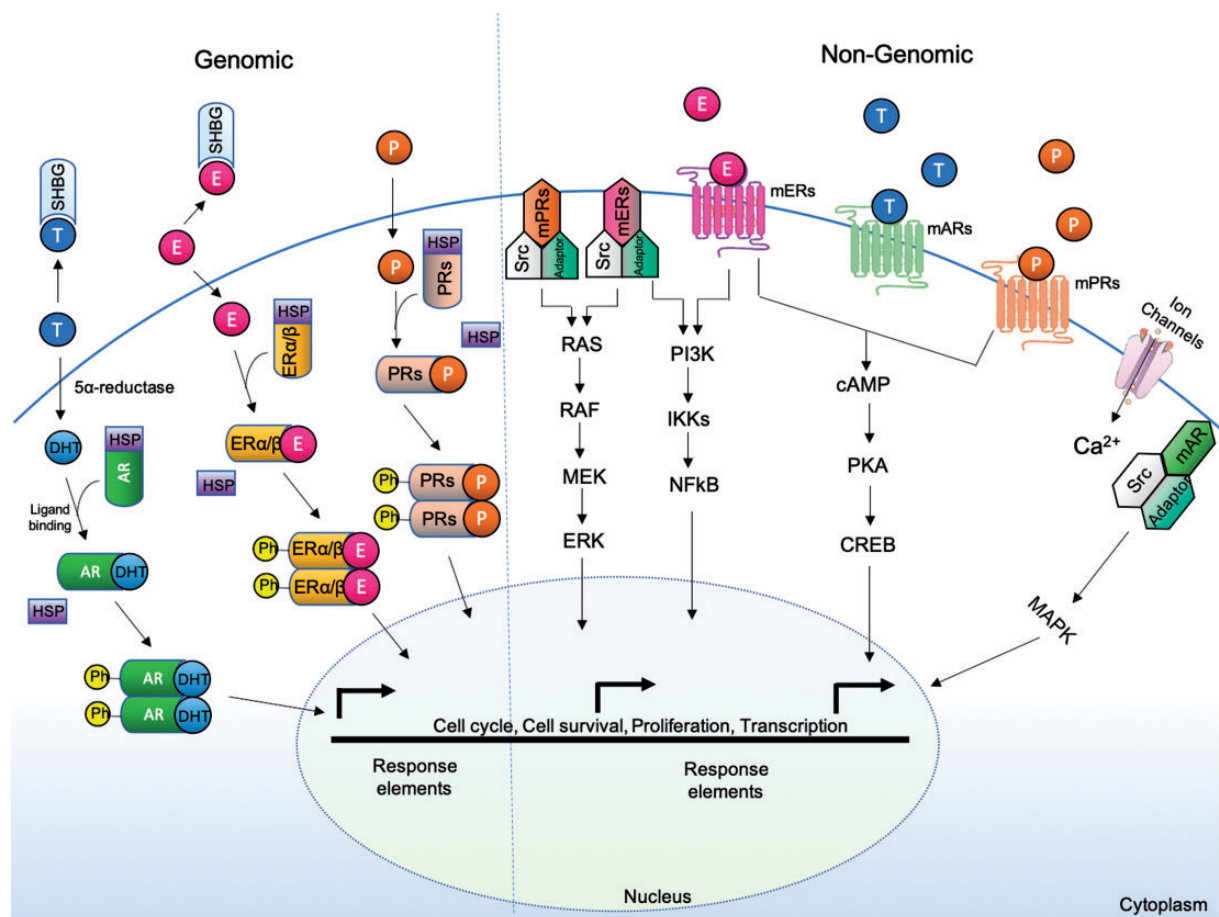


Figure 2. Summary of sex hormone receptors intracellular signaling pathways. (A color version of this figure is available in the online journal.)

types.⁹⁹ Some studies also reported that the expression of proinflammatory cytokines such as IL-1 β , IL-6, type I interferon (IFN), tumor necrosis factor alpha (TNF α), and NF- κ B in lung cells is strongly induced by estrogen.⁶⁴ In the case of

NF- κ B, ER α can obstruct its intracellular trafficking mechanisms, thus inhibiting the expression of inflammatory genes and modulating immune function.¹⁰⁰ On the other hand, a recent study reported that transforming growth

Table 1. Influence of sex hormones on cytokines and inflammatory mediators in the lung.

Sex hormones	Up-regulation	Down-regulation/ Inhibition	Sources
Estrogen	IL-1 β , IL-6, type I IFN, TNF- α , NF- κ B, TLR8	TGF- β 1, IL-10	64,65
Progesterone	IL-10, IL-1 β , IL-5, IL-6, IL-22, TNF α , IL-4, Src/ p21, Erk, IL-9, IL-13	NF- κ B, TGF- β 1, CTGF, TAGLN, PAI-1, IFN- γ	45,51,66,67,68,69,70
Testosterone	IL-2, IFN γ , Hbb-b1, Hbb-y, Hbq1	IL-33, TSLP, IL-4, IL-5, IL-13, Angptl4, Cyp1a1	40,47,71,72,73,74

Table 2. Influences of sex hormones on lung disease.

Disease	Hormone effects			Sources
	Estrogen	Progesterone	Testosterone	
Asthma	+/-	+	+/-	2,24,67,75-80
COPD	-	+	+	28,81-84
Cystic fibrosis	-	-	nd	85-90
Allergic rhinitis	-	-	+/-	91-93
Lung cancer	-	+	-	94-97

Note: (+) positive effect, (-) negative effect, (+/v) conflictive data, (nd) no data.

factor beta1 (TGF- β 1) represses the expression of ER α in bronchial epithelial cells.⁶⁵

There are two classes of ERs: the nuclear ERs: ER α (ESR1) and ER β (ESR2), and the membrane ERs: mERs (G protein-coupled ER 1, GPER/GPER30).¹⁰¹ Estrogen directly binds to the nuclear ERs, triggering receptor dimerization and binding to estrogen response elements (EREs) in the promoter region of target genes. Indirectly, ERs can also interact and form complexes with transcription factors in the nucleus.¹⁰² ERs are expressed in various types of immune cells, including lymphocytes, macrophages, and dendritic cells (DCs).^{103,104} In human lung tissue, ER α and ER β have been found differentially expressed in asthmatic and non-asthmatic airway smooth muscle (ASM). Interestingly, ER β expression is significantly greater in asthmatic ASM in both males and females.¹⁰⁵ Moreover, ER β inhibits platelet-derived growth factor (PDGF)-stimulated ASM proliferation.⁴⁴

There is experimental evidence that the ERs are also involved in lung development. ER α modulates alveolar size and number, and induces alveolar regeneration after their loss in adult ovariectomized mice.¹⁰⁶ Also, ER- β positively regulates the extracellular matrix initiating normal elastic tissue recoil in the lungs.¹⁰⁷ More recently, it has been shown that the ERs are also under the control of microRNAs (miRNAs). For example, miRNA-221/222 has been reported to target ER α .¹⁰⁸ In addition, ER α is upregulated by miR-625-5p and miRNA-22-3p in pediatric patients with dust mite-induced asthma.¹⁰⁹ Interestingly, our recent work indicates that both sex and hormonal status can influence lung miRNA expression in ozone-induced lung inflammation.¹¹⁰ We have shown that miR-221/222 are differentially expressed in females exposed to ozone in proestrus, which is the stage of the mouse estrous cycle where estrogen levels are high. Other studies have also shown that estrogen down-regulates lung miRNA

expression leading to up-regulation of target proto-oncogenes, cellular proliferation, and lung tumor development following cigarette-smoke exposure.¹¹¹ Collectively, these studies have suggested that estrogens regulate multiple functions in the lung via interactions with the ERs and subsequent control of transcription, potentially influencing the outcomes of developmental, inflammatory, and disease processes. More research is needed to unveil the implicated mechanisms and identify potential points of intervention for lung disease.

Progesterone

While the regulatory effects of estrogen have been considerably researched, less is known about the role of progesterone, although both hormones may contribute to sex differences in lung immunity. Progesterone exerts its effect through the activation of the PRs. There are two PR isoforms conserved in murine and humans: PR-A and PR-B. These isoforms exhibit distinctive transcriptional patterns on progesterone response promoters.¹¹² PR-B is the principal activator of gene transcription, while PR-A represses PR-B and ERs transcription.^{71,113} It has been shown that agonist-activated PR-B associates with ERs causing the activation of the Src/p21(ras)/Erk pathway.⁶⁶

In terms of lung inflammation, studies have found that progesterone decreases contractility and increases relaxation of bronchial smooth muscle.⁶⁷ Compared to estrogen and testosterone, it has the most powerful vasodilator effect in pulmonary arteries of both male and female rats.¹¹⁴ Moreover, progesterone stimulates the development of T-helper 1 cells and inflammatory cytokines such as IL-10, IL-1 β , IL-5, IL-6, IL-22, TNF α , and IL-4 in an allergic model of lung inflammation.^{68,69} In a study using a mouse model of influenza, treatment with progesterone reduced inflammation and improved lung function restoring tissue homeostasis.⁶⁹ In humans, serum progesterone is positively associated with peak expiratory flow rate during the luteal phase of the menstrual cycle when the progesterone levels are high.¹¹⁵ Interestingly, PRs are expressed in the fibrotic areas of patients with usual interstitial pneumonia, but the mechanisms by which PRs exert these effects remain unknown.¹¹⁶

Testosterone

It has been known for decades that androgens control multiple physiological functions in the lung.¹¹⁷ Protective roles of testosterone have been proposed based on the

associations of puberty Tanner stages with decreased symptoms observed in boys with asthma.¹¹⁸ Testosterone also causes bronchial tissue relaxation and reduces the response to histamine.¹¹⁹ In animal studies, testosterone has been shown to attenuate airway inflammation induced by *Alternaria alternata* and house dust mite extracts exposure, by diminishing a population of cells called lung group 2 innate lymphoid cells (ILC2), and by decreasing expression of IL-33 and thymic stromal lymphopoietin (TSLP), which are ILC2-stimulating cytokines.⁷²

The AR regulates the activity and effects of male sex steroids, and is mainly expressed in the bronchial epithelium of the murine lung.⁷³ The AR is a nuclear receptor that is activated by binding to testosterone or to its more active metabolite, 5 α -dihydrotestosterone (DHT) in the cytoplasm, and then translocating into the nucleus where it acts as a DNA-binding transcription factor that controls gene expression. Because the AR is very similar to the PRs, it has been shown that, in higher dosages, PRs can actually antagonize the AR.¹²⁰ The AR has also been reported to affect expression of lung gene expression and modulate function of lung immune cells. For example, mechanisms mediated by AR signaling result in decreased Th17 and Th2 cells via reduction of IL-4 production in the lung.⁷⁴ Overall, studies exploring the roles of androgens in allergic airway inflammation have mainly demonstrated their protective and anti-inflammatory effects, but more studies are needed to elucidate the specific contributions of AR signaling in these mechanisms.

Influence of sex hormones in lung immune cells

Studies have shown that sex hormones can affect airway tone and inflammation, and exert effects in different lung cell types, including airway smooth muscle,¹²¹ and immune cells,^{48,122,123} although these effects are still under investigation. In the next paragraphs, we discuss the available literature on the effects of sex hormones on the key cell players of lung immunity. These include: lung macrophages, neutrophils, DCs, and eosinophils.

Macrophages

Alveolar macrophages (AMs) provide one of the first lines of defense in the lower airway and have emerged as important mediators of inflammation and tissue remodeling. AMs are professional phagocytes highly specialized in removal of foreign materials. It has been discovered that female mice treated with ovalbumin (OVA) have greater amounts of AMs in lung tissue than males, and that these cells increase allergic airway inflammation.¹²⁴ Also, it has been suggested that sex hormones may regulate macrophage polarization states. Studies have shown that estrogen enhances the resolution phase (M2) gene expression, shortens the duration of the pro-inflammatory stage (M1), and thereby contributes to sex differences observed in asthma.¹²⁵ On the other hand, progesterone but not estradiol can inhibit the release of microparticles, which are membrane-bound vesicles that display proinflammatory

properties, by stimulated AMs.¹²⁶ Studies associated with the role of testosterone in AMs are limited; however, researchers determined that testosterone reduces the production of TNF α and expression of nitric oxide in AMs.^{127,128}

Neutrophils

Neutrophils are considered to be central to the pathogenesis of most forms of acute lung injury.¹²⁹ We have previously shown that females displayed significantly higher neutrophil number than males in an ozone-induced lung inflammation model.¹³⁰ Moreover, in a murine model of CF, scientists found a higher mortality rate and slower bacterial clearance in females than males, but this effect was reverted when neutropenia was induced in estrogen-treated ovariectomized mice. In addition, neutrophils treated with estrogen enhanced oxidative burst, but reduced bacterial killing in the lung independent of progesterone.¹³¹ Lastly, testosterone has been shown to decrease neutrophilic lung inflammation in an allergic asthma mouse model.¹³²

DCs

DCs induce T-cell responses after migration to lymphoid tissue. There are a higher number of DCs migrating from the lungs to the lymph nodes in female mice sensitized with OVA than males. However, the effect of sex hormones on lung DCs has not been well studied. In studies not associated with the lung, estrogen has been shown to stimulate the functional DCs formation and DCs stimulation of T cells.¹³³

Eosinophils

Eosinophils are key cellular participants in the development of allergic airway disease and asthma.¹³⁴ In an OVA model, researchers demonstrated that females showed more severe eosinophilia than males. However, the effects were reversed after gonadectomy.¹³⁵ Another study showed that estrogen treatment significantly enhanced eosinophil adhesiveness; however, treatment with both estrogen and progesterone induced degranulation.¹³⁶ Treatment with only progesterone exacerbates eosinophilic airway inflammation and bronchial hyperreactivity. Contrarily, testosterone significantly reduced eosinophil adhesiveness and viability.⁷⁰

Conclusion

From the literature reviewed above, it is evident that sex hormones play major roles in pulmonary diseases and lung immunity. This minireview emphasizes the significance of sex-specific research and the importance of taking into consideration sex and hormonal status as factors when studying respiratory physiology and disease. Overall, while opposite effects for male and female hormones have been generally found with regard to inflammatory mechanisms, studies remain inconclusive as to whether specific sex hormones exert pro- or anti-inflammatory effects in the lung. We believe that rather than direct actions of individual

hormones, a balance of the contributions of multiple hormones and their receptors, as well as interactions of several pathways activated by these are likely to be responsible for the physiological outcomes and sex disparities observed in lung diseases. A better understanding of the roles of sex hormones in the control of lung function and inflammation will likely help in the development of more effective sex-specific preventative and therapeutic options for these diseases.

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DECLARATION OF CONFLICTING INTERESTS

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