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Immunity

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Review

Implications of Sex Differences in Immunity for SARS-CoV-2 Pathogenesis and Design of Therapeutic Interventions

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SUMMARY

Men present more frequently with severe manifestations of coronavirus disease 2019 (COVID-19) and are at higher risk for death. The underlying mechanisms for these differences between female and male individuals infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are insufficiently understood. However, studies from other viral infections have shown that females can mount stronger immune responses against viruses than males. Emerging knowledge on the basic biological pathways that underlie differences in immune responses between women and men needs to be incorporated into research efforts on SARS-CoV-2 pathogenesis and pathology to identify targets for therapeutic interventions aimed at enhancing antiviral immune function and lung airway resilience while reducing pathogenic inflammation in COVID-19.

INTRODUCTION

Our immune system defends us from pathogens. Optimal immunological homeostasis is achieved when the pathogen is removed with high efficiency while avoiding collateral tissue damage for the host (Holt et al., 2008). This immunological balance is different between women and men. Increasing data demonstrate that women mount stronger immune responses against viruses and vaccines (Flanagan et al., 2017; Klein and Flanagan, 2016; Ziegler and Altfeld, 2017) and also exhibit superior immune-mediated tissue repair capacities (Vom Steeg and Klein, 2019). The current severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic highlights the clinical consequences of these sex differences in antiviral immunity and tissue resilience (Klein et al., 2020; Scully et al., 2020), with older men in particular suffering from severe coronavirus disease 2019 (COVID-19) and experiencing higher case mortality rates (Docherty et al., 2020; Grasselli et al., 2020; Jin et al., 2020; Salje et al., 2020). Compiled data from Europe, for example, show male to female ratios of 1.5 for COVID-19 hospitalizations and of 1.7 to 1.8 for COVID-19 case fatality rates (Gebhard et al., 2020). Although sex differences in manifestations of viral infections have been established for multiple viruses, including SARS-CoV, hepatitis C virus, Zika virus, respiratory syncytial virus, human immunodeficiency virus 1 (HIV-1), and influenza virus (Baden et al., 2014; Gabriel and Arck, 2014; Klein and Flanagan, 2016; Mazur et al., 2015; Meier et al., 2009; Robinson et al., 2011; Stanelle-Bertram et al., 2018; van Lunzen and Altfeld, 2014), sex-specific treatment strategies are rarely applied outside the field of oncology. However, sex differences in case fatality rates seem to be higher in COVID-19 than in these other infections (Gebhard et al., 2020), emphasizing the need to develop treatment strategies for COVID-19 that take these differences between the sexes into account. Indeed, in response to the urgency of the COVID-19 health crisis, sex-based treatment options in COVID-19 patients, including the use of estrogen, estrogen antagonists, and androgen antagonists (NCT04359329, NCT04397718, NCT04374279, and NCT04389580), are currently being tested and planned. However, given the complexities underlying sex-specific differences in infectious diseases, ranging from environmental to biological factors, such as differences in sex hormones and expression of X-chromosome-encoded genes, supplementing men with female hormones might not be the final answer. The rapidly expanding knowledge on the differential regulation of antiviral immunity and immune-mediated tissue repair pathways between women and men needs to be harnessed for the design and testing of novel treatment strategies for SARS-CoV-2 infection aimed at enhancing antiviral immunity, preventing pathological immune activation, and strengthening tissue resilience. Here, we discuss biological pathways that provide women advantages over men in achieving immunological homeostasis in response to viral infections and address their potential implications for the treatment of severe COVID-19.

SARS-CoV-2 Pathogenesis

COVID-19, caused by SARS-CoV-2, was first reported in China in December 2019 (Zavascki and Falci, 2020; Zhang, 2020). Although Middle East respiratory syndrome coronavirus (MERS-CoV) and SARS-CoV infections have higher mortality rates than SARS-CoV-2, the more successful person-to-person spread of SARS-CoV-2 has resulted in high numbers of worldwide infections and deaths. Initial manifestations of viral infections depend on the tissue distribution of the receptors that allow for viral binding and entry into host cells. Angiotensin-converting enzyme 2 (ACE2) serves as the principal entry receptor for SARS-CoV-2 (Hoffmann et al., 2020; Zhou et al., 2020a) and is expressed in numerous tissues, including nasal, respiratory,

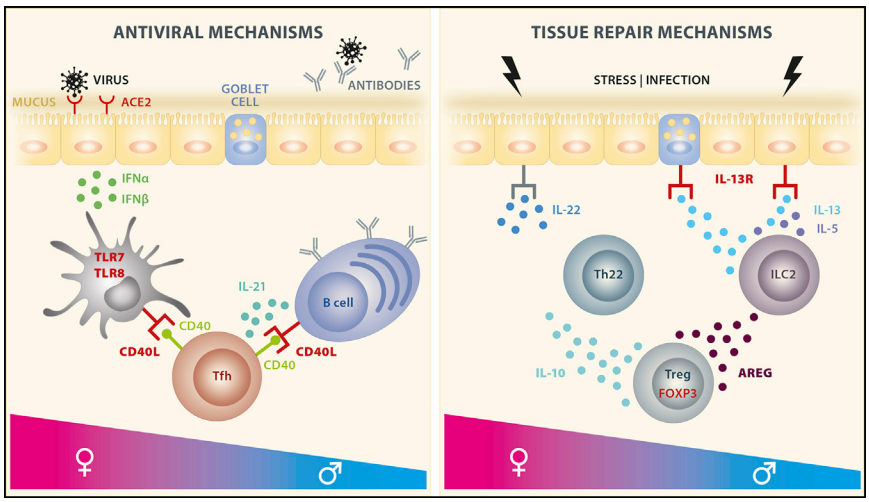

Figure 1. Sex Differences in Immune-Mediated Antiviral and Tissue Repair Mechanisms in COVID-19

Sex-specific differences in immune-mediated antiviral mechanisms are described on the left and tissue repair mechanisms on the right.

Left: SARS-CoV-2 binds to ACE2 receptors to gain entrance into cells. SARS-CoV-2 can be sensed by TLR7 and TLR8 and induce the production of type I IFNs by pDCs. Tfh cells provide help through cytokines and CD40/CD40L to B cells that produce neutralizing antibodies against SARS-CoV-2. These antiviral mechanisms are stronger in females and might be partially regulated by higher expression of genes encoded by the X chromosome, including TLR7, TLR8, and CD40L.

Right: Th22 cells and ILC2s produce cytokines (IL-22, IL-5, IL-13, and AREG) that promote lung airway epithelial cell growth and function. Stronger Treg cell and ILC2 function as well as higher expression of IL-13R in women might promote lung airway tissue resilience and function in SARS-CoV-2-infected women.

Molecules encoded by genes located on the X chromosome are shown in red, including ACE2, TLR7, TLR8, CD40L, and IL-13R. Wedges on the bottom of the figure represent overall higher immune-mediated antiviral and tissue repair mechanisms in women compared to men.

and intestinal epithelial cells; kidney; and blood vessels (Lamers et al., 2020; Puelles et al., 2020; Sungnak et al., 2020; Teuwen et al., 2020; Tukiainen et al., 2017). The principal mode of SARS-CoV-2 transmission appears to be the respiratory route, with initial infection of the upper respiratory tract (Sungnak et al., 2020), and infected individuals suffer from symptoms similar to those of other upper respiratory tract infections. Control of further viral dissemination at this early stage prevents the development of more severe COVID-19 symptoms; however, SARS-CoV-2 can spread through aerosols to new hosts. It has been suggested that SARS-CoV-2 is able to spread efficiently among the human population due to a higher affinity for ACE2 binding compared to SARS-CoV (Walls et al., 2020; Wrapp et al., 2020) and efficient cell fusion facilitated by TMPRSS2 (Hoffmann et al., 2020; Zang et al., 2020). Failure to prevent viral dissemination beyond the upper respiratory tract results in infection of the lower respiratory airways, apoptosis of pneumocytes, and decreased capacity for gas exchange, leading to reduced oxygenation and eventually requirement for respiratory support. Attempts of the immune response to control SARS-CoV-2 infection in the lower respiratory tract can aggravate oxygenation by causing collateral lung tissue damage, resulting in pulmonary edema and further occlusion of small airways and eventually leading to acute respiratory distress syndrome (ARDS). The broad tissue expression of ACE2 furthermore enables SARS-CoV-2 to spread to other tissues and infect the vascular endothelium, resulting in multiorgan failure accompanied by vaso-occlusion, enhanced coagulation, and impairment of vital functions (Puelles et al., 2020; Wichmann et al., 2020). An additional characteristic of severe COVID-19 is a massive cytokine release syndrome believed to be triggered by SARS-CoV-2-induced cytokine production by macrophages and dendritic cells that further contributes to pathogenesis (Hirano and Murakami, 2020; Mangalmurti and Hunter, 2020; Merad and Martin, 2020; Moore and June, 2020). In the following, we will address the different stages of SARS-CoV-2 pathogenesis, including viral entry and sensing, induction of antiviral immune responses and inflammation, and immune-mediated tissue repair, in the context of critical differences in immune responses that exist between the sexes and contribute to the male bias in development of severe COVID-19.

Sex Differences in SARS-CoV-2 Entry

ACE2 has been described as the principal receptor enabling SARS-CoV-2 to enter human cells through binding of the spike (S) glycoprotein (Figure 1) (Hoffmann et al., 2020; Zhou et al., 2020a), and blocking these interactions using antibodies against ACE2 or soluble human ACE2 can prevent infection of human cells (Monteil et al., 2020; Wrapp et al., 2020). Differences in expression of ACE2 in the nasal epithelium of small children and adults have been linked to a reduced risk of children to present with severe COVID-19 (Bunyavanich et al., 2020), suggesting that lower ACE2 expression levels might be protective. ACE2 is encoded by the X chromosome, but studies have demonstrated that ACE2 expression is lower in lung tissues of women compared to men (Tukiainen et al., 2017), and it has been suggested that estrogen downregulates the expression of ACE2 (Liu et al., 2010). Furthermore, circulating plasma concentrations of ACE2 are higher in men with heart failure than in women (Sama et al., 2020) and in sputum cells of men compared to women (Peters et al., 2020). These data suggest that differences in ACE2 levels between women and men can translate into differences in the development of severe COVID-19, emphasizing the clinical promise of interventions that reduce binding of SARS-CoV-2 to ACE2, including antibodies directed against the ACE2-binding site. More efficient entry of SARS-CoV-2 into cells from men might be furthermore facilitated by higher expression of the mucosa-specific serine protease TMPRSS2 that promotes virus entry into human host cells (Hoffmann et al., 2020; Zang et al., 2020). TMPRSS2 expression has been suggested to be enhanced by androgens (Stopsack et al., 2020; Wambier and Goren, 2020; Wambier et al., 2020); and enhanced expression in male sputum cells has been described (Peters et al., 2020). Furthermore, androgen-deprivation therapies for prostate

Table 1. Differential Role of ACE2 in Early and Late Stages of COVID-19

	ACE2 Function	Female Sex Bias	Implication
Initial SARS-CoV-2 infection	SARS-CoV-2 entry receptor	lower baseline ACE2 expression	lower infectious burden; limited spreading to lower respiratory tract
COVID-19 pneumonia	reduction of inflammation; enhanced airway ventilation	higher ACE2 induction as ISG	reduction of cytokine storm; prevention of ARDS

cancer have been suggested to partially protect patients from SARS-CoV-2 infection in a population-based study from Italy (Montopoli et al., 2020), although data on TMPRSS2 expression were not included in that study. These data suggest that sex differences in the expression of molecules involved in SARS-CoV-2 entry might facilitate the spread of SARS-CoV-2 in men. However, the role of ACE2 in SARS-CoV-2 infection is likely more complex (Table 1). While being highjacked by SARS-CoV-2 as an entry receptor, ACE2 has important anti-inflammatory properties by catalyzing angiotensin II, resulting in the production of Angiotensin 1-7 (Ang 1-7), which can ameliorate ARDS (Oudit and Pfeffer, 2020). ACE2 mRNA expression is upregulated by type I IFNs, and ACE2 has been suggested to serve as an interferon (IFN)-stimulated gene (ISG) during respiratory infections that promotes lung airway function (Ziegler et al., 2020). Future studies are needed to determine whether ACE2 expression in lung tissues differs between women and men during SARS-CoV-2 infection and whether potentially higher ACE2 expression in infected women, resulting from a stronger ISG response (Chang et al., 2013; Meier et al., 2009; Ziegler et al., 2020), might translate into beneficial anti-inflammatory effects mediated through Ang 1-7 in COVID19. Sex differences in ACE2 expression might therefore have different effects between the sexes at different stages of SARS-CoV-2 infection (Table 1). While lower estrogen-mediated baseline expression of ACE2 might reduce spreading of SARS-CoV-2 beyond the initial infection of the upper respiratory tract, higher IFN-induced ACE2 expression in women during progressive SARS-CoV-2 infection of the lower respiratory tract might protect from ARDS. The potential beneficial effect of clinical interventions currently tested in patients with severe COVID-19, such as the administration of estrogens to men or the addition of IFN-β to antiviral interventions, will therefore critically depend on the stage of the disease and also might result in different effects between the sexes that need to be considered in the design of these studies, including sample size calculations.

Sex Differences in Immune Responses against SARS-CoV-2

In general, women develop stronger innate and adaptive immune responses against most viral infections and vaccines (Flanagan et al., 2017; Klein and Flanagan, 2016), and significant sex differences in the induction of type I IFN responses, B cell functions, and T cell functions have been described. Type I IFN responses that are critical for not only restriction of viral replication but also induction of antiviral immune responses are differentially regulated between men and women (Figure 1) (Ziegler and Altfeld, 2017). Infections by RNA viruses, such as SARS-CoV-2, are sensed by Toll-like receptors (TLRs), including TLR7, resulting in the induction of IFN-β and IFN-α production by plasmacytoid dendritic cells (pDCs) (Heil et al., 2004). TLR7 is encoded by the X chromosome, and studies have shown that the gene encoding for TLR7 can escape inactivation of the second X chromosome in women, resulting in higher TLR7 expression in immune cells of women compared to men (Souyris et al., 2018). Several studies have demonstrated that pDCs from women produce more IFN-α/β in response to TLR7 ligands, including viral RNAs, resulting in higher induction of ISGs in women (Berghöfer et al., 2006; Chang et al., 2013; Meier et al., 2009; Seillet et al., 2012). Both X chromosomal factors and sex hormones have been implicated in these sex differences in type I IFN responses (Griesbeck et al., 2015; Laffont et al., 2014; Scheuplein et al., 2015; Seillet et al., 2012). Coronaviruses, including MERS-CoV and SARS-CoV, can induce type I IFN responses through TLR7 (Karnam et al., 2012; Li et al., 2013, 2016; Scheuplein et al., 2015), and SARS-CoV and SARS-CoV-2 have been shown to be sensitive to viral restriction by ISGs *in vivo* and *in vitro* (Haagmans et al., 2004; Mantlo et al., 2020). The first studies assessing type I IFN responses induced by SARS-CoV-2 infections suggest induction of ISGs by SARS-CoV-2 (Blanco-Melo et al., 2020; Chu et al., 2020; Zhou et al., 2020b), but to a lower level than observed in SARS-CoV infection (Blanco-Melo et al., 2020; Chu et al., 2020), indicating a potential immune evasion mechanism. Remarkably, the presence of genetic loss-of-function variants of TLR7 was observed in four men with severe COVID-19 (van der Made et al., 2020), further highlighting the critical role of TLR7 and type I IFNs in SARS-CoV-2 pathogenesis. These studies have provided rationale for the treatment of COVID-19 patients with IFNs (O'Brien et al., 2020; Park and Iwasaki, 2020; Sallard et al., 2020). Results from a retrospective study suggest that therapeutic interventions using IFN-α early in SARS-CoV-2 infection can reduce mortality, while IFN-α administration during late-stage severe COVID-19 was associated with increased mortality (Wang et al., 2020). However, significantly fewer women were included in the groups of patients receiving IFN-α (Wang et al., 2020), representing a potential bias in the interpretation of the clinical outcomes. Some studies have furthermore reported that SARS-CoV-2 might be detected in nasal swabs for longer periods in men compared to women (Xu et al., 2020; Zheng et al., 2020), suggesting a reduced ability to restrict viral replication and enhanced risk for transmitting the virus in men. Enhancing type I IFN-mediated restriction of viral replication, for example by subcutaneous administration of IFN-β, might therefore represent an early intervention with particular benefit for men that needs to be evaluated in randomized controlled clinical studies that take the sex differences in type I IFN responses into account.

Sex Differences in Antibody Responses against SARS-CoV-2

The development of antibodies against SARS-CoV-2, including neutralizing antibodies, has been shown in SARS-CoV-2-infected persons and rhesus macaques (Chandrashekar et al., 2020; Kreer et al., 2020; Ni et al., 2020; Robbiani et al., 2020; Rogers et al., 2020; Wolfel et al., 2020; Zhao et al., 2020).

SARS-CoV-2-specific and SARS-CoV-specific antibodies (Ni et al., 2020; Pinto et al., 2020) can block infection and prevent disease manifestations in rhesus macaques (Chandrashekar et al., 2020; Yu et al., 2020), and rhesus macaques receiving experimental vaccines that induce antibodies against SARS-CoV-2 infection are protected from disease (Mercado et al., 2020). Furthermore, potential clinical benefits in COVID-19 patients receiving adoptive transfer of antibodies from convalescent plasma of SARS-CoV-2-infected individuals have been described (Shen et al., 2020a), indicating that antibodies against SARS-CoV-2 might provide a clinical benefit in severe COVID-19 and prevent infection in vaccinated individuals (Figure 1). Multiple studies have demonstrated that women develop more rapid and stronger antibody responses to infections and vaccinations and have implicated sex hormones and X chromosomal factors into these sex differences in antibody responses against influenza virus (Flanagan et al., 2017; Klein and Flanagan, 2016). Studies in mice have demonstrated that estrogens promote and testosterone can suppress the development of antibodies (Fink et al., 2018; Flanagan et al., 2017; Klein and Flanagan, 2016), and studies in humans described lower immune responses to influenza vaccination in men than in women, particularly in men with high levels of testosterone at the time of vaccination (Furman et al., 2014). The results from these studies demonstrate an important role of sex hormones in mediating sex differences in antibody responses. More recent studies have however also implicated X chromosomal factors, including higher expression of TLR7 in B cells from females due to escape from X chromosome inactivation (XCI) that resulted in the enhanced propensity to immunoglobulin G (IgG) class switch in females (Souyris et al., 2018). Other genes located on the X chromosome encoding for proteins that play an important role in the regulation of antibody responses, including CD40L and BTK, can also escape XCI (Tukiainen et al., 2017) and might contribute to better induction and maintenance of antibody responses in women. This is further supported by studies demonstrating sex differences in T follicular helper (Tfh) cells that support B cell maturation, including higher interleukin-21 (IL-21) and IL-27 expression in females (Dimitrijević et al., 2020), and an increase in circulating Tfh cells at the time of induction of plasma cells was recently described in a case study of a woman with nonsevere COVID-19 (Thevarajan et al., 2020). Finally, the ability to induce or maintain antibody responses further decreases with age, in particular in men (Márquez et al., 2020). These data strongly suggest that women have an immunological advantage in developing antibody responses against SARS-CoV-2. These sex differences might translate into clinical benefits for women, as early antibody signatures have been associated with COVID-19 outcome (Atyeo et al., 2020; Shen et al., 2020b), suggesting that they can curb the initial infection and prevent further spreading of the virus. This female bias has to be considered when clinical studies aimed at inducing SARS-CoV-2-specific antibodies by vaccination are designed, both in the evaluation of potential adverse events as well as immunological and clinical endpoints (Flanagan et al., 2017). Given the described relatively short persistence of antibodies directed against SARS-CoV (Cao et al., 2007; Liu et al., 2006) and a significantly more rapid decline of these antibody titers in men (Liu et al., 2006), differences between women and men need to be in particular accounted for in studies investigating the persistence of antibody responses directed against SARS-CoV-2 and their ability to prevent infection or reinfection.

Sex Differences in T Cell Responses against SARS-CoV-2

T cells play a critical role in viral infections, with $CD4^+$ T cells providing help to B cells for antibody production and $CD8^+$ T cells mediating direct antiviral activity by killing infected cells. Furthermore, T helper 17 (Th17) and Th22 $CD4^+$ T cells support tissue regeneration (discussed below), and $CD4^+$ regulatory T (Treg) cells can reduce dysregulated immune activation that contributes to immunopathology. Sex differences in T cell phenotypes and functions have been reported, including an expansion of Treg cells through estrogen (Polanczyk et al., 2004; Tai et al., 2008). Furthermore, the gene encoding for FoxP3, the transcription factor that determines Treg cell differentiation, is expressed on the X chromosome, as is the gene encoding for CD40L that is involved in $CD4^+$ T-cell-mediated help for B cells (Tukiainen et al., 2017). The enhanced ability of T cells from women to reduce excessive immune activation and promote B cell differentiation might therefore contribute to the less frequent development of severe COVID-19 in women (Figure 1). However, recent studies have shown that males have higher Treg numbers than females (Vasanthakumar et al., 2020), and additional studies assessing the implication of Treg cells in SARS-CoV-2 pathogenesis are required. Furthermore, data regarding the role of T cells in SARS-CoV-2 pathogenesis are very limited. $CD4^+$ and $CD8^+$ T cell populations tend to be activated and reduced in the peripheral blood of patients with COVID-19 (Chen et al., 2020; Kuri-Cervantes et al., 2020; Mathew et al., 2020; Qin et al., 2020), potentially due to recruitment into affected tissues, and the degree of T cell reduction has been associated with the severity of COVID-19 (Chen et al., 2020; Kuri-Cervantes et al., 2020; Mathew et al., 2020; Qin et al., 2020). In addition, a reduction in Treg cells has been described in severe COVID-19 cases (Chen et al., 2020; Qin et al., 2020). SARS-CoV-2-specific $CD4^+$ and $CD8^+$ T cells have been detected in COVID-19 patients (Grifoni et al., 2020; Le Bert et al., 2020; Weiskopf et al., 2020), but little is known regarding their antiviral activity, and no data on differences between women and men have been included in these first reports. Furthermore, neither $CD4^+$ nor $CD8^+$ T cell responses directed against SARS-CoV-2 showed a correlation with protection from disease in vaccinated or re-convalescent rhesus macaques (Chandrashekar et al., 2020; Yu et al., 2020). The sparsity of data emphasizes the need for additional studies to determine the role of T-cell-mediated immunity in SARS-CoV-2 infection, and such studies need to take differences in T cell responses between the sexes into account and report data in the context of the sex of the study subjects.

Sex Differences in the Immune-Mediated "Weep and Sweep" Response of Airway Epithelium

In addition to their direct antiviral activities, cells of the immune system can also shape local host defense mechanisms exerted by epithelial cells (Vivier et al., 2018). Key to the prevention of severe COVID-19 is the containment of SARS-CoV-2 to the upper respiratory tract. Mucosal tissues employ the so-called weep and sweep response to contain and remove pathogens (Gause et al., 2020). Respiratory epithelial cells can secrete fluid that

contains antimicrobial products and sweep infected cells or pathogens caught in the mucus up to the oral cavity, where it can be removed. This weep and sweep response is enhanced by cytokines such as IL-4, IL-5, and IL-13, which are secreted by $CD4^+$ Th2 cells and type 2 innate lymphocytes (ILC2s), referred to as type 2 immunity (Gause et al., 2020) (Figure 1). Although reduced levels of IL-13 have been detected in COVID-19 patients compared to healthy controls, other studies suggest IL-13 to be increased in severe COVID-19 (Lucas et al., 2020; Schultheiss et al., 2020). Type 2 immunity is more pronounced in women (Laffont et al., 2017a), who also suffer more frequently from diseases linked to dysregulated type 2 immunity, including allergies and asthma (Holgate et al., 2015). An analyses of multiple studies showed an overall low prevalence of preexisting respiratory diseases in COVID-19 patients (de Lusignan et al., 2020; Guan et al., 2020; Lupia et al., 2020), which is in line with reports from previous coronavirus epidemics (Moni and Liò, 2014). However, in a recent study, patients with severe COVID-19 had suffered from a recent asthma exacerbation requiring treatment, suggesting that preexisting respiratory illnesses can predispose to severe COVID-19 (Bhatraju et al., 2020). Upon damage signals, cytokines secreted by Th2 and ILC2s promote epithelial cell turnover in general and in particular that of secretory cells such as goblet cells (Gause et al., 2020), which are increased in the female respiratory tract and patients with asthma (Hayashi and Huber, 1977; Kuperman et al., 2005). Sex hormones can impact ILC2 numbers, as androgens reduce ILC2 numbers and cytokine production in male mice (Laffont et al., 2017b; Ricardo-Gonzalez et al., 2018). In addition, the receptor for IL-13 (IL-13RA1) is encoded by the X chromosome, providing women a gene-dosage advantage upon escape from XCI (Tukiainen et al., 2017), potentially resulting in enhanced IL-13 signaling in epithelial cells (Figure 1). A recent study showed that IL-13 decreased the expression of ACE2 in epithelial cells *in vitro*, and respiratory epithelial cells of asthma patients with enhanced type 2 signaling exhibited reduced ACE2 expression compared to healthy controls (Peters et al., 2020). Together, these data provide potential mechanisms by which sex differences in ILC2s and Th2 cells and the IL-13-IL-13R axis mediate a stronger airway weep and sweep response in women that can impact early stages of SARS-CoV-2 infection.

Sex Differences in Immune Pathways Mediating Tissue Repair with Implications for COVID-19

Immune cells furthermore have a critical role beyond host defense in regulating tissue regeneration (Karin and Clevers, 2016; Vivier et al., 2018), ranging from ILCs, Th17 cells, and Th22 cells maintaining mucosal integrity (Chung et al., 2012) to natural killer (NK) cells and macrophages shaping the architecture of the placenta (Vento-Tormo et al., 2018). Frequencies of IL-22- and IL-17-producing $ROR\gamma t^+$ $CD4^+$ T cells are enhanced in women compared to men and have been shown to be regulated by sex hormones (Fuseini et al., 2018, 2019; Newcomb et al., 2015; Sankaran-Walters et al., 2013). IL-22 promotes epithelial stem cell proliferation via STAT3 signaling (Lindemans et al., 2015), contributing to tissue resilience upon damage. Protective effects of IL-22 have also been demonstrated in several viral infections, including influenza, where IL-22 reduces inflammation, protects against bacterial superinfections, and promotes lung epithelial repair (Pociask et al., 2013). Amphiregulin produced by ILC2s is a member of the epidermal growth factor family and promotes tissue repair (Figure 1), resulting in improved barrier integrity and lung function in influenza-infected mice (Monticelli et al., 2011). Amphiregulin is also produced by Treg cells and, together with IL-10 and transforming growth factor β, allows Treg cells to promote tissue repair (Forbes and Rosenthal, 2014; Zaiss et al., 2006) Treg cells have been described to ameliorate severe complications in influenza infection in mice (Egarnes and Gosselin, 2018; Moser et al., 2014; Oliphant et al., 2015). These data suggest that immune cell profiles in women are skewed toward tissue repair responses compared to men (Figure 1), potentially contributing to reduced COVID-19-associated morbidity. However, amphiregulin is also produced by epithelial cells and expressed at higher levels in male mice in an animal model with enhanced morbidity in influenza-infected female mice (Vermillion et al., 2018). Furthermore, cell-intrinsic non-immune-mediated tissue regeneration has been described to be better in men (Grishina et al., 2014; Joseph and Dyson, 1965; Kadel and Kovats, 2018), indicating that sex-biased tissue repair pathways both in epithelial and immune cells can contribute to the different outcomes of respiratory infections between the sexes and need to be included in models assessing SARS-CoV-2 pathogenesis.

The dual role of immune cells in host defense and tissue repair have shaped dimorphic immune responses between the sexes to maximize reproductive success in females, providing women with a superior capacity for immune-mediated tissue repair. An enhanced utilization of these immune-mediated tissue repair pathways might therefore provide women with better resilience upon SARS-CoV-2 infection and protection from development of severe COVID-19. These observations provide a rationale to test interventions that promote tissue resilience in clinical studies. Treatment strategies are available to antagonize androgen-mediated effects, which can promote protective ILC2 and Th22 cell responses when initiated early during SARS-CoV-2 infection. Recombinant amphiregulin has shown beneficial effects in influenza-infected mice, and IL-13 has been proposed as a therapeutic intervention to reduce inflammation and promote tissue repair in preclinical models of stroke (Kolosowska et al., 2019). However, given the pro-inflammatory role of cytokines in immune-mediated diseases such as Crohn's disease and rheumatoid arthritis, as well as enhanced levels detected in COVID-19 patients (Lucas et al., 2020; Mateen et al., 2019; Shah et al., 2018), the timing of initiation of immune-therapies in SARS-CoV-2 infection will be critical to promote viral containment and tissue resilience without contributing to the cytokine release syndrome in the advanced stages of COVID-19.

Conclusions

The female immune system has evolved to optimize antiviral immune responses protecting the unborn or newborn infant and enable cyclic promotion of tissue development and regeneration required for reproduction. This has resulted in differences in immune functions between women and men, which are manifested by not only stronger immune responses in women against pathogens and vaccines but also higher susceptibility to autoimmune diseases. The emerging understanding of the mechanisms underlying these sex differences in immune

functions provides important insights into protective as well as disease-promoting pathways during SARS-CoV-2 infection, which can be targeted therapeutically. Interventions aimed at enhancing antiviral mechanisms, reducing excessive inflammation, and promoting tissue-protective immune functions during COVID-19 have to take these sex-specific differences into account to optimize treatment outcomes for women and men. Furthermore, sex has to be taken into account as a critical variable in the analysis of immunological and clinical data from COVID-19 patients to better understand the biology of the disease.

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