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Progesterone and Autoimmune Disease

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Abstract

Sexual dimorphism in human immune systems is most apparent in the female predominance of certain autoimmune diseases (ADs) like systemic lupus erythematosus (SLE). Epidemiologic, observational and experimental evidence strongly suggest sex steroids are important modulators of genetic risk in human AD. In this regard, the roles of progesterone (Pg), an immunomodulatory female sex steroid, are poorly understood. Several lines of investigation indicate Pg and synthetic progestins impact risk of AD and immune-mediated injury in different ways depending on their concentrations and their engagement of various Pg receptors expressed in immune organs, immune cells or tissues targeted by immune attack. At low physiologic levels, Pg may enhance interferon-alpha (IFN- α) pathways important in SLE pathogenesis. Commonly used synthetic progestins may have the opposite effect. At pregnancy levels, Pg may suppress disease activity in rheumatoid arthritis (RA) and multiple sclerosis (MS) via inhibition of T helper type 1 (Th1) and Th17 pathways and induction of anti-inflammatory molecules. Importantly, Pg's immunomodulatory effects differ from those of estrogens and androgens. An additional layer of complexity arises from apparent interdependence of sex hormone signaling pathways. Identifying mechanisms by which Pg and other sex steroids modulate risk of AD and immune-mediated injury will require clarification of their cellular and molecular targets in vivo. These future studies should be informed by recent genetic discoveries in human AD, particularly those revealing their sex-specific genetic associations.

Keywords

progesterone; autoimmunity; sex hormones; sex steroids; systemic lupus erythematosus; SLE

1. Introduction

At roughly the same time 500 million years ago, two major adaptations arose in primitive vertebrates: the adaptive immune system and highly specific steroid hormone receptors [1, 2]. The subsequent development of placental reproduction posed immunological “problems” for the adaptive immune system, as Sir Peter Medawar, pioneer in transplantation immunology, put it in 1953 [3]. He posited that the fetus might avoid attack from its mother's immune system by means of physical barriers, immunological inertness and

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suppression of maternal immune responses. As Medawar himself suspected [3], physical separation of maternal and fetal circulations is critical, but so too are certain adaptations of the mother's immune system. Accordingly, the human immune system bears evidence of sexual selection. This is most obvious in the female predominance of certain autoimmune diseases (ADs) (Fig. 1), and to a lesser extent, sexual dimorphism in responses to infections. Several theories attempt to explain the female predominance of ADs: immunomodulatory effects of sex hormones; sex-dependent genetic factors; microchimerism; and gender-related factors [4]. The importance of sex hormones, particularly the sex steroids, in human AD is supported by considerable observational and experimental evidence. In this regard, much attention has been given to estrogen (Es) and androgens, important determinants of sexual dimorphism, but far less has been given to progesterone (Pg), the hormone of pregnancy. Long known for its immunoregulatory properties, Pg's impacts on human AD are not well understood. This review article will summarize what is known about Pg and AD.

First, I will outline observations supporting a role for female sex steroids in AD, correlating them with recent genetic discoveries. Next, I will briefly discuss the molecular actions of Pg, followed by a more detailed description of how Pg impacts functions of select components of the immune system. With this framework in place, I will discuss what is known about Pg, individual ADs and their animal models.

2. Progesterone and mammalian biology

Pg is a cholesterol-derived hormone critical to pregnancy [5]. Indeed, the name ultimately derives from the prefix *pro* and the Latin *gest re* to carry. Through a variety of mechanisms, Pg is required for normal function at multiple stages of mammalian reproduction: oocyte maturation, differentiation of the endometrium, implantation of the embryo, growth of the placenta, quiescence of uterine muscle during fetal development and differentiation of mammary gland tissues. Pg also contributes to some of the changes in maternal physiology and metabolism during normal pregnancy. [5] More recently it has been appreciated that Pg actions in the brain also regulate reproductive behaviors and reparative responses to central nervous system (CNS) injury [6, 7]. As will be discussed in section 5, fluctuations in endogenous Pg during the ovulatory cycle and pregnancy are associated with reversible changes in a woman's immune system. How these changes contribute to successful pregnancy or risk of AD is not well understood.

3. Sex steroids and the risk of AD

3.1. Sexual dimorphism in human AD

The female predominance of AD remains unexplained, but several non-competing hypotheses have been proposed. The first idea is that female sex hormones modulate the immune system to increase risk of AD in genetically susceptible individuals; the converse is that male sex steroids are protective. While this may be the most intuitive explanation, it is not the only one. X-linked immune genes, particularly if they escape inactivation or are duplicated [8], could play a major role in female predominance of AD, though convincing evidence that this is a *common* factor in female-predominant forms of AD is currently lacking. Microchimerism, the persistence of allogeneic cells acquired by the mother or the fetus during pregnancy, may contribute to loss of tolerance in certain female-predominant ADs, like systemic sclerosis (scleroderma) (SSc) [9]. Gender -- those behavioral, cultural or psychological factors tightly linked to one's sex -- likely play a role in some ADs, especially those where exposure to exogenous triggers or protective factors are determined by gender-related behavior. For example, female predominance of multiple sclerosis (MS) may in part reflect gender differences in protective exposure to sunlight [10]. Finally, given an increasing appreciation that microbial environments influence adaptive immunity and

autoimmunity [11], it may be that factors unique to vaginal microbial environments contribute to female-predominance of certain ADs – a possibility that remains largely unexplored. These various hypotheses are well summarized by McCombe, Greer and Mackay [4]. The following section will highlight evidence supporting a major role for female sex hormones in AD, particularly that for Pg and Es.

3.2. Sex hormones and risk of human AD

AD can strike both children and adults. Most often, pediatric AD is defined as having onset before age 16 – 18. This is not necessarily a biological cutoff, because puberty onset is around age 10, at least in the U.S. [12], and for diseases like rheumatoid arthritis (RA), SLE and SS, the distribution of age of onset is uni-modal, not bimodal [13, 14]. This artificial segregation of pediatric and adult AD has tended to obscure an important relationship between sex hormones and the incidence of AD: i.e., that extreme female predominance occurs mainly *after* puberty. In SLE, for example, the overall female:male ratio is close to 9:1 (Fig. 1), but in pre-pubertal SLE, the ratio is around 3–4:1 [15, 16]; and in SLE patients presenting under the age of 5, it is essentially 1:1 [17]. A strikingly similar pattern is seen in autoimmune thyroid disease (AITD) [18], another female predominant group of ADs (Fig. 1, Hashimoto's thyroiditis and Grave's disease). Pediatric Sjögren syndrome (SS) appears to be quite rare [19], so analyses of sex ratios in pre-pubertal vs. pubertal/post-pubertal onset cases are not readily available. Pediatric onset primary biliary cirrhosis (PBC) is exceedingly rare [20], and pre-pubertal cases have apparently not been reported. Interestingly, in atopic disease and asthma, the male predominance in pre-pubertal disease is reversed after puberty [21], suggesting that sex hormones can modulate incidence other forms of immune-mediated disease. Finally, the sole AD in Fig. 1 with mean age of onset before puberty, type 1 diabetes mellitus (T1D), shows no female predominance. Overall, these observations indicate female reproductive factors such as sex steroids are important determinants of risk for female-predominant ADs. This hypothesis is supported by considerable evidence in human and animal studies, discussed in sections 5 and 6. This body of literature was recently reviewed by González et al. [22] and Martocchia et al. [23]

3.3. Sex hormones and genetic risk of AD

In general, human ADs demonstrate polygenic patterns of inheritance. A prevailing model holds that a person's overall risk for any given AD reflects the sum of genetic, environmental and stochastic factors. Environmental factors could include both endogenous triggers (e.g., endogenous sex hormones, endogenous retroviruses) and external exposures (e.g., toxins, UV light, exogenous hormones, infections). Over the last several years, genome wide association studies (GWAS) have identified numerous genetic variants associated with risk of individual ADs. These variants are common (>10% prevalence) and tend to confer low risk (e.g., odds ratios [ORs] 1.1 – 2.0). Candidate gene studies have identified rarer (< 1% prevalence) genetic variants, particularly loss-of-function mutations and gene copy number variants, associated with much higher ORs. [24–26] An individual's genetic risk burden for any given AD varies widely. Theoretically, someone with extremely high genetic risk burden might develop AD early in life, because fewer environmental or stochastic triggers are needed to reach critical risk burden, above which development of AD is essentially guaranteed. In this setting, sex steroids and other environmental triggers are unnecessary. Conversely, a person with relatively low genetic risk burden may present later in life, only after accrual of sufficient triggers (here, hormones) and stochastic events, if at all. Again, SLE provides a good example. The strongest known genetic risk factor for SLE is complete deficiency in the complement factor C1q [24]. Over 90% of individuals with this rare homozygous mutation will develop SLE [27]. The age of onset in C1q-deficient children is frequently before age 5 [27], and the female:male ratio is close to 1 [28] – consistent with the idea that extreme genetic risk obviates the need for additional stochastic

or hormonal factors. These and other observations have prompted the hypothesis that some very early onset ADs are largely genetic diseases [29]. What about adult-onset SLE in males? If female sex hormones are important environmental risk factors, and male sex hormones like testosterone (T) are protective (see section 6), this model would predict that in order to develop SLE, men would require a higher genetic burden than women. An initial report [30] from a large adult-onset SLE cohort indicates this is likely the case – men had significantly higher frequency of SLE risk loci than women. It is reasonable to hypothesize that similar studies comparing pediatric-onset SLE to adult-onset SLE would reveal higher genetic risk burden in pediatric-onset disease.

Can recent genetic advances inform our understanding of the female bias of certain ADs and how sex steroids might be involved? We already know that the most female-predominant ADs share certain phenotypes. At least 5 of the top 6 ADs shown in Fig. 1 are strongly associated with anti-nuclear Abs (ANA): SS, SLE, Hashimoto's thyroiditis (HT), PBC, Grave's disease (GD), and SSc [31]. This suggests that sex steroids impact tolerance to ubiquitous antigens (Ags) such as those contained in dead and dying cells. Another aspect that links several of them (SS, HT, PBC, SSc) is evidence for the pathogenic involvement of the anti-viral cytokine interferon-alpha (IFN- α), whose production and signaling appears to be under hormonal regulation (section 5.4.7). Consistent with this idea, genetic variation of the *IRF5* gene, whose protein product is integral to IFN- α production [32], is reported in several GWAS studies to be associated with risk of SLE, PBC, SSc and RA, but not any of other ADs for which there are published GWAS data [33], except ulcerative colitis (UC) [32, 33] (Fig. 1). A similar if not more compelling association can be made between the *STAT4* gene and the most female-predominant ADs. *STAT4* is an IFN- α -inducible intracellular signaling molecule important for Th1- and Th17-related responses, and cell-mediated immunity [34]. In published GWAS studies, *STAT4* is reported to be associated with risk of SLE, PBC, SSc and RA, but none of the other ADs (Fig. 1) [33]. That a genetic association of *both* *IRF5* and *STAT4* is reported only among the most female predominant diseases suggests IFN- α and Th1/Th17 pathways could be important nodes where hormonal action and genetic risk interact. If true, then *IRF5* and *STAT4* may eventually prove to be risk genes for AITD and SS, but not other ADs lacking strong female predominance, like pemphigoid or ITP. Indeed, candidate genes studies link variations in both *IRF5* and *STAT4* to risk of SS [8]. Another prediction is that risk variants should result in changes in gene function concordant or synergistic with effects of female sex hormones, or antagonistic with those of androgens. Finally, differences in any gene's risk association in male vs. female adult-onset AD could reflect pathways where male vs. female sex hormones enhance or counteract genetic risk. For example, in genetic risk studies comparing male and female SLE, risk alleles in three IFN- α pathways genes, *TLR7* [35], *IRF5* [30] and *SPP1* [36], show significantly *higher* ORs in men vs. women. One explanation for the enrichment of these variants in male SLE is that in order for a man to develop SLE, more dysregulation of the IFN- α pathway is needed to overcome the protective effects of androgens, or to compensate for lack augmentation conferred by female sex steroids. Clearly this is an oversimplification, but it illustrates one way sex-specific genetic analysis might be used to inform future investigation into the hormonal basis of sex bias in human AD. More sex-specific genetic risk analyses need to be performed in human ADs.

3.4. Effects of sex steroids on risk of autoimmunity vs. immune-mediated injury

It is essential to appreciate that the biological processes leading to autoimmunity, i.e., generation of auto-reactive lymphocytes, are not necessarily the same as those mediating immune injury and organ damage. Autoimmunity does not necessarily mean autoimmune *disease*. For example, disease-specific anti-thyroid Abs, e.g., anti-thyroperoxidase Abs [37], are frequently found in people without clinically evident thyroid dysfunction. Strikingly,

RA- and SLE-specific autoAbs appear in the blood years before diagnosis [38, 39]. Moreover, results from GWAS studies in SLE [40] and genetic analysis of lupus-prone mice [41] together demonstrate that loci associated with development of autoimmunity are *different* from those associated with kidney damage. Therefore, the effects of sex steroids on risk of AD may be different than effects on immune-mediated injury (i.e., disease activity). RA is a useful example in this regard. The strong female predominance of RA (Fig. 1) suggests female sex steroids may enhance risk of disease in genetically predisposed individuals. Yet RA often remits during pregnancy [42], when Es and Pg are extremely elevated systemically [5]. The same is not true, however, for all female-predominant ADs, as will be discussed in section 6. Thus, when talking about the impact of female sex steroids on AD, it is essential to distinguish effects on risk from those on immune-mediated injury.

4. Progesterone – Mechanisms of Action

Steroid hormones exert their influence on physiological processes via direct effects on cellular functions. Sex steroids are synthesized primarily in the gonads, adrenal glands and, during pregnancy, the placenta. They are delivered via the bloodstream, largely protein-bound, to target tissues. Steroid hormones signal via highly specific receptors found in the plasma membrane, cytosol and nucleus of cells. [5]

Pg utilizes both cell surface and intracellular receptors. Best characterized are intracellular Pg receptors (iPRs). iPRs are ligand-sensitive transcription factors of the nuclear receptor superfamily most closely related to glucocorticoid receptors (GRs) and mineralocorticoid receptors [1]. The expression, functions and regulation of iPRs in female reproductive tissues (and their related cancers) are well characterized and underlie the use of synthetic progestins and anti-progestins in modern gynecology and obstetrics. Nevertheless, it remains controversial whether steroid hormones enter target cells via passive diffusion or active transport. Within the last decade, a group of membrane-associated molecules was found to act as highly specific Pg receptors [43]. Structurally unrelated to iPRs, these membrane Pg receptors (mPRs: mPR- α , mPR- β , mPR- γ) are linked to inhibitory G-coupled proteins, potentially explaining some of Pg's rapid non-transcriptional actions [44]. The functions of mPRs in reproductive and non-reproductive tissues are just now being uncovered [45]. A putative membrane-associated Pg receptor, Pg receptor membrane component 1 (PGRMC1), binds Pg but also to many other molecules. PGRMC1's functions are largely unknown. [44] Pg has also been shown to alter cellular functions through specific interactions with plasma membrane ion channel proteins.

Pg binds iPRs and mPRs with half-maximal inhibitory concentrations around 7 nM and 90 nM, respectively [43, 44]. In addition, Pg at high-physiologic and pharmacologic concentrations (> 200 nM) binds GRs [46], which are highly expressed in most immune cell types [47]. Synthetic progestins show unique patterns of Pg receptor usage. For example, medroxyprogesterone acetate (MPA), one of the commonest forms of hormonal birth control world-wide [48, 49], is both an iPR and GR agonist [50]; its binding to mPRs has not yet been characterized. Mifepristone (RU-486), a widely used abortifacient and emergency contraceptive, is an iPR and GR antagonist [51] but does not bind mPRs with significant affinity [44]. Conversely, several synthetic molecules can bind with high affinity to mPRs but not to iPRs [43, 44]. For iPR signaling, an additional layer of complexity arises from the fact that iPR's transcriptional activity varies depending on the ligand activating it. Thus, the immunomodulatory effects of various progestins depend on their concentration and their receptor usage.

What are the patterns of Pg receptor expression in tissues of the immune system? This question has not been addressed in a systematic fashion, and thus we must rely on a

collection of studies employing disparate methods. Still, some important patterns emerge. The expression of various Pg receptors in some immune cell subsets (Table 1) strongly supports the idea that progestins can act *directly* on immune cells to modulate their functions. iPR expression in human immune cells appears to be restricted to certain subsets like peripheral natural killer (NK) cells and tissue macrophages [52]. We and others have failed to detect either iPR protein or *PGR* mRNA in human total peripheral blood mononuclear cells (PBMCs), CD4⁺ T cells, CD8⁺ T cells, or plasmacytoid dendritic cells (pDCs) [52, 53] (and unpublished results). The expression and functions of mPRs in immune cells remains largely unexplored. Nor is it known, as it is for reproductive tissues, if expression of these receptors in immune tissues is regulated by sex steroids. Answers to these basic questions are currently lacking but are essential for full understanding of Pg's immunomodulatory actions during physiologic states when both Pg and Es are elevated, such as pregnancy, ovulatory cycle and treatment with combined oral contraceptive pills (OCs) or hormone replacement therapy (HRT). Finally, it is important to note that Pg may impact human AD by acting directly on tissues of immune attack, e.g. the brain, or indirectly on immune cells via paracrine or endocrine actions of non-hematopoietic tissues bearing Pg receptors, e.g., thymic stromal cells [54].

5. Effects of Progesterone on Immune Functions

Four general lines of evidence together indicate that Pg modulates immune functions in vivo: 1) post-pubertal female predominance of ADs; 2) systemic immunomodulation during times of high circulating Pg (pregnancy, luteal phase of the ovulatory cycle); 3) immunomodulation after Pg treatment; and 4) in vitro experiments showing direct effects on immune cells. In this section, I will discuss these last three lines of evidence, reserving the first for section 6, "Progesterone and Autoimmune Disease."

5.1. Pregnancy-associated changes in the maternal immune system

Successful human pregnancy is associated with marked and reversible changes in maternal immune functions. For comprehensive reviews on this subject, please see Poole and Claman [55] and Munoz-Suano et al. [56]. In the decades since Medawar's famous postulate, it has become clear that the fetus is not immunologically inert; nor is the mother systemically immunosuppressed. Rather, pregnancy is a state of *immunomodulation*: intense at the maternal-fetal interface and more subtle systemically in the mother. Many of these changes are believed to be induced by Pg, in part because maternal serum Pg and estradiol (E2) levels rise 5- to 10-fold throughout gestation then normalize quickly post-partum. In mouse pregnancy, Pg is produced by the ovaries, but in human pregnancy, most of the Pg is synthesized in the placenta; tissue levels can be 10 – 100 times higher than those in the maternal circulation, high enough to engage GRs. [5] In the uterine lining where the (fetal) placenta invades, called the decidua, there is marked suppression of cytotoxicity [56], infiltration by specialized uterine natural killer (NK) cells [57], blockade of fetal antigen (Ag) delivery to maternal lymph nodes (LNs) [58], and accumulation of fetus-specific regulatory T cells (Tregs) [59]. Some of these effects likely involve induction by Pg at the maternal-fetal interface of soluble immunomodulatory molecules like Pg-induced blocking factor (PIBF) [60] and glycodelin A (GdA) [61]. It is important to remember that the fetal and maternal circulations do not intermingle but are kept separate by a highly specialized interface that allows selective exchange of circulating molecules, and in some cases, cells. Nevertheless, several important pathogens like *Toxoplasma*, cytomegalovirus (CMV), *Plasmodium* (malaria), and HIV are able to breach if not exploit this interface to cause serious congenital infection in the fetus [62].

Although pregnancy is not thought to cause general immunosuppression in the mother, certain pathways may be targeted for modulation. Complement (C) protein levels and

activation are increased (though C activation at the maternal-fetal interface is strongly suppressed), and there are increased levels of circulating levels of anti-inflammatory molecules IL-1 receptor antagonist (IL-RA) and soluble TNF- α receptor (TNF-R), along with decreased IL-1 β and TNF- α . Circulating maternal NK cell functions are diminished as is the capacity for T cell proliferation. This is accompanied by decreased numbers of IFN- γ -producing CD4⁺ T cells and alterations in numbers of FoxP3-expression regulatory T cells (Tregs). [55, 56, 63, 64] Small changes have also been reported in serum IgM, IgG, IgE and IgA levels, but more important may be pregnancy-associated functional changes in circulating immunoglobulin (Ig) resulting from altered glycosylation [65]. Strikingly, mammalian pregnancy is associated with transient reduction in cellularity of both the thymus [66] (section 5.4.10) and the bone marrow [67], although an impact on immune functions has yet to be demonstrated. That some of these phenomena can be induced by maternal serum/plasma factors, Pg or E2 (section 5.4) strongly supports the idea that circulating sex steroids modulate systemic maternal immune functions during pregnancy.

5.2. Progesterone birth control and risk of sexually acquired HIV

The use of a particular injection Pg birth control, depot medroxyprogesterone acetate (DMPA), appears to significantly increase a woman's risk of sexually acquired HIV-1 infection [48]. This is of major concern because over 50 million women use injection Pg birth control, mainly DMPA [49], increasingly in Sub-Saharan Africa where HIV is pandemic [48]. DMPA may increase risk of HIV infections through altered mucosal defenses, suppression of anti-viral IFN- α , and suppression CD8⁺ T cell functions [48, 68]. Because of selective Pg receptor and GR usage, Pg and MPA may have very different effects on anti-viral immune pathways and AD (see sections 5.4.7, 5.4.9 and 6.1).

5.3. Differential immunomodulation by progesterone and estrogen

It is important to understand that Pg and Es, the chief female sex steroids, do not necessarily modulate immune functions in the same way. In fact, there are many examples where the effects of Pg and Es oppose one another: Uterine inflammation [69], Th1-related autoimmune processes [70], dendritic cell (DC) activation [71] and B cell differentiation [72] are just a few examples. This fact should be born in mind when interpreting immunomodulation during states when both hormones are increased simultaneously, such as the ovulatory cycle, pregnancy and treatment with combined OCPs or HRT. Moreover, the effects of Pg and Es in immune organs and cells may be interdependent, as is the case in reproductive tissues.

5.4. Progesterone effects on immune system components

This section summarizes what is known about the effects of Pg on select components of innate and adaptive immunity, highlighting the most recent discoveries and those pertinent to AD. An overview is provided in Table 1. For a more comprehensive discussion on the subject of female sex steroids and immune functions, see the recent review article by Muñoz-Cruz et al. [73].

5.4.1. Complement—Little is known about the effects of Pg on C functions. Maternal circulating C protein levels [74] and C system activity [75] rise significantly with serum Es and Pg levels during normal human pregnancy, and this effect is mirrored after use of combined HRT in women [76], but the relationship of these phenomena with autoimmune processes of C activation, e.g. SLE and antiphospholipid syndrome (APS), is not clear. Given the likely involvement of C activation in APS [77], however, it is reasonable to speculate that hormonal effects on C activation could synergize with anti-phospholipid antibodies (Abs) to increase the risk of APS-associated thrombotic disease in pregnancy.

(preeclampsia, fetal loss, premature delivery) or after OCP/HRT use. The relationships between pregnancy-related C activation and SLE disease activity remain to be studied.

5.4.2. Neutrophils—Very little is known about the effects of Pg on neutrophil functions. In human neutrophils, Pg can suppress both superoxide release and apoptosis and antagonize enhancement of chemotaxis by Es [73, 78]. These effects could relate to Pg's ability to suppress end-organ damage in models of SLE, MS and RA (section 6). An unexplored area of potential importance is how Pg affects release by neutrophils of extracellular chromatin traps, which, in addition to bactericidal actions, may induce IFN- α in SLE [79] and tissue damage in anti-neutrophil cytoplasmic Ab (ANCA)-associated vasculitis syndromes [80].

5.4.3. Eosinophils, mast cells and basophils—Sex steroid regulation of atopy and asthma is suggested by reversed sex ratio after puberty, exacerbation (and sometimes improvement) of these conditions during pregnancy or use of exogenous Pg [81], and expression of iPRs in mast cells (Table 1). Pg, in combination with Es, enhances human eosinophil degranulation [82], an effect inducible by Pg alone in mouse eosinophils [83]. Pg also appears to induce uterine infiltration by mast cells during pregnancy, at least in mice [84], but whether this is true of mucosal tissues involved in atopy and asthma is not clear. Pg also can enhance Th2-related Ab responses that are associated with generation of IgE in atopy (see section 5.4.8). Accordingly, it will be important to study how Pg impacts functions of basophils, which can present Ag and drive Th2 responses in mice [85].

5.4.4. Natural killer (NK) cells—NK cells are lymphocytes involved in innate anti-viral defense, tumor surveillance [86] and differentiation of the endometrial decidua [87]. Pregnancy and hormonal changes of the ovulatory cycle are associated with altered endometrial and peripheral NK cells numbers and functions [56, 73, 78, 87]. In vitro studies indicate Pg may both directly and indirectly inhibit NK cells functions. High levels of Pg produced by the human placenta likely induce two factors at the maternal-fetal interface that inhibit NK cytolytic activity and IFN- γ secretion: major histocompatibility complex, class I, G (HLA-G) [88] and PIBF, a soluble factor released by uterine lymphocytes [89]. Recently, it was shown that Pg can directly induce apoptosis and suppress IFN- γ production in human peripheral blood NK cells in vitro, possibly via iPRs [90]. Substantiating a requirement for iPR in this regard would identify a possible immunologic mechanism linking the finding that certain iPR gene polymorphisms are associated recurrent spontaneous abortion and premature delivery and elevated serum IFN- γ levels in these conditions [91, 92]. Regulation of NK functions by Pg in AD is essentially unexplored but deserves more attention given increasing appreciation of a role for NK cells in AD.

5.4.5. Macrophages—Macrophages (MPs) are tissue-resident phagocytes that have important roles in inflammation, tissue repair and innate and adaptive immune responses [86]. Sex-dependent differences in MP functions may contribute to sexual dimorphism in atherosclerosis, wound healing and bone metabolism [52]. MP numbers and functions in the human endometrium appear to be under hormonal control during pregnancy [93] and the ovulatory cycle [94]. In vitro, Pg has largely inhibitory effects on MP functions, including suppression of lipopolysaccharide (LPS)-induced nitric oxide synthase, TNF- α and release of pro-thrombotic microparticles [73, 95, 96]. Treatment of rodents with MPA resulted in down-regulation of Fc γ R expression on spleen MPs and decreased clearance of IgG-coated sheep red blood cells in vivo, the opposite effect of Es treatment [97, 98]. Differential regulation of Fc γ R functions by MPA (or Pg) and Es could be one way these two hormones exert opposite effects on autoimmunity and kidney damage in a model of SLE (section 6.1) or other immune complex (IC)-mediated ADs like RA or cryoglobulinemia. That iPRs mediated these Pg effects is at least suggested by evidence for the expression of this receptor

in MPs (Table 1). Direct Pg effects on synovial (joint) MPs in RA, particularly suppression of TNF- α or Fc γ R expression, could be an important mechanism of pregnancy-induced remission (section 6.2). Finally, because dysregulated clearance of dead and dying cells by MPs likely contributes to loss of tolerance against nuclear Ags [99], common among the most female-predominant ADs (Section 3.3), hormonal regulation of this pathway should be investigated.

5.4.6. Myeloid dendritic cells (mDCs)—The prominent role of mDCs in innate defense against infection, adaptive immunity and tolerance [86] suggests mDCs could be important targets of Pg in modulating AD. In 2007, we published a review of this topic [71], but several points deserve reiteration and refinement. In general, Pg inhibits toll-like receptor (TLR) activation of human and mouse mDCs (Table 1). Published *in vitro* experiments reveal that pregnancy-level Pg can significantly inhibit induction of TNF- α , IL-1 β , IL-6, IL-12p40, CD80, CD86 and MHC II in TLR-activated mDCs of rat or mouse origin [71, 73], possibly via iPRs [100]. In contrast, Pg can *enhance* IL-10 release by rodent [100] and human [101] mDCs. This finding is consistent with the idea that elevated Pg in pregnancy programs DCs to present Ag to CD4⁺ T cells in a manner that favors Treg and/or Th2 development but hinders that of Th1 cells [71] (section 5.4.8).

Pg and synthetic progestins appear to regulate mDC functions in both signal-specific and gene-specific manners, indicating Pg controls select immune programs in mDCs. For example, we have observed that high physiologic doses of Pg (likely via GRs) significantly inhibit in human monocyte-derived mDCs release of TNF- α , IL-6, IL-12p70, and IL-10 after ligation of CD40 (by CD40L) but not after TLR4 (LPS) stimulus (unpublished results), suggesting Pg targets for suppression mDC functions related to adaptive immunity. Jones et al. [102] recently showed that in mouse bone marrow-derived mDCs, a form of Pg highly selective for iPRs (norgestrel) could inhibit TLR3/Mda5- but *not* TLR4-activated up-regulation of CD40, indicating Pg may also selectively suppress pathways involved in CD4⁺ T cell responses after virus infection. Moreover, we showed that treatment of mice with MPA, an iPR/GR agonist, impaired *in vivo* up-regulation of a costimulatory molecule CD86 on spleen mDCs after virus infection [68]. Together, these observations suggest endogenous Pg modulates select immune programs in mDCs related to anti-viral defense, Ag presentation, and CD4⁺ T cell differentiation. Through differential engagement of steroid hormone receptors, synthetic progestins may vary widely in terms of these effects. Future studies should focus on how signals via iPR, mPR and GR differentially regulate TLR and non-TLR activation in mDCs, and how this relates to immunologic outcomes in pregnancy, T cell dependent immunity and AD.

5.4.7. Plasmacytoid DCs (pDCs) and IFN- α —pDCs are circulating and lymphoid tissue-resident cells important for anti-viral defense and in some forms of AD, most notably SLE. pDCs are poised, through accumulation of intracellular signaling molecules, to release large amounts of IFN- α upon sensing viruses through TLRs 7, 8 and 9. [86, 103] In SLE, autoAb-containing ICs activate pDCs through these same pathways to induce IFN- α , which is believed to act on multiple immune cell types to break tolerance and amplify autoimmunity [103]. Despite their prominence in one of the most female ADs, SLE, very little is known about how female sex steroids regulate pDC functions. Two studies [104, 105] indicate that blood pDCs from women produce more IFN- α than do those from men, but only after stimulation through TLR7 or TLR8, and not via TLR9. This difference does not appear to reflect either increased transcription of the X-linked *TLR7* or *TLR8* genes in female pDCs or Es effects [104]. Subsequently, Meier et al. [105] observed in blood of HIV-infected individuals a similar sex-dependent difference in percentages of blood pDCs making IFN- α after TLR7/8 but not TLR9 stimulation. In the female subjects, serum Pg was significantly and positively correlated with IFN- α ⁺ pDCs upon TLR7/8 stimulation.

Together, these studies suggest Pg augments TLR7/8-induced IFN- α release by pDCs in women, a potentially important mechanism by which Pg increases a woman's risk of SLE. Similarly, we have observed that physiologic levels of Pg (10^{-7} M) significantly enhanced IFN- α -induced expression of several immune genes in PBMCs from healthy premenopausal female donors, but not in those from male donors. In these experiments, Pg enhancement of IFN- α -induced gene expression correlated positively with mPR- α gene (*PAQR7*) mRNA levels (unpublished results). Indeed, mPR- α expression in blood CD8⁺ T cells is increased in the luteal phase (high Pg + E2) compared with follicular phase (high E2) [53], together suggesting hormonal milieu in females may enhance downstream effects, and thus, pathogenicity, of SLE-related IFN- α . This may be one reason female pDCs make more IFN- α than do male pDCs, because exposure of pDCs to IFN- α potentiates their production of IFN- α . Overall, these data suggest endogenous Pg may increase risk of SLE through enhanced IFN- α production and signaling. How androgens like testosterone (T) impact these pathways remains to be determined, but enrichment of *TLR7*, *IRF5* and *SPP1* risk alleles in male SLE suggest important interactions between male sex factors and the IFN- α pathway (section 3.3).

Modulatory effects on the IFN- α pathway seem to depend on the dose and form of progestin involved. We showed that high-physiologic - pharmacologic doses of Pg could *inhibit* TLR9-induced IFN- α production by human and mouse pDCs in vitro [68]. In vivo, these levels of Pg occur at the maternal-fetal interface, potentially explaining the fetus's susceptibility to infection by select viruses, e.g., HIV and HSV [62], against which pDCs may be innate sentinels. Treatment of mice with the synthetic progestin birth control, DMPA, resulted in selective impairment of TLR9-induced IFN- α production by pDCs ex vivo and serum IFN- α responses after virus infection [68]. This likely reflects MPA's ability to signal through GRs, since Pg inhibition of TLR9-induced IFN- α production by mouse spleen pDCs does not require iPRs (our unpublished results), and in human pDCs, GR agonists are potent inhibitors of TLR-induced IFN- α induction [47]. These distinctions are clinically important. We and others have postulated that DMPA's ability to suppress this particular pathway helps explain why women using DMPA birth control are at increased risk of sexually acquired HIV infection (section 5.2). By the same token, in women with SLE, DMPA may have dual benefit as an effective contraceptive and suppressor of pathogenic IFN- α and Th1-related autoimmunity.

5.4.8. CD4⁺ T cells—CD4⁺ T cells are critical to development of long-lasting Ab responses, cell-mediated immunity (CMI) and tolerance [86]. They are also involved in chronic inflammation found in several ADs. A useful scheme classifies CD4⁺ T helper cells based on their effector functions: 1) Th1 cells produce IFN- γ and IL-2, important inducers of CMI and induction cytotoxic and inflammatory IgG subclasses believed to be pathogenic in SLE and AITD; 2) Th2 cells produce IL-4 and IL-5 and are important inducers of neutralizing IgG subclasses and IgE; 3) Tregs suppress functions of other CD4⁺ T cells in part through release of IL-10 and TGF- β ; 4) Th17 cells release IL-17 and IL-21 and are important in chronic inflammation during chronic infections and ADs like RA and MS. [86, 106] Overall, in vivo and in vitro evidence indicates Pg has some capacity to suppress CD4⁺ T cell proliferation and Th1/Th17 differentiation and effector functions. In contrast, Pg can enhance Th2 and Treg differentiation (Table 1) [59, 73, 107]. These effects are prominent at the maternal-fetal interface, where Pg levels are extremely elevated, but appear much weaker or are absent in the mother's circulating CD4⁺ T cells (reviewed in [59]). In vitro, high-physiologic concentrations of Pg, but not Es, are able to enhance IL-4 secretion by human CD4⁺ T cell clones [108, 109], suggesting one way Pg might favor Th2 memory responses in pregnancy. One report [110] indicates pregnancy-level Pg can inhibit differentiation of human Th1 cells, driving them toward an IL-10-secreting Th2-like phenotype. In contrast, E2 treatment in mice primes naïve CD4⁺ T cells towards Th1

differentiation through transcriptional promotion of the T-bet gene [111]. Interestingly, PIBF can suppress activation of STAT4 protein in human lymphocytes [112], while E2 has the opposite effect in mouse splenocytes [113]. Together, these results suggest that Th1 or Th17 differentiation may be an important pathway on which Es and Pg differentially influence risk of certain ADs associated with *STAT4* (Fig. 1) (see section 6).

Maternal Tregs are required for maintenance of allogeneic pregnancy in mice [114], but it remains to be determined how fluctuations in maternal circulating Treg numbers during the ovulatory cycle and human pregnancy in humans relate to fertility and to what extent Pg is involved [56, 59]. However, a recent study [115] showed that high-physiologic doses of Pg could directly *enhance* differentiation of neonatal (but not adult) naive CD4⁺ T cells into functional Foxp3-expressing Tregs while suppressing their differentiation into Th17 cells. Together, these observations indicate that high levels of Pg can alter CD4⁺ T cell differentiation and effector functions, generally enhancing those of Th2 and suppressing those of Th1/Th17 cells. These processes could play important roles in the remission of RA and MS during pregnancy (section 6).

Finally, we have observed that iPRs selectively suppress CD4⁺ T cell-dependent immune responses *in vivo*. Mice lacking functional iPRs (PRKO mice) [116] show exaggerated Ag-specific IgM and IgG responses after immunization with T-dependent (TD) but not T-independent (TI) Ags (unpublished results), indicating that iPRs (and probably endogenous Pg) are selective suppressors of CD4⁺ T cell functions and adaptive immunity. Further experiments defining the cellular and molecular mechanisms by which Pg modulates CD4⁺ T cell responses are critical to understanding modulation of Th1, Th2, and Th17 responses during pregnancy and the potential therapeutic effects of natural and synthetic progestins in ADs involving dysregulation of these pathways.

5.4.9. CD8⁺ T cells—CD8⁺ T cells are cytotoxic T cells important for recognizing and killing virally infected or neoplastic cells [86]. CD8⁺ T cells also have regulatory functions and are aberrantly activated in several ADs [117]. Some reports indicate CD8⁺ T cell functions are under the control of Pg and/or Es. White et al. [118] found that the cytolytic activity of CD3⁺CD8⁺ T cells in the uterine lining of women in the secretory phase of the menstrual cycle (Pg + E2 effects) was greatly diminished compared to that in the proliferative phase (E2 dominant), suggesting Pg and E2 together suppress cytotoxicity. Pg effects in this setting might be direct, via mPR- α , because this receptor's expression is selectively upregulated on blood CD8⁺ T cells during the luteal phase [53]. However, Pg may also regulate uterine CD8⁺ T cell indirectly, via induction in the E2-primed endometrium of GdA, a potent inhibitor of CD8⁺ T cell cytotoxicity [119]. Pg effects on CD8⁺ T cells (and/or CD8⁺ DCs) appears to be important in preventing stress-induced abortions in mice [120]. One idea is that uterine CD8⁺ T cells, when exposed to Pg, elaborate immunoregulatory molecules like indolamine 2,3-dioxygenase (IDO) or PIBF, involved in Treg induction and NK cell suppression, respectively [120]. These Pg-induced molecules, or Pg receptors expressed in CD8⁺ T cells, may prove to be therapeutic targets for the prevention of recurrent miscarriage and premature delivery, a major health issue [121]. The ability of MPA to suppress virus-specific IFN- γ and lytic granule release by CD8⁺ T cells [122] may be another mechanism by which DMPA increases a woman's risk of HIV infection (section 5.2).

5.4.10. Thymic involution during pregnancy and after puberty—The thymus is the organ where T cells develop. Beginning with puberty, the thymus undergoes a gradual decline in cellularity (thymic involution) that likely involves testosterone effects in males and combined estrogen and progesterone effects in women. Marked and transient thymic involution also occurs during mammalian pregnancy. [66] While thymic involution during

pregnancy does not result in reduced numbers of circulating T cells, it appears to be required for normal fertility, at least in mice [54]. The mechanisms linking thymic involution and fertility are unknown, but one hypothesis is that the processes associated with thymic involution are important for induction of maternal T cell tolerance to fetal alloAg, perhaps via induction of natural Tregs. Importantly, thymic involution of pregnancy in mice can be mimicked by administration of pregnancy-level Pg and/or Es; and this process requires iPR expression in thymic stromal cells [54]. Thus, Pg, through paracrine actions of iPR-bearing cells, is a negative regulator of T cell development. The interplay between male and female sex steroids, thymic functions and risk of AD, particularly after puberty, remains to be explored.

5.4.11. B cells—B cells are Ab-secreting and Ag-presenting cells critical for humoral immunity and autoimmunity [86]. Hormone effects on B cell differentiation and function are at least suggested by the fact that women have modestly higher serum levels of IgM and IgG than do men [73, 78]. In mice, pregnancy reversibly suppresses B cell development in the bone marrow, a phenomenon likely involving direct E2 action on B cell precursors [123], and its potentiation by Pg [124]. How these phenomena contribute to the immune requirements of pregnancy remains to be determined.

Surprisingly few studies have examined the effects of Pg on humoral immune responses. Vermeulen et al. [125] showed that after treatment with pharmacologic doses of MPA, mice exhibited increased primary and secondary Ab responses against sheep red blood cells (TD Ab responses); iPRs were detected in B cells, but GR agonism by MPA was not excluded as a mechanism. Indeed, our results with iPRKO mice indicate iPRs are *suppressors* of TD Ab responses, suggesting MPA modulates TD Ab responses via other receptors, i.e., GRs or mPRs. Consistent with this idea, two recent reports [72, 126] indicate Pg, via iPRs, and Es, via Es receptors, exert opposing effects on mouse B cell differentiation via competing transcriptional regulation of a gene whose product, activation-induced deaminase (AID), is required for B cell class switch recombination (CSR) and somatic hypermutation (SHM). Es enhances CSR and SHM [72], while Pg suppresses them [126]. These observations further suggest that the relative effects of Pg vs. Es may be important determinants of B cell differentiation in immunity and autoimmunity. Finally, Pg may induce important post-translational modifications of secreted Ig molecules that alter their avidity and effector functions [127]. In RA, serum IgG shows abnormally low levels of terminal galactose residues [128], increases in which are associated with successful pregnancy and RA disease remission during pregnancy [129]. In vitro, Pg can induce some of these pregnancy-related Ig glycosylation patterns [65]. Thus, pregnancy-induced remission of RA may rely in part on Pg-mediated changes in Ig glycosylation. Interestingly, a recent study [130] showed that terminal galactose residues on glycoproteins are natural suppressors of pDC IFN- α production via ligation of the human pDC-specific molecule BDCA-2. Together, these observations suggest that Pg, via iPRs, may suppress pathways of B cell differentiation involved in many ADs, and that Pg may modulate immune-mediated injury in AD through post-translational modification of Ig. MPA may have different effects on these processes. Clearly, much more research is needed to clarify the impact of Pg and synthetic progestins on B cell differentiation and functions in human AD.

6. Progesterone and Autoimmune Disease

As summarized in the previous section, Pg can impact many immune pathways involved in AD. This section will examine what is known about Pg and the female-predominant ADs, drawing on the previous sections to highlight possible mechanisms and future lines of investigation. For general review of the topic of female sex steroids and AD, see McCombe et al. [4] and Matocchia et al. [23]

6.1. Systemic lupus erythematosus (SLE)

While the relationships between Es and SLE autoimmunity have been relatively well studied, much less is known about Pg in this regard. Several observations indicate female sex steroids increase risk of SLE. As mentioned in section 3, incidence and female predominance of SLE rise after puberty. Moreover, risk of SLE is associated with early menarche (i.e., increased exposure to endogenous sex steroids) [131]. Two large observational studies [131, 132] indicate use of exogenous Es in the form of OCPs or HRT is associated with an approximately 1.5- to 3.0-fold increased risk of SLE. In contrast, one unpublished study [133] suggests use of Pg-only contraception *protects* against incident SLE, but this has not been replicated. Thus, Pg and Es appear to modulate risk of SLE in different ways. Interestingly, women with SLE show luteal phase deficiency in serum Pg [134], although it is unknown whether this precedes illness or is a consequence of it. However, a causal link between abnormal sex steroid signaling and risk of SLE is suggested by the discovery of the SLE risk gene *UBE2L3* [33], whose protein product is a co-activator of iPRs and other sex steroid receptors [135]. Accordingly, it will be informative to assess if *UBE2L3* risk variants result in altered Pg sensitivity in terms of its effects on IFN- α production or sensitivity (section 5.4.7).

The model that Pg and Es have different effects on the development of SLE autoimmunity is further supported by animal studies. In the NZB $\times$ NZW F₁ (NZB/W) model of SLE, multiple risk loci from both parental strains combine to result in spontaneous lupus-like disease, earlier and more severe in female mice compared to male mice. In the NZB/W strain, early mortality is tightly linked to emergence of class-switched Th1-related IgG_{2a} anti-DNA Abs and immune complex (IC) glomerulonephritis. [136, 137] A series of incisive experiments by Talal et al. (reviewed in [137]) clearly showed that autoimmune disease in NZB/W mice was under gonadal and thymic control. In these experiments, pre-pubertal castration of male mice led to anti-DNA IgG and mortality similar to those of intact females, and this could be prevented with continuous T exposure. Thus, T has a dominant protective effect in this model. Interestingly, increased autoAb levels after castration of male NZB/W mice could be prevented by neonatal thymectomy, suggesting that protective effects of T might involve modulation of thymic functions (see 5.4.10). In contrast to male mice, pre-pubertal ovariectomy in female NZB/W mice had little effect on survival, indicating ovarian factors (e.g., Pg and E2) were not required for full expression of disease. This is consistent with the idea, outlined in section 3.3, that when genetic risk burden is high, as it is in NZB/W mice, female sex steroids become a subordinate risk factor. In the NZB/W model, E2 treatment invariably increases mortality, a process that likely involves a combination of enhanced Th1-related autoimmune responses [71] and induction of lymphoid neoplasia [138], possibly through oncogenic activation of AID in B cells [72].

Studies assessing Pg treatment in the NZB/W model have led to different results. Keisler et al. [138] showed that treatment of pre-morbid female NZB/W mice with any of three synthetic progestins (including MPA) had little to no effect on either survival or serum anti-DNA reactivity. However, Roubinian et al. [139] showed that continuous Pg treatment of pre-morbid female NZB/W mice whose ovaries had been removed modestly worsened survival, but markedly *increased* levels of serum anti-DNA IgG, far more than did E2 treatment. In castrated male NZB/W mice, Pg also markedly increased anti-DNA IgG but *decreased* mortality, suggesting an uncoupling of autoimmunity from end-organ damage, perhaps through suppression of Fc γ R expression in the kidneys or diversion of pathogenic Th1-related anti-DNA IgG_{2a} towards protective IgG₁ [106]. Consistent with the latter of these mechanisms, we recently showed that treatment of pre-morbid female NZB/W mice with continuous MPA resulted in markedly decreased death, kidney damage and selective suppression of pathogenic Th1-related anti-dsDNA IgG_{2a} in the serum and kidneys [70]. How DMPA suppresses Th1 autoimmune responses is not clear but could involve direct

actions, likely via GRs, on the differentiation of autoreactive Th1 cells, suppression of Th1-related IL-12, IFN- α or CSR in autoreactive B cells. Together, these results indicate Pg and MPA have different effects on the development of autoimmunity in this model, likely due to differential engagement of iPRs, mPRs, and GRs. The importance of these pathways could be sorted out by treating lupus mice with selective Pg receptor agonists and by introducing Pg receptor knockout mutations into models of SLE.

Compared with their impact on disease development, female sex steroids appear to have weaker effects on SLE disease activity. Numerous studies together indicate that pregnancy can increase the risk of disease “flare” [31, 140]. However, interpretation of these data is confounded by inconsistent disease classification, inadequate measures of disease activity, and a tendency by patients and physicians to alter medical therapy during pregnancy. The most important predictor of SLE flare during pregnancy, however, is high disease activity in the 6 months before conception [31, 141], indicating that the effects of pregnancy are subordinate. Do exogenous hormones affect SLE disease activity? Results of a recent meta-analysis [142] indicate that for women with mild or inactive SLE, use of combined (Es + progestin) OCPs poses no increased risk of flare. The same is true for post-menopausal women with SLE taking combined HRT [143]. Two recent studies examined the risk of flare of in women with SLE taking (synthetic) progestin-only HRT [144] or contraception [145] and found either no or *reduced* rates of flare, respectively. Indeed, DMPA may be able to suppress certain pathways of SLE immune-mediated injury, like IFN- α induction in pDCs and Fc γ R-signaling in MPs and Th1 differentiation (Table 1). These results together suggest that in women with SLE, synthetic forms of Pg-only contraception, particularly DMPA, are safer than those containing Es and may even have therapeutic effects.

Overall, observations in humans and animal models indicate that individually, Es and Pg have very different effects on SLE disease development: Es can promote it, and progestins in some situations can inhibit it. Future studies should compare how natural and synthetic progestins modulate SLE risk and immune-injury pathways. In terms of risk pathways, special attention might be given to those associated with *TLR7*, *IRF5*, *SPP1* and *STAT4*.

6.2. Rheumatoid arthritis (RA)

RA is a chronic inflammatory polyarthritis syndrome associated with serum rheumatoid factor (RF) and Abs recognizing post-translationally modified (citrullinated) peptides [146]. Little is known about the effects of Pg on risk of disease. A protective effect of parity (the number of pregnancies a woman has experienced) has been observed in some studies but not others [147]. In the largest retrospective studies, OCP use was not associated with risk of RA [148]. In animal models of RA, such as collagen-induced arthritis (CIA), pregnancy-level E2 treatment before immunization with collagen *retards* disease development in association with reduced anti-collagen Abs, TNF- α , IFN- γ and prostaglandin E2 (PGE2) responses [149–151]. In rat CIA, pre-treatment with pregnancy-level Pg had little effect on joint swelling or serum TNF- α and prostaglandin E2 (PGE2), but appeared to reduce the beneficial effects of pregnancy-level Es treatment in terms of these parameters [149]. Interestingly, neither Pg nor Es treatment appeared to alter anti-collagen Ab responses in these mice, suggesting hormones were not modulating autoimmunity but rather acting primarily at the level of joint inflammation. Indeed, recent evidence [152] suggests that Es exerts most of its protective effects in CIA on the effector phase (immune injury) rather than induction of autoimmunity.

While use of low-dose exogenous HRT (usually Es + progestin) does not appear to impact disease activity in post-menopausal women with RA [143], pregnancy-level sex steroids appear to have pronounced effects. RA disease usually remits during pregnancy, provided disease was active beforehand, then flares post-partum [42]. A similar pattern is seen in

mouse models of arthritis [153, 154]. Several Pg-inducible changes in systemic immune functions could be involved in this form of RA remission, including increased IL-1RA, induction of Tregs, suppression of Th1 or Th17 responses, increased Th2-related responses, and increased levels of terminal galactose residues on circulating Ig. A role for Th1-suppression/Th2-enhancement is supported by experiments [153] in a model pregnancy-induced remission of immune-mediated arthritis after infection with *Borrelia burgdorferi* (causative agent in human Lyme disease). Infection during pregnancy results in less severe arthritis, decreased spirochete-specific Th1-related responses (IFN- γ , IgG_{2a}), and increased spirochete-specific IL-4; and these effects could be mimicked by Pg pre-treatment of non-pregnant mice. Interestingly in the study [149] of Pg in CIA mentioned above, the combination of pregnancy level Pg + Es did not alleviate arthritis, suggesting that pregnancy-induced remission of certain forms of inflammatory arthritis requires additional factors, such as those released at the maternal-fetal interface. Dissecting the mechanisms of pregnancy-induced remission in RA and its animal models is important because it will likely reveal new pathways, or new combinations of known pathways, that could be targeted to treat people with RA.

6.3. Multiple sclerosis (MS)

MS is a female-predominant demyelinating disease of the CNS associated with activation of Th1 and Th17 pathways [155]. Like with RA, female sex steroids appear to have stronger effects on MS disease activity compared to risk of disease. For example, even though MS is a female-predominant AD (Fig. 1), multiple observational studies have failed to find an association between either OCP use [156, 157] or parity [157, 158] and disease risk. However, in the experimental autoimmune encephalomyelitis (EAE) model of MS, pre-treatment with pregnancy-level Es invariably reduces subsequent neurologic disease [157], perhaps through direct suppression of Th1 and Th17 cell functions [159]. In this model, Pg pre-treatment protects against neurological damage [160], but its effects on immunological parameters were not addressed. Interestingly, in rats whose ovaries were removed, Pg treatment before EAE induction worsened brain inflammation and neurological symptoms [161], indicating that the protective effects of Pg require gonadal factors. Overall, however, these observations do not support a significant role for either Es or Pg in explaining the female predominance of MS.

In contrast, female sex steroids appear to have major impacts on MS disease activity. Pregnancy is associated with remission of MS and reduced rates of flare, which rise markedly post-partum [162]. How this occurs is not known but is believed to involve the ability of Pg to prevent neurological damage and foster regeneration [163, 164]. Consistent with this idea, Pg treatment after onset of EAE halts disease progression and fosters CNS myelin regeneration [163, 165]. Moreover, Yates et al. [165] recently showed that the protective effects of Pg treatment after induction of EAE autoimmunity involves suppression of IL-2 and IL-17, consistent with Pg's ability to suppress Th17 effector functions and T cell proliferation (section 5.4.8). Another potential target in this regard is release by DCs of IL-23, a critical inducer of Th17 differentiation in EAE and probably MS [155]. Thus, it is likely that pregnancy-induced improvement in MS reflects Pg's ability to 1) suppress Th17 differentiation or effector functions, 2) protect against CNS injury, and 3) foster repair of prior neurological damage. A clinical trial [166] is underway testing the efficacy of progestin treatment in the prevention of post-partum flares in women with MS. If this therapy proves effective, it will be important to determine which Pg receptors expressed in the CNS mediate protective effects, because these receptors could be selectively targeted in MS and other diseases of inflammatory injury to the CNS.

6.4. Autoimmune thyroid disease (AITD)

Autoimmune thyroid diseases are characterized by immune-mediated attack of the thyroid gland. Two important forms of AITD are Hashimoto's thyroiditis (HT) and Grave's disease (GD). [167] HT and GD are among the ADs with the highest female:male ratios (Fig. 1). Epidemiological data strongly implicate female reproductive factors in the pathogenesis of AITD. First, like with SLE, the extreme female to male ratio arises after puberty [18]. Second, large retrospective studies show that increasing parity is positively associated with risk of AITD or anti-thyroid autoimmunity [158, 168], although this could reflect immune responses to increasing fetal alloantigen [169] rather than hormone effects. In one retrospective study [168], use of Es-containing OCPs appeared to protect against thyroid disease (here, presumed GD) independent of parity, consistent with Es's protective effects in a mouse model of AITD [170]. In this same model, Pg treatment modestly increased anti-thyroid Abs and thyroiditis. Thus, Pg and Es appear to modulate risk of AITD differently than they do in SLE (section 6.1). Why Es in particular would protect against GD but enhance risk of SLE is unclear, but one possibility relates to differential IgG subclass usage by autoAbs in GD (IgG1 and IgG4) [171] and SLE (IgG2 and IgG3 in severe GN) [172]. Through modulation of CD4⁺ T cell differentiation and B cell CSR, Es could differentially impact ADs mediated by neutralizing IgG subclasses (e.g., IgG4) vs. complement-fixing and cytotoxic subclasses (e.g., IgG3) [173]. Less is known about the impact of Es or Pg on AITD activity, but GD apparently can remit during pregnancy and flare post-partum [174]. Much more research is needed to clarify hormonal risk factors for AITD.

6.5. Other female-predominant autoimmune diseases

Very little is known about the impact of Pg on Sjögren syndrome (SS), SSc or PBC. SS is a highly female-predominant AD characterized by ANA and immune-mediated dysfunction of salivary and other mucosal exocrine glands [146]. Though SS shares many features with SLE, including risk association with *IRF5* and *STAT4*, its median age of onset is 40 – 60, 1 – 2 decades later than SLE [175]. Thus, risk modulation by female sex steroids in SS, if present, appears to be slower than in SLE, perhaps because SS comes to clinical attention only after sufficient damage to exocrine glands has accrued to cause symptoms, as is the case with thyroid gland damage in HT, which also shows peak incidence between 40 and 60 [175, 176]. It is unclear whether female sex steroids impact immune-mediated injury in SS, but there is evidence that androgens [177], Es, and to a lesser extent, Pg [178], modulate exocrine gland function and thereby disease symptoms.

SSc is characterized by ANA, progressive skin hardening (sclerosis), vascular dysfunction and sometimes fibrosis of internal organs [146]. Studies examining the relationship of parity and risk of SSc have shown either negative, positive, or no correlation [158, 179]. OCP use did not appear to be correlated with risk of SSc in one study [180]. In PBC, a female-predominant disease of progressive liver scarring, rheumatologic symptoms and ANA, a large retrospective study [181] found no correlation with parity or use of HRT with risk of disease, but found a modest protective effect of past OCP use. Two trials [182, 183] tested the safety of HRT for bone health in women with PBC and found no adverse effects on liver disease, while a therapeutic trial [184] of MPA in PBC found no benefit. Clearly, more research, particularly with animal models, is needed to explain the female predominance of these ADs.

7. Summary and Future Directions

The evolutionary requirements of placental reproduction have driven sexual dimorphism in mammalian immune systems. This dimorphism is most obvious in the extreme female predominance of certain human ADs. Sexual immune dimorphism almost certainly involves

modulatory actions of sex steroids like T, Es and Pg. Pg exerts these effects via direct actions on immune cells and induction of immunomodulatory molecules in non-hematopoietic tissues. The effects of Pg and synthetic progestins depend greatly on their concentrations and differential engagement of various intracellular and membrane-associated Pg receptors expressed in immune cell subsets, immune organs and tissues of autoimmune attack. Via these mechanisms, Pg has profound and complex modulatory actions, different than those of Es or T, on inflammation, adaptive immune responses and autoimmunity. Moreover, Pg modulates risk of AD and immune-mediated injury in different ways in different ADs. Since the effects of Pg and Es on immune functions appear to be interdependent, as they are in reproductive tissues, relationships between hormonal status, their impacts on risk of AD and immune-mediated injury will defy simple classification. Thus, basic research is needed to clarify the cellular and molecular mechanisms by which Pg and Es modulate immune functions, both individually and together. Similar mechanistic dissection of pregnancy-induced remission in RA and MS should reveal novel therapeutic approaches. Finally, emerging understanding of sex-specific genetic risk should be used to guide basic scientific investigation into the hormonal causes of sexual dimorphism in human AD.

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Figure 1.

Female:male prevalence ratios for selected autoimmune and inflammatory disorders. Shown are the means and ranges of female:male ratios ($\log_{10}$ transformed) compiled in a non-weighted manner from Beeson et al. [175], Whitacre [185], Cooper and Stroehla [176], McCombe et al. [4] and Jørgensen et al. [158] For those disorders with published GWAS data, reported risk associations with *IRF5* or *STAT4* genes shown as either detected (+) or not detected (-). GWAS data extracted from the National Human Genome Research Institute GWAS Catalog [33]. SLE, systemic lupus erythematosus; ITP, immune (idiopathic) thrombocytopenic purpura; CIDP, chronic inflammatory demyelinating polyneuropathy.

Table 1

Reported effects of progesterone and synthetic progestins on functions of individual immune cell types.

Cell Type		Reported effects	iPRs	mPRs
Granulocytes	Neutrophils	<u>↓ superoxide release</u> <u>↓ apoptosis</u> <u>↓ chemotaxis</u>		
	Eosinophils	<u>↑ degranulation:</u>		
	Mast cells	<u>↑ uterine infiltration (? direct)</u>	H	
NK Cells		<u>↑ apoptosis (iPRs)</u> <u>↓ IFN-γ (iPRs)</u> <u>↓ cytotoxicity (indirect: via HLA-G, P1BF)</u>	H	
Macrophages		<u>↓ nitric oxide</u> <u>↓ TNF-α</u> <u>↓ FcγR expression (MPA)</u> <u>↓ microparticle release</u>	H	
DCs	Myeloid DCs	<u>↑ ↓ IL-10</u> <u>↓ TNF-α, IL-6</u> <u>↓ IL-12p40, IL-12p70</u> <u>↓ CD80/86, MHC II</u>	r	
	Plasmacytoid DCs	<u>↑ IFN-α (low-dose Pg, ? direct)</u> <u>↓ IFN-α (high-dose Pg, MPA)</u>		
T cells	CD4 ⁺	<u>↑ IL-4</u> <u>↑ Treg differentiation</u> <u>↓ IFN-γ</u> <u>↓ proliferation</u> <u>↓ T-dependent Ab responses (iPRs, ? direct)</u> <u>↓ Th17 differentiation</u> <u>↓ IL-6 receptor</u>		H
	CD8 ⁺	<u>↓ IFN-γ (MPA)</u> <u>↓ cytotoxicity (MPA)</u>		H
B cells		<u>↑ primary and secondary Ab responses (MPA)</u> <u>↓ class switch recombination (iPRs)</u> <u>↓ T-dependent Ab responses (iPRs, ? direct)</u> <u>⇔ altered Ig glycosylation</u>	m	

Results from human cells underlined. All effects are direct and involve Pg unless otherwise noted in parentheses. When Pg receptor usage for given effect is known, that receptor is shown in parentheses. Evidence supporting iPR or mPR *protein* expression in immune cell types indicated by letter: H, human; m, mouse; r, rat. Blank spaces indicate lack of data. Receptor expression data based on Gilliver et al. [52] See section 5 for specific citations.