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Pregnancy Immunogenetics and Genomics: Implications for Pregnancy-Related Complications and Autoimmune Disease

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Abstract

Pregnancy presents a singular physiological scenario during which the maternal immune system must accommodate the semiallogeneic fetus. Fluctuations between pro- and anti-inflammatory states are required throughout gestation to facilitate uterine tissue remodeling, fetal growth and development, and finally birth. Tolerance for the fetus must be established and maintained without fundamentally compromising the maternal immune system function, so that both the mother and fetus are protected from foreign insults. Here, we review our current understanding of how genetic variation at both maternal and fetal loci affects implantation and placenta formation, thereby determining the likelihood of a successful pregnancy outcome or the development of pregnancy-related complications. We also consider the impact of pregnancy on both the maternal and fetal systemic immune systems and the related implications for modulating ongoing autoimmune diseases and triggering their development.

INTRODUCTION

Pregnancy is a unique physiological state whereby cells from two individuals who share only half of their genomes coexist while blastocyst implantation and fetal development occur. The genetic disparity between the mother and the fetus has presented a conundrum for immunologists, given the analogy first described in 1953 by Medawar (78) of the fetus as a semiallogeneic graft that expresses paternally derived antigens without being rejected by the maternal immune system. With the discovery of the major histocompatibility complex (MHC) and the self/nonself immune recognition hypothesis, which proposed that lymphocytes with receptors for nonself antigens and allogeneic cells should lead to rejection of the allograft, this transplantation immunology model was extrapolated to the fetus. Acute graft rejection occurs when recipient T cells recognize nonself donor MHC molecules, which are highly polymorphic, with more than 15,000 classical human leukocyte antigen (HLA) class I and II alleles identified to date (111). The recipient T cells then mount a response against the donor cells. Initial theories for the absence of this phenomenon during pregnancy postulated a systemic, constant maternal immunosuppression. Such a mechanism could not, however, explain the later findings of fetal antigen-specific T cell and antibody-mediated responses present in pregnant mothers (128). Instead, these findings provided the first hints that there are much more intricate involvement and regulation of the maternal immune system during pregnancy.

Genetic research into immune recognition during pregnancy has focused largely on the interactions between HLA molecules and their ligands—in particular the killer-cell immunoglobulin-like receptors (KIRs) of natural killer (NK) cells—and how these interactions affect events at the maternal–fetal interface, the placenta. Placenta formation and function can affect fetal survival, growth, and development and can modulate maternal immune responses. Following fertilization, the inner cell mass of the blastocyst gives rise to the embryo, while the outer cell layer, the trophectoderm, gives rise to the placenta. The placenta forms once implantation occurs, as extravillous trophoblast cells at the tips of anchoring villi attach to and invade the maternal decidua that develops from the uterine mucosa. Decidualization requires changes in the morphology and function of endometrial stromal cells, remodeling of the maternal spiral arteries, and immune cell infiltration and action. Approximately 40% of the cells that make up the decidua are immune cells (130); some two-thirds of these cells are NK cells, a quarter are macrophages, a tenth are T cells, and smaller proportions are dendritic cells (DCs) and B cells (1, 86, 90). The decidual and myometrial immune cells can come into contact with the extravillous trophoblasts. Deletion of immune cells at the implantation site or inhibition of their signaling pathways can have profound effects, even resulting in the loss of pregnancy (2, 84). This suggests that although immune tolerance for the growing fetus is necessary, maternal immune cells also have an active role in promoting a successful pregnancy outcome.

During fetal growth, the placenta has classically been considered to act as a barrier, limiting the interaction of the maternal immune cells to the trophoblast, preventing interaction with the somatic cells of the fetus, facilitating evasion of maternal immune surveillance, enabling tolerogenesis, and promoting an anti-inflammatory microenvironment (84). However, a growing body of data indicates that the immunological barrier function of the placenta is not absolute. The villous trophoblast cells that progressively fuse into syncytiotrophoblasts come into contact with the maternal blood that circulates in the intervillous space. Syncytial nuclear aggregates or knots can be shed into the circulation, as can soluble fetal antigens, such as paternally derived HLA antigens, which can lead to the development of anti-HLA alloantibodies, for example (82). In addition, a form of genetic sharing effectively occurs because trophoblast cells can be released into the maternal circulation in a phenomenon termed fetal microchimerism, particularly during the physical

trauma that accompanies parturition. These cells can persist in the blood and in maternal organs, including the bone marrow, liver, kidney, and heart, for decades after pregnancy (11, 62, 94). Maternal microchimerism, as evidenced by the presence of maternal immune cells and platelets in umbilical cord blood, can also occur. Maternal microchimerism has been observed in as many as 40% of healthy pregnancies, and such maternal cells have even been identified in healthy immunocompetent adults (76). However, alterations in the degree of microchimerism and in the nature of the trafficked cells have been implicated in autoimmune disease development (54).

Here, we review our current understanding of the genetically determined molecular and cellular interactions that allow the maternal immune system to accommodate and tolerate the fetus. We consider how KIR–HLA gene interactions, as well as variation at other maternal and fetal loci, can affect the implantation and placentation processes, altering risk for a range of pregnancy-related complications. Lastly, we discuss the intricate, bidirectional relationship between pregnancy and autoimmune disease during the gestational period and the lifelong impact that pregnancy can have on the development of these diseases in both the mother and the fetus.

FETAL EVASION OF MATERNAL IMMUNE SURVEILLANCE AND THE ROLE OF NONCLASSICAL HLA MOLECULES

Classical HLA molecules are highly polymorphic and include class I HLA-A, HLA-B, and HLA-C, which present antigens to $CD8^+$ cytotoxic T cells, and class II HLA-DP, HLA-DQ, and HLA-DR, which present antigens to $CD4^+$ helper T cells. HLA class II protein expression is restricted largely to professional antigen-presenting cells, and the lack of class II molecule expression on extravillous and villous trophoblasts indicates that these cells cannot act as antigen-presenting cells, thereby evading direct allorecognition by maternal $CD4^+$ T cells. Unlike most cells of the body, villous trophoblasts have no HLA class I expression, while extravillous trophoblasts lack expression of HLA-A and HLA-B, which facilitates evasion of maternal $CD8^+$ T cell responses. Extravillous trophoblasts do express HLA-C molecules, and as these molecules are polymorphic, paternal alleles derived from the fetus will likely differ from those of the mother. However, compared with HLA-A and HLA-B, HLA-C has an approximately 15-fold-lower cell surface expression (5), is not as polymorphic, and is thought to have evolved predominantly to interact with KIRs—particularly the lineage III KIRs—rather than with the $CD8^+$ T cell receptors (7, 39). Notably, the abundance of decidual NK cells relative to other immune cell types early in pregnancy implies the importance of KIR–HLA-C interactions, as does the finding that, compared with peripheral NK cells, uterine NK cells display a bias toward lineage III KIR expression (115). Relative to peripheral NK cells, uterine NK cells also differ in their cell surface expression of CD56 and CD16 ($CD56^{bright}$ and $CD16^-$, respectively), and they possess a less cytotoxic and more tolerogenic function, driven by trophoblast-derived interleukin 15 (IL-15) and transforming growth factor β (TGF-β) (42). Moreover, these specialized NK cells are thought to play an active role in maternal tissue remodeling and vascularization, in a process that has been likened to micrometastasis (86) and is required for trophoblast implantation and placentation. An in-depth characterization of the full functional capacity of uterine NK cells has previously been somewhat hampered by the difficulty of obtaining relevant human tissue. However, a recent Human Cell Atlas study has now transcriptionally profiled the maternal–fetal interface at single-cell resolution and has identified three main decidual NK cell subsets. The first of these subsets is characterized by an active metabolism, increased KIR expression, and increased cytotoxic capacity and may thus be particularly involved in interacting with extravillous trophoblasts (129).

HLA-E and HLA-F

In addition to HLA-C, extravillous trophoblasts express the nonclassical HLA-E, HLA-F, and HLA-G molecules, which are oligomorphic. For example, the 20 reported *HLA-F* alleles encode only four HLA-F proteins (87), while the 51 *HLA-G* alleles recognized to date encode 16 different HLA-G proteins (29). Despite this limited polymorphism, there has been an interest in characterizing the binding partners and function of these nonclassical HLA molecules in pregnancy and in investigating the impact of their genetic variation on pregnancy-related complications. HLA-E–self-peptide complexes can bind to inhibitory CD94/NKG2A and activating NKG2C receptors on NK cells. Two nonsynonymous *HLA-E* alleles have been described: *HLA-E*01:01*, which encodes a glycine at amino acid residue position 107 of the α2 domain, and *HLA-E*01:03*, which encodes an arginine instead (38). These alleles have some association with recurrent spontaneous abortion (30), perhaps in keeping with the role of decidual NK cells in regulating trophoblast invasion and blastocyst implantation.

HLA-F interacts with the inhibitory leukocyte immunoglobulin-like receptor B1 (LILRB1) and LILRB2 molecules found on decidual NK cells, macrophages, and DCs (4). In addition, there is evidence that in the absence of peptide presentation, open conformers of HLA-F have the capacity to bind the inhibitory KIR3DL2 NK cell receptor and the activating KIR2DS2 and KIR3DS1 receptors (33, 36). *HLA-F* genetic associations with pregnancy-related phenotypes have not been widely reported, although the major *A* allele of the rs2523393 single-nucleotide polymorphism (SNP) has been implicated in fecundability (16). This allele correlates with increased HLA-F expression levels (16) by generating a GATA2 binding site in a distal progesterone-responsive regulatory element that loops to and interacts with the *HLA-F* promoter (80). From an evolutionary perspective, the *A* allele is derived in the human lineage, arising before the divergence of modern and archaic humans (80). Intriguingly, the *A* allele also increases risk for multiple sclerosis (MS), although this association has been attributed to rs2523392 serving as a tagging SNP for the *HLA-B*44:02* allele (25).

HLA-G

Unlike the other HLA molecules found on extravillous trophoblasts, HLA-G expression is specifically restricted to these cells (63), with the exception of certain cancer cells, where it may confer an immunosuppressive function that mimics the function of HLA-G in pregnancy (69). The specificity of HLA-G expression relative to that of other class I molecules suggests a unique mode of gene expression regulation. Compared with the other HLA genes, the classical promoter of *HLA-G* is enriched for nonfunctional regulatory elements (118), and instead transcription may rely at least partly on the long-range interaction between the promoter and Enhancer L, found approximately 12 kb upstream. In addition, a long interspersed nuclear element, LINE1, found approximately 4 kb upstream of the promoter, is implicated in repressing HLA-G expression in nonextravillous trophoblast cells through the formation of a hairpin loop (53). HLA-G expression is also subject to posttranscriptional modulation. Variation in its 3′ untranslated region is correlated with differential HLA-G levels, likely due to the action of microRNAs (miRs). Notably, miR148a and miR152, which can downregulate HLA-G, are not expressed in trophoblasts (105). Intriguingly, however, the human chromosome 19 miR cluster is expressed virtually solely in trophoblasts (26) and might contribute to the lack of trophoblast expression of other HLA genes (29). Numerous studies have interrogated the effect of *HLA-G* locus variation on the risk of recurrent spontaneous abortion, pre-eclampsia, and preterm birth but with inconclusive results, suggesting a need for more systematic and larger-scale investigations (29).

Apart from its cell-type-specific expression, HLA-G possesses further unusual features relative to the other HLA class I molecules. Its short cytoplasmic tail has been postulated to contribute to a prolonged half-life at the cell surface, and it can exist as both a monomer and a homodimer, by virtue of disulfide bond formation between the cysteines at position 42 in the α1 domain (15). It is unclear whether HLA-G ligands show a differential preference for monomer or dimer binding, but HLA-G dimers have the capacity to bind the inhibitory LILRB1 and LILRB2 receptors, although structural analyses reveal that the former tends to bind more to β2 microglobulin, while the latter binds more to the α3 domain (83). These interactions have been suggested to drive localized tolerance to the fetus by acting on decidual antigen-presenting cells, thus still allowing the mother's antigen-presenting cells at other sites of the body to retain normal function in orchestrating responses against pathogens. In addition to binding LILRs, KIR2DL4, which is an atypical KIR, is thought to be the main HLA-G receptor on decidual NK cells (107). KIR2DL4 has an activating function in inducing NK cell cytotoxic function, but it may also have an inhibitory potential given that it possesses a single immunoreceptor tyrosine-based inhibition motif (ITIM) in its long cytoplasmic tail. The HLA-G–KIR2DL4 interaction may rely not only on cell–cell contact but also on the actual transfer of HLA-G from the extravillous trophoblasts to decidual NK cells via trogocytosis. A possible explanation for a need for HLA-G trogocytosis is that KIR2DL4 has a predominantly intracellular localization in endosomes, thereby requiring HLA-G uptake to stimulate and perhaps sustain KIR2DL4-mediated signaling to enable the secretion of cytokines and proangiogenic factors for placental development and to promote immune tolerance (108).

A final mechanism by which HLA-G could function during pregnancy is by providing a high-affinity nonamer peptide for presentation by HLA-E. In the absence of this peptide, HLA-E binds to CD94/NKG2A, thereby triggering a strong inhibitory signal in decidual NK cells. However, in vitro analyses show that binding of the HLA-G signal peptide leads to a high-affinity interaction with the activating CD94/NKG2C receptor, as well as an increase in cell surface HLA-E levels. This interaction promotes NK cell cytotoxicity over a wide range of peptide concentrations (73). The importance of this mechanism of HLA-G action relative to its direct receptor binding is unknown but indicates that nonclassical HLA molecules may have a multifaceted role in pregnancy, perhaps reflecting a highly specialized function required to coordinate the complex immunological events accompanying implantation, placentation, and subsequent fetal development.

KIR–HLA-C INTERACTIONS IN PREGNANCY AND RELATED DISORDERS

The polymorphic KIR–HLA-C interactome acting at the maternal–fetal interface is postulated to have coevolved at least partly as a result of reproductive pressures occurring with the evolution of hominin bipedalism and the development of larger brains (83). NK cell allorecognition through the KIR–HLA-C interaction is a physiological, cooperative requirement in early pregnancy for blastocyst implantation and placental development to occur through a controlled process of invasion and maternal arterial remodeling. This process must achieve a balance whereby the uterus is altered enough to effectively and efficiently support delivery of the maternally derived oxygen and nutrients demanded by the growing fetus, but without causing an unnecessary penetration of the uterus or excessive resource transfer that might jeopardize the health or survival of the mother. However, different combinations of maternal KIR and fetal HLA-C molecules may perturb this balance, as they have been found to be associated with birth weight extremes and with pregnancy-related disorders.

The KIR Gene Cluster

KIR gene evolution has occurred in primates over approximately the last 40 million years via tandem duplication and deletion. The KIR genes are densely clustered on human chromosome 19q13.4 into haplotypes with an intergenic space of only approximately 1 kb and with a homology between alleles of different genes of approximately 90% (21). Recombination rates are high in the KIR cluster: A transposon-rich region drives recombination events during meiosis that may be intergenic or even intragenic, potentially giving rise to novel fusion proteins (95). This recombination hot spot localizes between the centromeric and telomeric regions of the haplotypes. The centromeric region is bound by the *KIR3DL3* and *KIR3DP1* framework genes, while the telomeric region is bound by *KIR2DL4* and *KIR3DL2*. KIR haplotypes are classically categorized into two main groups, A and B, based on the inhibitory and activating KIR genes they possess; the KIR framework genes are found on all haplotypes (**Figure 1**). The KIR gene nomenclature relates to the key structural features of KIR proteins, reflecting whether they possess two or three extracellular immunoglobulin-like domains (2D and 3D, respectively) and whether they have long (L) or short (S) cytoplasmic tails. At the protein level, inhibitory KIRs, which include the KIR2DL and KIR3DL groups, have ITIMs in their long cytoplasmic tails. By contrast, activating KIRs, which include the KIR2DS and KIR3DS groups, have shorter cytoplasmic tails and require the binding of adaptor proteins such as DAP12 for productive intracellular signaling, as these adaptors contain immunoreceptor tyrosine-based activating motifs. The KIR A haplotypes show little or

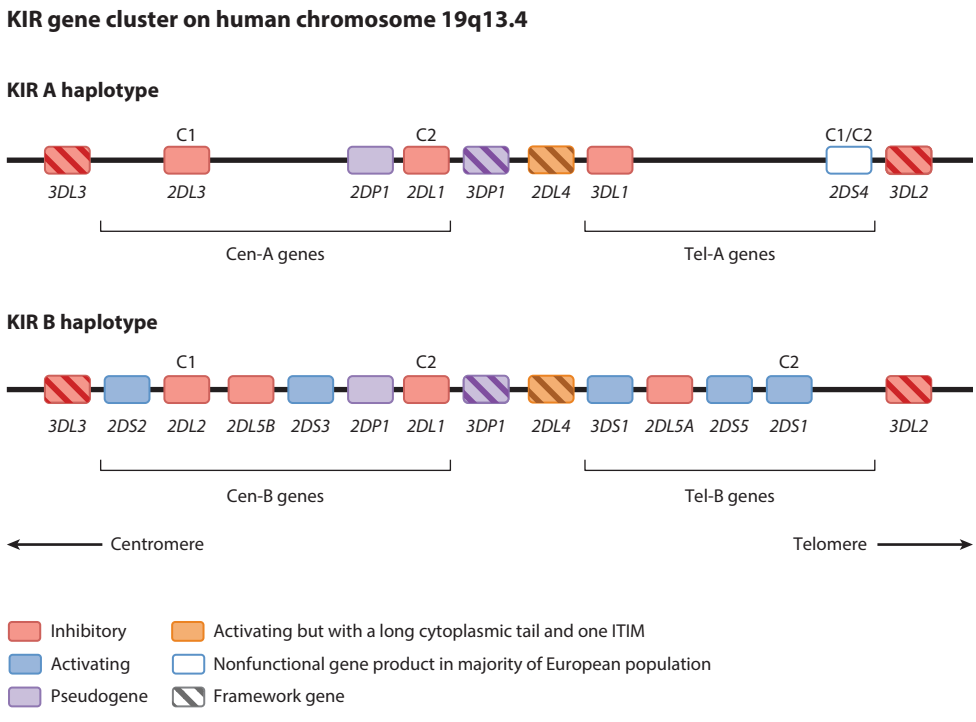

Figure 1

Representative schematic showing the overall gene structure of the KIR A and KIR B haplotypes. KIR genes in the centromeric (Cen-A and Cen-B) and telomeric (Tel-A and Tel-B) regions on both haplotypes are depicted. The HLA-C group C1 and C2 ligands are denoted above their respective cognate KIR receptors. Abbreviation: ITIM, immunoreceptor tyrosine-based inhibition motif.

no structural variation and are enriched for inhibitory genes, with the exception of *KIR2DS4* and the atypical *KIR2DL4* gene, whose product binds HLA-G. The majority of *KIR2DS4* alleles in the European population carry a 22-base-pair frameshift deletion in exon 5 that results in the production of a soluble protein with a single immunoglobulin-like domain that is not capable of binding HLA-C (37). The KIR B haplotypes display a much greater structural diversity in the number and combination of genes they contain but typically have at least one functional activating KIR (106) (**Figure 1**).

Natural Killer Cell Allorecognition in Pregnancy

In the context of NK cell allorecognition in the placenta, the mother will carry a specific set of KIR genes, having inherited a KIR haplotype from each of her parents, such that she may be homozygous for either KIR A or KIR B or may be heterozygous. If the mother has the A/A diplotype, she will have no activating KIRs; if she is A/B, she may have 1–5 activating KIRs; and if she is B/B, she may have 1–10 activating KIRs. The KIR proteins encoded by these haplotypes will come into contact with fetal HLA-C molecules expressed on the extravillous trophoblast cells, and the paternally derived HLA-C proteins may differ from those of the mother. HLA-C molecules are often classified into one of two groups, C1 or C2, depending on their amino acid sequence at position 80 of the α1 domain, which determines binding to different KIRs. HLA-C group C1 proteins carry an asparagine at this residue, while C2 proteins have a lysine. C1 proteins can bind to KIR2DL2 and KIR2DL3, leading to weak inhibitory signaling, and C2 proteins can bind either to KIR2DL1, leading to strong inhibitory signaling, or to KIR2DS1, which is an activating receptor (**Figure 1**). Thus, only a specific subset of the KIRs encoded by the different KIR haplotypes are relevant to uterine NK cell and extravillous trophoblast interactions (83).

KIR expression on NK cells depends on the KIR haplotype, gene copy number, allelic variation, epigenetic regulation, and infection. At any point in time, an individual NK cell can express no, one, or multiple different KIR genes, and this expression is monoallelic (83). KIR expression occurs relatively late in the development of NK cells, driven by IL-15, which in the uterus is produced by stromal cells as a response to progesterone. As uterine NK cells develop from progenitor cells found in the uterus rather than the periphery, their KIR repertoire is likely to be shaped by signals present in their local milieu that are derived not only from the uterine stromal cells but also from the extravillous trophoblasts and infiltrating maternal immune cells (74). Consistent with this, the decidual NK cell population in the first trimester has a higher proportion of NK cells expressing KIRs that can bind to HLA-C when compared with the peripheral NK cells and with uterine NK cells derived from the endometrium of nonpregnant women (75). This finding also suggests that HLA-C expression on the extravillous trophoblasts might contribute to uterine NK cell education.

Natural Killer Cell Education

NK cell education describes the balancing of NK cell effector function based on sensitivity to inhibitory signals from self HLA class I molecules, and several models for the education process have been proposed. In the arming model, signaling by inhibitory receptors potentiates NK cell function, and mutations that disrupt ITIMs render NK cells hyporesponsive. In the disarming model, NK cells become hyporesponsive if they are exposed to chronic activating stimuli in the absence of inhibitory signals. The rheostat model suggests a more quantitative scenario whereby the net strength of inhibitory signals modulates the degree of NK cell responsiveness. Lastly, the confining model proposes that NK cell activation depends on inhibitory and activating receptor compartmentalization at the cell surface and on cell adhesion (43). In addition, the demonstrated

variation in cell surface HLA-C allotype expression levels may further fine-tune NK responsiveness (6, 57, 117), and HLA-C expression on NK cells themselves, which is intricately regulated by mechanisms such as splicing, has recently been implicated in NK cell education as well (14, 68). This indicates that NK cell education is a highly regulated process, and the relative relevance of the potentially implicated mechanisms may display interindividual and perhaps even intraindividual variation.

KIR–HLA-C Interactions in Pregnancy-Related Complications

With respect to how NK cell education may relate to KIR–HLA-C interactions relevant in pregnancy, comparisons of different maternal KIR haplotypes and fetal *HLA-C* genotypes indicate that the combination of certain inhibitory KIRs and paternally derived HLA-C allotypes can increase the risk of a range of pregnancy-related disorders, including recurrent spontaneous abortion, pre-eclampsia, and fetal growth restriction. Genetic analyses using case–control cohorts of European ancestry have revealed that risk is associated with maternal KIR A haplotype homozygosity, but only when the fetus has more C2 genes than the mother (44–47). An intriguing question is whether this simply reflects a C2 dosage effect or is specifically due to deleterious allorecognition of the paternally derived C2 allotype. An analysis of pregnancies with a single fetal C2 genotype that could be distinguished as being paternally or maternally inherited provided suggestive evidence for the latter scenario (46). Conversely, there is a decreased risk of pregnancy disorders related to defective placentation and an increase in birth weight in mothers carrying the KIR B haplotype in the presence of the paternally derived C2 (44–47). A postulated explanation for these findings is that the strong inhibitory interaction between paternal C2 allotypes and KIR2DL1, whose gene is located in the centromeric region of both the KIR A and KIR B haplotypes, leads to suboptimal activation of decidual NK cells, promoting poor trophoblast invasion. This effect can be counteracted by C2 protein binding to an activating KIR receptor, found on the KIR B but not the KIR A haplotype, thereby shifting the balance toward decidual NK cell activation, more pronounced trophoblast invasion, and increased spiral artery remodeling. KIR2DS1 was originally suggested to be the activating receptor in question, as its gene is found in the telomeric region of the KIR B haplotype and is absent from KIR A (46), although genetic analysis of an African case–control cohort implicates *KIR2DS5* instead, and functional alleles of the activating *KIR2DS4* gene may also contribute to successful pregnancy (58).

The degree of linkage disequilibrium in the KIR cluster, the level of polymorphism, the different signaling strengths of different KIR genes, and the need to consider KIR gene and *HLA-C* allele combinations complicate genetic analyses aiming to definitively pinpoint the genetic determinants that drive KIR–HLA-C interaction-dependent differences in NK cell education and pregnancy-related phenotypes. Implementation of improved statistical models, such as the quantitative maternal–fetal genotype test, which is a linear mixed-effect model (22), may facilitate progress when applied to large-scale data sets, as may methods for statistically imputing KIR copy number from SNP genotype (131). The combination of genetic and functional analyses may provide added benefits. A strategy for analyzing KIR2DL1 allotypes encoded by the different KIR haplotypes has employed a panel of anti-KIR antibodies in combination with genotyping to show that *KIR2DL1* on the KIR A but not the KIR B haplotype is associated with increased risk of pre-eclampsia (52). A method for quantifying individual KIR gene transcript expression has also recently been developed using full-length transcript Smart-seq2 data (129). Further progress in dissecting the effects of specific KIR–HLA-C interactions may be made by the generation and use of appropriate humanized transgenic mouse models (14, 126).

NON–NATURAL KILLER IMMUNE CELLS IN PREGNANCY

Tolerance at the Maternal–Fetal Interface

In addition to NK cells, T cells are the other main cell type with a capacity for allorecognition and are the next most abundant lymphocyte population in the decidua, increasing in relative abundance throughout the course of gestation (122). Decidual T cells are heterogeneous and include $CD4^+$ and $CD8^+$ effector T cells, $CD4^+$ $CD25^{++}$ $FOXP3^+$ regulatory T cells (Tregs), $CD4^-$ $CD8^-$ $\alpha\beta$ T cells, and $\gamma\delta$ T cells. Given that extravillous trophoblasts do not express HLA-A, HLA-B, or HLA class II molecules, direct allorecognition could occur only through the interaction between HLA-C and infiltrating $CD8^+$ T cells. $CD8^+$ T cells are the most abundant T cell type in the decidua during pregnancy, and they display an antigen-experienced, effector, or effector memory phenotype, although this phenotype is characterized by a lower perforin and granzyme B expression relative to that typically observed in effector cells in the periphery (123). This suggests that an antigen-specific $CD8^+$ T cell response occurs in the decidua, as also indicated by the clonal expansion that has been observed in this cell population through the use of single-cell transcriptomic profiling (129). The antigens that can drive such expansion are unknown but could include mismatched paternally derived HLA-C molecules or other polymorphic non-HLA fetal antigens. However, murine studies have shown that the presence of maternal $CD8^+$ T cells that are alloreactive for fetal MHC does not compromise pregnancy (28).

Several mechanisms may explain why direct allorecognition of mismatched HLA-C or other fetal antigens does not typically contribute to pregnancy failure. Once implantation occurs, facilitated by the inflammation that enables the required immune cell filtration and activation, pregnancy becomes increasingly characterized by a local anti-inflammatory tissue milieu. If proinflammatory signaling occurs instead—for instance, due to bacterial, viral, or parasitic infection—then this signaling can promote a range of pregnancy-related complications and neonatal health problems (86). During the anti-inflammatory phase of pregnancy, decidual $CD8^+$ T cells express PD1, and its ligand PD-L1 is expressed by extravillous trophoblast cells (129), implying that T cell activation is inhibited. Consistent with this, blocking of PD-L1 in pregnant mice leads to a fetal resorption rate of over 80%. Trophoblast cells also express other inhibitory molecules, including tumor necrosis factor (TNF)–related apoptosis-inducing ligand (TRAIL) and indoleamine 2,3-dioxygenase (IDO) (48, 101), and IDO deficiency in pregnant women has been associated with pre-eclampsia (64).

In addition to the inhibitory function of trophoblast cells, T cell activation is suppressed by the action of Tregs that are induced due to the action of, for example, decidual NK cells and macrophages (109). These Tregs persist in the mother after birth and can quickly accumulate in subsequent pregnancies, demonstrating that they have a memory phenotype (112). Both infertility and spontaneous abortion have been linked to Treg dysfunction, emphasizing the necessity of their action (17), as has the altered ratio of Tregs relative to $CD4^+$ T helper 17 (Th17) cells (113). Because Th17 cells produce proinflammatory cytokines, their exact relevance in the uterus is unclear, although some role in combating infection and thereby preventing pathogens from crossing the maternal–fetal interface has been hypothesized. Notably, the importance of preventing transplacental infection of the fetus has been highlighted by the recent Zika virus epidemic and its association with microcephaly (32).

The modulation of decidual DCs during pregnancy is also thought to contribute to T cell tolerance, and this is particularly critical because decidual DCs express maternal HLA-A, HLA-B, and HLA-C allotypes and are thus capable of antigen presentation to T cells. A murine study has demonstrated that decidualization ultimately promotes a loss of DC density in the tissue, likely reducing antigen presentation to the infiltrating T cells. Decidual DCs are stimulated by thymic

stromal lymphopoietin produced by trophoblasts to express TGF-β, which can in turn induce Treg polarization (27). DC emigration from the decidua to the draining lymph nodes is inhibited such that indirect allorecognition is limited, especially during the first half of the gestational period. Therefore, fetal antigens presented by lymph node DCs arrive there by passive transfer, a process that leads to impaired T cell priming and induction of tolerogenesis (23).

Pregnancy and the Peripheral Immune System: Longitudinal Profiling

In the periphery, myeloid DC profiling during human pregnancy demonstrates that these cells have an increased level of tolerogenic surface proteins such as PD-L1 and CD200 in the first trimester compared with the third, and the DCs show reduced signaling in response to lipopolysaccharide stimulation (3). Such longitudinal immunoprofiling analyses of peripheral blood from pregnant women have also demonstrated a reduction in T and B cell frequencies and an increase in STAT5-mediated signaling, which may be triggered during pregnancy by higher circulating cytokines such as IL-2 and/or hormones such as prolactin (3). As IL-2 is required for Treg development, this STAT5 signaling signature may relate at least partly to the Treg expansion observed throughout pregnancy (**Figure 2**). Additional cytokines have also been implicated, including TGF-β, IL-4, and IL-10, which are produced by anti-inflammatory $Tim3^+$ peripheral NK cells (70). Murine research has shown that, particularly in early pregnancy, there is a systemic expansion of Tregs specific for paternal antigens (112). In humans, T cells specific for antigens encoded on the Y chromosome have been detected in approximately half of women pregnant with a male fetus, and the Tregs specific for these antigens can mediate suppression via CTLA-4 (127).

A Proinflammatory Environment for Parturition

Upon the completion of fetal development, triggers such as damage-associated molecular patterns (e.g., HMGB1) (103) promote conversion to a proinflammatory, Th1-like local milieu required for labor and delivery (**Figure 2**). Resumed immune cell infiltration into the myometrium promotes uterine contractions, delivery, and finally the separation of the placenta. Infiltrates include innate cells such as neutrophils and mast cells, which have the capacity to produce factors that degrade the extracellular matrix of fetal membranes and stimulate contraction of the cervix. However, because the numbers of these cells rise further following parturition, they may be more important in mediating repair of the uterine tissue (13). During spontaneous labor at term, decidual $CD4^+$ effector T cells express matrix metalloproteinase 9, IL-1β, and TNF (35), and T cells become preferentially localized at the rupture zone of the fetal membranes. By contrast, the suppressive activity of local Tregs is diminished in both term and preterm labor (114).

Therefore, the dynamic changes that occur to the immune system—both at the maternal–fetal interface and systemically—are complex, involving the orchestration of multiple immune cell types and signals from the mother and the fetus. These changes are necessary for successful pregnancy and must thus be carefully modulated. Given this finely tuned modulation, a fundamental question has been what key factors can perturb this balance and promote the development of pregnancy-related complications.

GENOME-WIDE ASSOCIATION AND GENE EXPRESSION ANALYSES FOR PREGNANCY-RELATED COMPLICATIONS

Apart from the established role of specific KIR haplotypes and *HLA-C* allele groups and the associations with nonclassical HLA class I gene region variants, studies have investigated the

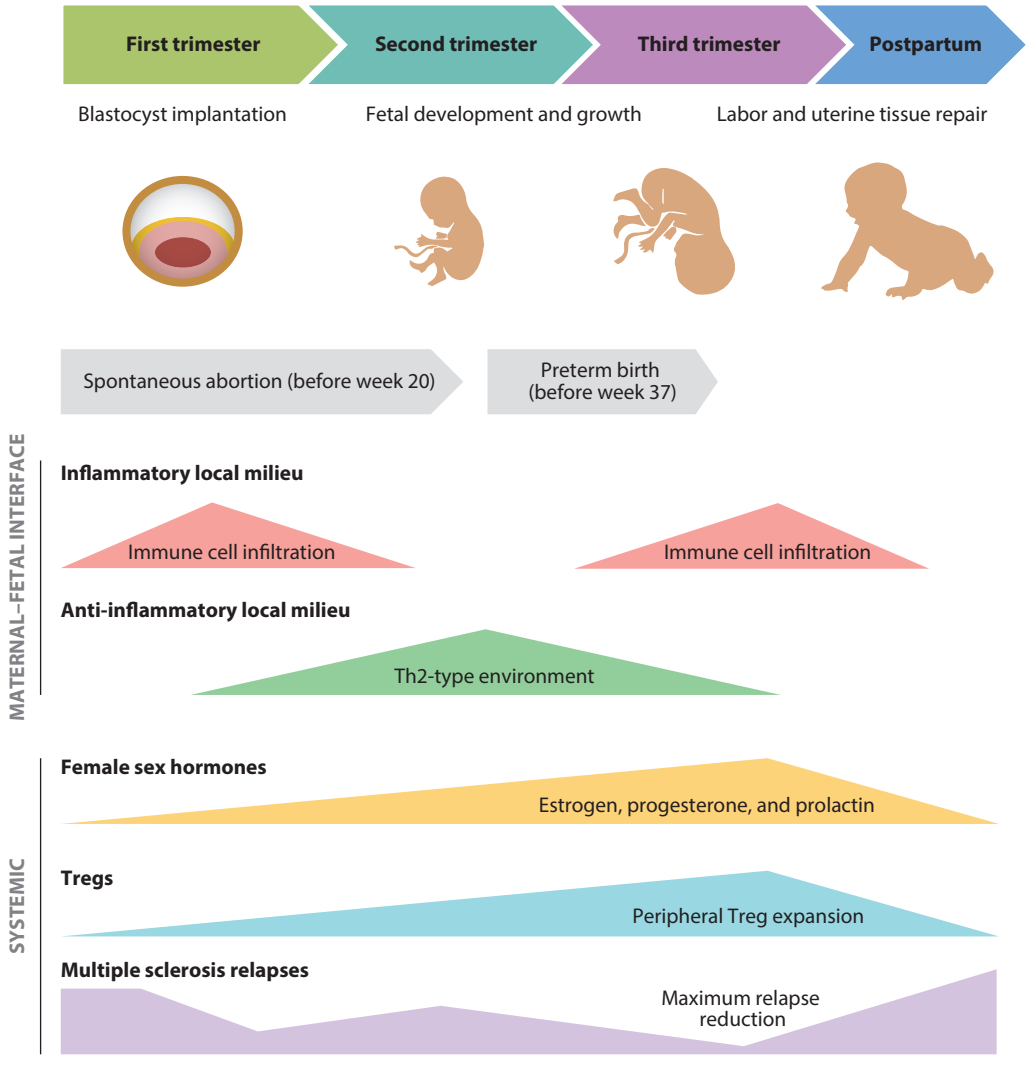

Figure 2

Key events and processes during gestation, labor, and delivery. Blastocyst implantation and placentation in the first trimester coincide with immune cell infiltration into the uterus and an inflammatory local milieu, which are necessary for these processes to occur appropriately as the uterine tissue undergoes remodeling. Defective remodeling can lead to pregnancy-related complications, such as spontaneous abortion and preterm birth. As the fetus develops and grows, the uterine environment shifts to an anti-inflammatory state, promoting tolerance for the fetus. Immune cell infiltration resumes in the third trimester to facilitate labor, placenta detachment, and uterine tissue repair. Systemically, gestation is accompanied by increasing levels of female sex hormones and changes in the peripheral immune system, including regulatory T cell (Treg) expansion. These changes can modulate the activity of autoimmune diseases such as multiple sclerosis.

involvement of other loci across the genome in determining the risk for recurrent spontaneous abortion, pre-eclampsia, fetal growth restriction, preterm labor, and birth weight extremes. Given the pleiotropic role of the immune system during pregnancy, it has been hypothesized that non-HLA and non-KIR associated loci would include candidate immune genes, but it is intuitive that genetic variants influencing cell proliferation, differentiation, migration and adhesion,

extracellular matrix remodeling, angiogenesis, coagulation, and metabolism are also likely to be associated with pregnancy-related complications.

Recurrent Spontaneous Abortion

Recurrent spontaneous abortion occurs in approximately 1% of fertile couples, although different countries vary in the minimum number of such abortions occurring before the 20th gestational week that are required for a clinical diagnosis (two in the United States and three in the United Kingdom, for example) (100). In approximately half of cases, the cause of recurrent spontaneous abortion is unknown, but a genetic component has been postulated given the higher sibling recurrence risk for cases compared with controls (61). This has led to testing of, for example, the contributions of X chromosome inactivation, sperm DNA fragmentation, and DNA methylation, but no reproducible evidence has been found for the involvement of any of these processes. Candidate gene studies and genome-wide association studies (GWASs) have also produced results that are often inconsistent, potentially due to variable case–control cohort sizes, differences in diagnostic definition, and differences in reproductive history. For instance, recurrent spontaneous abortion is considered primary if no successful pregnancies have occurred, secondary if a series of miscarriages have taken place after a live birth, or tertiary if there have been three nonconsecutive miscarriages. Taking such variables into account, a recent review and meta-analysis of more than 400 genetic association studies in idiopathic recurrent spontaneous abortion suggested that associated loci have only modest effect sizes and may include immune candidates genes, such as *IFNG*, *IL10*, and *TNF* in addition to KIR genes; coagulation genes, such as *F2* and *F5*; genes involved in angiogenesis, such as *VEGFA* and *NOS3*; and metabolism genes, such as *MTHFR* (100).

In the other half of recurrent spontaneous abortion cases, which are nonidiopathic, the disorder can be attributed to one of three main recognized causes: (*a*) obstetric antiphospholipid syndrome (APS), which is an autoimmune condition that promotes thrombosis and is also implicated in intrauterine death, pre-eclampsia, and fetal growth restriction; (*b*) anomalies of the uterine anatomy; and (*c*) maternal or fetal chromosome abnormalities (100). The antibodies implicated in obstetric APS are lupus anticoagulant, anticardiolipin antibodies, and/or anti-β2-glycoprotein I antibodies. As many as 40% of systemic lupus erythematosus (SLE) patients have been found to have APS as a complication. A small-scale GWAS for obstetric APS has provided some evidence for associations of SNPs at the *C1D* and *TSHR* loci (119), both of which are involved in thyroid function. The risk allele of the rs2288493 SNP at the latter locus correlates with reduced expression of thyroid-stimulating hormone receptor, as indicated in the Genotype-Tissue Expression (GTEx) database (119). Notably, thyroid function is normally enhanced during pregnancy due to human chorionic gonadotropin and hyperestrogenemia, and hypothyroidism and the presence of thyroid autoantibodies are related to infertility, pregnancy loss, and preterm labor (121).

Pre-Eclampsia

As with recurrent spontaneous abortion, non-HLA and non-KIR genetic risk factors for pre-eclampsia have been relatively inconsistently reported across different studies, likely due to small sample sizes and population differences. Pre-eclampsia occurs in 3–5% of pregnancies and is diagnosed on the basis of de novo hypertension after the 20th gestational week, proteinuria, and maternal organ dysfunction affecting the kidneys, liver, nervous system, blood, or placenta. In developing countries, pre-eclampsia is one of the leading causes of maternal, fetal, and neonatal morbidity and mortality and may also increase the risk for cardiovascular disease development

later in life (85). Genetic predisposition to the condition has been suggested due to its familial clustering. A meta-analysis of more than 500 genetic association studies has provided more robust evidence for a handful of associations at loci such as the negative immunological regulator gene *CTLA4*; the lipoprotein lipase gene *LPL*; the *ACE* gene, which acts in the renin–angiotensin system; the coagulation genes *F2* and *F5*; and *SERPINE1*, which functions in fibrinolysis (18). In addition to genetic variants altering risk for pre-eclampsia in mothers, a study analyzing 4,380 cases and 310,238 controls identified variants in the fetal genome proximal to the *FLT1* gene as being associated with pre-eclampsia, particularly in pregnancies where pre-eclampsia developed late during gestation and when the offspring birth weight was above the 10th percentile. *FLT1* encodes Fms-like tyrosine kinase 1, and a soluble placental isoform of this protein has been described to promote endothelial dysfunction, hypertension, and proteinuria in pre-eclampsia (77).

As a parallel approach to investigating the pathophysiological pathways involved in pre-eclampsia, numerous studies have performed transcriptomic profiling of placental and decidual tissues from cases and controls. A genome-wide transcriptome-directed pathway analysis of potential pre-eclampsia candidate susceptibility genes suggested that, based on their expression in decidua basalis samples, these candidates can be organized around key genes acting as regulatory hubs, including the immune genes *IFNG*, *IL6*, and *TGFB1*; the fibrinolysis gene *SERPINE1*; the angiotensinogen-encoding gene *AGT*; the angiogenic factor gene *VEGFA*; and the inhibin gene *INHBA* (133). These hub genes act on a range of downstream genes, including those producing the IL-10 and TNF cytokines, insulin, nitric oxide synthase, FLT1, and matrix metalloproteinases. A meta-analysis of differentially expressed genes in pre-eclamptic placentas found that some 40 genes, including *FLT1*, *INHBA*, *VEGFA*, and *F5*, may contribute to the transcriptional signature for pre-eclampsia (60). An analysis focusing on differential expression of imprinted genes has also implicated the transcription factors GATA3 and DLX5, with the latter having some effect on trophoblast cell proliferation, growth, and metabolism (134). Collectively, the genetic association and gene expression studies implicate immunological, coagulatory, angiogenic, and metabolic pathways in the development of pre-eclampsia.

Fetal Growth Restriction

Pre-eclampsia and other hypertensive disorders, such as diabetes-related vasculopathy, contribute to fetal growth restriction, which arises when the fetus does not fulfill its intrauterine growth and developmental potential due to compromised placental function. Fetal growth restriction is generally defined as a statistical deviation from fetal size below a particular percentile—often the 10th—for a given population. In addition to hypertensive disorders, other causes of fetal growth restriction include multiple gestation pregnancies; nutritional disorders; autoimmune conditions, including obstetric APS; thrombophilia; anemia; smoking; drug use; viral and parasitic infections; and fetal chromosomal abnormalities (92). Consequently, large-scale analyses for the genetic components of fetal growth restriction have been complicated by the underlying heterogeneity in the etiology of the condition. However, rare fetal variants, such as mutations in the *IGF1R* gene (which encodes the insulin-like growth factor 1 receptor) and the *SHOX* transcription factor gene (which is involved in bone development), are associated with fetal growth restriction (20), and maternal variants in the *F2* and *F5* coagulation genes, in *TNF*, and in the superoxide dismutase gene *SOD3* have been implicated as well (116). Continued research into genetic and other factors that contribute to fetal growth restriction is necessary, as it affects approximately 5–10% of pregnancies, is a common cause of fetal and neonatal mortality, and is the most common cause of intrapartum asphyxia and preterm birth.

Preterm Birth

The largest GWAS of preterm birth performed to date used a discovery set of samples from 43,568 women of European ancestry and a replication set of 8,642 Nordic samples; gestational duration was considered to be a continuous trait with a dichotomous outcome of preterm (before the 37th gestational week) or term birth (135). Preterm birth can affect as many as 10% of pregnancies and is the leading cause of death of children under five years of age (72). The GWAS found six loci robustly associated with gestational duration: *WNT4*, *ADCY5*, *RAP2C*, *EBF1*, *EEFSEC*, and *AGTR2*, the latter three of which are specifically associated with the risk of preterm birth. Variants at the *WNT4*, *ADCY5*, and *EBF1* loci have previously been associated with birth weight (49), although only the association signal at the *EBF1* locus is the same as that for preterm birth, with the rs7729301 allele that correlates with reduced birth weight also being associated with a shorter duration of gestation. *EBF1* encodes early B cell factor 1, which is required for normal B cell development but is also implicated in cardiovascular and metabolic traits. *EEFSEC* encodes selenocysteine tRNA-specific eukaryotic elongation factor, which has a role in cellular homeostasis and modulation of inflammation, and *AGTR2* encodes angiotensin II receptor type 2, which regulates the uteroplacental circulation and may be involved in pre-eclampsia as well (135).

Birth Weight

Birth weight is influenced by both maternal and fetal genetic factors, and very low or high birth weights at the extremes of the population distribution are correlated with both neonatal and later-life morbidity and mortality. As for the pregnancy-related complications, KIR–HLA-C interactions are central to the immunogenetics of birth weight (22), but GWASs have revealed a plethora of other associated loci. A GWAS meta-analysis of genetic variation in 153,781 individuals identified 60 loci at which fetal genotype is associated with birth weight; notably, the majority of these loci are thought to be implicated in metabolism, growth, and development (49). More recently, a GWAS of offspring birth weight in 86,577 women identified loci whose impact is likely due to effects on the intrauterine environment rather than to allelic sharing with the fetus, and which likely modulate maternal metabolism, blood pressure, and immune function (8).

Large-scale, systematic efforts to investigate the genetics of the breadth of pregnancy-related phenotypes are required to identify statistically robust, replicable associations that may help to better elucidate the underlying pathophysiology of pregnancy complications and neonatal health. Substantial challenges include the need to carefully consider known nongenetic causes when selecting or stratifying cases, the need to investigate the impact of both maternal and fetal genetics and their interactions and to potentially control for any dominant effects, and the need to dissect truly causal relationships given that many of the pregnancy-related complications are interconnected.

PREGNANCY AND AUTOIMMUNE DISEASE

Although autoimmune diseases like APS can increase the risk of pregnancy-related complications or reduce the likelihood of conception, the impact that pregnancy has on the maternal immune system—not only at the maternal–fetal interface but also systemically—can reciprocally affect ongoing autoimmune disease in pregnant patients. In MS, pregnancy correlates with a reduced annual relapse rate, especially in the third trimester of gestation (**Figure 2**), even though MS patients do not typically receive immunomodulatory therapy for a period before and during gestation. This amelioration of disease ceases soon after delivery, with the relapse rate rising sharply

in the first trimester postpartum and eventually returning to the prepregnancy rate thereafter (24). Rheumatoid arthritis (RA) patients also tend to experience an improvement in their disease during pregnancy, but this is not necessarily the case for other autoimmune rheumatic disorders: Pregnancy might have no effect or might even worsen disease activity in some SLE patients, and exacerbation during gestation has also been reported for Sjögren syndrome (96). The exact mechanisms by which pregnancy alters autoimmune disease have not been definitively elucidated and may vary in different diseases.

Sexual Dimorphism in Autoimmune Disease and Implications for the Impact of Pregnancy

The fact that pregnancy can affect disease activity in patients with autoimmune conditions may be a result of the sexual dimorphism in these conditions, which may itself reflect sex-specific selection pressures affecting the immune system, such as those related to reproduction in females (50, 91). The precise drivers of sexual dimorphism in autoimmune disease are not well characterized but could relate to, for example, the expression and action of sex hormones or the influence on non-hormone-encoding genes on the X or Y chromosomes, such as X-linked variants in immune gene regions associated with SLE (10), potentially in conjunction with the effects of X chromosome inactivation in females (50, 71). However, there does not seem to be a straightforward relationship between the ratio of affected females to males for any given autoimmune disease and the impact of pregnancy on the disease. The neutral or detrimental effect of pregnancy on SLE and Sjögren syndrome might appear to be consistent with the high female preponderance of these diseases, as they both have a female-to-male ratio of 9:1, but in Hashimoto's thyroiditis, this ratio is 10:1, and yet pregnancy ameliorates disease activity. For RA and MS, the female-to-male ratio is approximately 3:1, while for ankylosing spondylitis, where pregnancy-related benefits have also been indicated, the ratio is 1:2 (102). Thus, the influence of pregnancy likely needs to be considered in the context of the precise immunological dysregulation and resulting organ damage occurring in specific autoimmune conditions.

Female Sex-Hormone-Mediated Immunomodulation

Gestation is accompanied by a rise in the levels of multiple hormones, including estrogen and progesterone (**Figure 2**), which have complex immunomodulatory functions, many of which may promote suppression of autoimmune disease during pregnancy. Consistent with this, the levels of these hormones are highest during the third trimester—which, for example, coincides with the period of greatest reduction of relapses in MS.

At the molecular and cellular levels, the hormones upregulated during pregnancy can act on several pathways and cell types. In a mouse model of MS, experimental autoimmune encephalomyelitis, estrone administration ameliorates disease and results in myeloid DCs that show reduced expression of the Th1 cell–inducing proinflammatory cytokine IL-12 and increased production of both IL-10 and TGF-β (98). High progesterone levels also reduce IL-12 production by murine myeloid DCs (55) and by macrophages, in which TNF and reactive oxygen species production is similarly suppressed (79). While diminished IL-12 would lead to less induction of Th1 cells that contribute to the pathology of many autoimmune conditions, female sex hormones can also have direct effects on T cells. For example, progesterone binding to its receptor on Th1 and Th17 cells can suppress interferon gamma (IFNγ) and IL-17 production, respectively (51, 67), and progesterone signaling in naive $CD4^+$ T cells increases FOXP3 expression, enabling the suppressing capacity of Tregs (66).

These effects on DCs, macrophages, and T cells do not explain why pregnancy has opposing effects on different autoimmune diseases. However, in vitro studies suggest discrepancies in the potential downstream impact of specific sex hormones. For example, estrogen can increase levels of the transcriptional repressor CREM, which can inhibit IL-2 expression, which in turn might have a detrimental impact on Tregs, but estrogen can also increase expression of the IL-2 inducer calcineurin (88, 110). The capacity for a sex hormone to have opposing effects on a given immunological pathway might suggest that prepregnancy cellular activation states in different types of patient—and thus the context in which the hormone is acting during pregnancy—could ultimately determine whether an increased hormone level would ameliorate or worsen specific autoimmune conditions. As another example, while IFNβ is administered to MS patients therapeutically, chronic type I IFN pathway activation is known to drive pathology in SLE. Estrogen has the capacity to increase IFNα production by plasmacytoid DCs, which can in turn lead to estrogen receptor upregulation, thereby enhancing hormone-induced signaling (97). There is also some evidence that risk alleles at several loci in the type I IFN pathway are enriched in male compared with female SLE patients, perhaps implying that an increased genetic risk is observed in males given a reduced contribution of female sex hormones (41).

In addition to an impact on IFNα, estrogen can have variable effects on B cells, which are involved in multiple autoimmune diseases but play a particularly prominent pathological role in SLE. One postulated B cell–specific mechanism by which a pregnancy-associated rise in estrogen might worsen SLE is by skewing antibody class switching to pathogenic immunoglobulin G (IgG) autoantibody subclasses, as observed in mouse models of SLE (19). However, autoantibodies also contribute to disease in RA, suggesting that an alternative mechanism may be implicated for the pregnancy-dependent amelioration observed for this condition. This mechanism may be the altered glycosylation of autoantibodies observed in pregnant RA patients, which reduces the capacity of these antibodies to bind Fc receptors and complement, and which may be hormonally regulated (12, 50).

Despite the many molecular and cellular pathways by which female sex hormones might affect autoimmune diseases during pregnancy, their relative importance in mediating pregnancy-related differences in the pathology of these diseases might also vary. For example, the relevance of estrogen in pregnant SLE patients is consistent with estrogen-containing contraceptives increasing the risk of the condition and with hormone replacement therapy promoting disease flares (50). In RA, by contrast, estrogen may not be prominently involved in ameliorating the disease during pregnancy given that oral contraceptives and hormone replacement therapy do not influence the disease (56, 132), indicating that unidentified factors may be the primary mediators of the effect of pregnancy on RA. Determining the impact of female sex hormones during pregnancy on autoimmunity; dissecting specific, opposing, or synergistic effects of different hormones; and elucidating their relative importance are ongoing challenges but may be aided by systematic investigations of their influence on individual immune cell subsets in vitro, transgenic studies in vivo, and detailed longitudinal profiling analyses.

Longitudinal Immunoprofiling and Antigen-Specific Modulation of Autoimmune Disease During Pregnancy

Efforts to characterize the pregnancy-related molecular and cellular changes that occur in autoimmune disease patients, regardless of their underlying causes, have included longitudinal analyses of peripheral blood samples collected in each trimester, and in some instances before and/or after pregnancy as well. For RA, a transcriptional profiling study of whole blood found that, in addition to longitudinal changes in neutrophil-related genes such as *OLFM4*, *MMP8*, and *CEACAM8*

observed in both cases and controls, several genes showed changes predominantly in the RA patients, such as *HLA-DRB3*, *G0S2*, *IFI27*, and *TNNI2*. The relevance of these latter changes in pregnancy-dependent amelioration of RA is indicated by the prior implication of these genes in anti-TNF therapy responsiveness and/or RA progression (81).

In MS, a similar study using peripheral blood mononuclear cells found that the levels of 347 transcripts were altered in nonpregnant patients compared with healthy controls. Seven of these genes were particularly affected during pregnancy, suggesting their potential involvement in pregnancy-dependent relapse reduction. These genes are all implicated in inflammatory responses and include *SOCS2*, *NR4A2*, *CXCR4*, *POLR2J*, *FAM49B*, *STAG3L1*, and *TNFAIP3*, the last of which is also a candidate MS risk gene based on GWAS associations (9, 34). The expression level of these genes in pregnant patients was closest to that observed in controls in the third-trimester samples, and there was a delay in skewing toward these levels in patients who experienced relapses during pregnancy. Postpartum, the expression of these genes in the MS patients returned to the levels observed before pregnancy (34).

Further dissection of longitudinal gene expression changes occurring before, during, and after pregnancy in autoimmune disease patients relative to controls would be aided by in-depth profiling of more specific immune cell subsets, as opposed to whole blood or peripheral mononuclear blood cells, potentially in conjunction with T and B cell receptor profiling, to assess clonal-specific changes. An intriguing notion with respect to how pregnancy worsens or ameliorates different autoimmune diseases is that, in addition to general effects on the systemic immune system, antigen-specific modulation may occur (99). For example, in a murine model of arthritis, exposure to an arthritis-associated antigen during allogeneic pregnancy was necessary for Tregs to confer a protective effect when transferred to nonpregnant recipients, suggesting a role for antigen-specific effects (89). Whether soluble fetal antigens or fetal microchimerism can have any impact on autoantigen-specific responses has yet to be definitely determined, but whatever the precise mechanism of action, pregnancy-dependent effects on antigen-specific responses are likely to be transient, given that autoimmune disease activity typically returns to the observed prepregnancy state by the second postpartum trimester. Thus, from a putative therapeutic perspective, harnessing an understanding of how pregnancy-related changes in autoantigen-specific responses occur also requires considering how such changes can be maintained in the long term. Notably, aside from any impact on maternal alloreactivity, fetal cell seeding in maternal tissues might in some cases help to specifically compensate for the autoimmune disease-driven loss of functional maternal cells, as has been observed in murine diabetes models, where fetal-derived acinar cells replace defective islet cells (59, 120).

Pregnancy and the Risk of Autoimmune Disease Development

Apart from affecting women with ongoing autoimmune disease, pregnancy can also alter the risk of de novo autoimmune disease development. Nulliparity is a risk factor for the development of SLE and RA (56, 125), and the risk for several autoimmune conditions decreases with an increasing number of prior pregnancies (40, 104). Therefore, although pregnancy-related modes of autoimmune disease suppression seem to be only transient in patients, pregnancy may confer a long-term, almost vaccine-like protection against the development of certain autoimmune diseases (40). However, for autoimmune conditions such as the autoimmune thyroid diseases and scleroderma, pregnancy may instead instigate their development. One mechanism hypothesized to contribute to this is fetal microchimerism. For example, fetal microchimeric cells are significantly increased in the peripheral blood of scleroderma patients compared with controls, and the numbers of fetal cells are increased in women who are HLA matched with their offspring

(65). These results suggest that such cells can drive maternal allogeneic responses and, if retained, might help drive autoimmunity through the presentation of fetal alloantigens. By this model, fetal microchimeric cells may induce alloreactive responses, causing a pathology that might not be clinically distinguishable from true autoimmunity.

Apart from a role for fetal microchimerism in triggering autoimmune or autoimmune-like disease, a putative tolerogenic effect has also been postulated, although there is no experimental evidence for which mechanism of action might prevail in a given individual and how this might relate to the differential impact of pregnancy on the risk for developing different conditions. Similarly, a possible discrepant role has been described for the impact of maternal microchimerism on autoimmune disease in the offspring. Once thought to be completely immature, the functional capacity of the fetal/neonatal immune system is being increasingly appreciated, ranging from the presence of viral or parasite antigen-specific T cells in neonates born to infected mothers to the recent finding that alloreactive fetal T cells can promote uterine contractility in preterm labor through the action of TNF and IFNγ (31). These findings suggest that maternal microchimerism could potentially elicit fetal or neonatal adaptive immune alloresponsiveness. Consistent with this, increased numbers of maternal microchimeric cells have been reported in scleroderma, type 1 diabetes, and juvenile dermatomyositis patients, for example (93). Protective effects of maternal microchimerism have yet to be formally demonstrated but conceivably might occur by influencing tolerogenesis or by seeding offspring tissues and thereby compensating for loss of functional cells driven by autoimmune disease, or even indirectly by enhancing antipathogen defense against viruses that can promote risk for autoimmune disease development (124).

CONCLUSION

Pregnancy is increasingly emerging as a highly dynamic but also highly regulated process characterized by immunological plasticity and complex interactions between the maternal and fetal genomes both at the maternal–fetal interface and systemically. Intricate KIR–HLA interactions occur between maternal NK cells and fetal extravillous trophoblasts in the decidua and are key not only for maintaining tolerance to the fetus but also for active tissue-remodeling events that occur during implantation and placentation. Given the many other immune and nonimmune cell types involved in these processes, genetic variants at multiple non-KIR and non-HLA loci in both the mother and the fetus that influence immune, cardiovascular, and metabolic pathways are also involved in determining a successful pregnancy outcome. If any of these pathways are perturbed via the impact of genetic variation or environmental factors, then pregnancy-related complications can arise.

The systemic effect of pregnancy on the immune system is evidenced by changes in peripheral immune cell frequencies and signatures, which are substantial enough to alter disease activity in women with ongoing autoimmune conditions. Moreover, pregnancy can also influence the risk of both maternal and fetal autoimmune disease development. However, these effects are not mediated through a generalized immunosuppression, as pregnancy can have opposing effects on the activity and development of different autoimmune conditions, suggesting that the impact of pregnancy may be modulated in a context-dependent manner and may be partly antigen specific.

Larger-scale analytical and functional investigations of the genetic and genomic contributions to the full range of pregnancy-related complications and to the pregnancy-related modulation of autoimmune disease are still required to better understand the molecular and cellular mechanisms underpinning these pathologies, how they interact with environmental factors, and how they might even be modulated therapeutically. This is particularly important because nonfatal perinatal complications, including those arising from emerging infectious threats, and changes in

the risk of developing autoimmune conditions have serious, lifelong consequences for the health of both the mother and the offspring.

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