71 The maternal immune system during pregnancy

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INTRODUCTION

The effects of pregnancy on the immune system are intriguing and clinically recognizable. A viral pharyngitis in pregnancy may persist for weeks on end while fulminate vulvar condyloma may suddenly regress in the postpartum period. At first glance, these changes seem to defy logic. Why does multiple sclerosis improve in pregnancy (1), while an active lupus flare is fueled? (2). Why does ankylosing spondylitis worsen (3), yet rheumatoid arthritis improves (4)?

Deepening the mystery is the remarkable coexistence of the fetus—a semi-allograft recognized by the maternal immune system—living freely within the maternal host without rejection. This phenomenon first caught the attention of Nobel laureate Sir Peter Medawar over 50 years ago, prompting him to advance his now-famous four nonexclusive postulates about maternal–fetal tolerance: (i) the fetus may not be immunogenic, (ii) the uterus may be immunoprivileged, (iii) the placenta may be an immunologic barrier, and (iv) the mother may be immunosuppressed (5). From the time that Medawar first enunciated these postulates, rapid advances in maternal–fetal immunology have evolved, giving great hope for an approaching era of practical clinical application.

The immune system is an exceptionally complex and elegant network of cells, cytokines, chemokines, antibodies, and regulatory proteins. Because of this complexity, it is useful to artificially partition the immune system to facilitate study and dialog. The broadest categories have been classically described as the immune system's innate and adaptive arms. The cellular constituents of these arms are summarized in Table 1.

THE INNATE ARM OF THE IMMUNE SYSTEM

The innate arm of the immune system is the first line of defense and includes (i) epithelial cells, (ii) macrophages, (iii) neutrophils, (iv) natural killer (NK) cells, and (v) complement. Innate sentinel cells include epithelial cells and macrophages that sample the local environment and rapidly respond when pathogens are detected. Neutrophils and NK cells are the primary effector cells of the innate immune system. Eosinophils and basophils play an important role in allergic and parasitic infections and will not be discussed in detail in this chapter. Serum complement does just that—"complement" immune processes by weakening or marking pathogens for destruction.

Epithelia

The epithelial barrier to the environment provides the first line of defense against the intrusion of pathogens. Some epithelia, such as endometrium, possess the ability to synthesize and secrete cytokines, and to process and present antigens to adaptive immune cells, driving proliferation of autologous

lymphocytes (6). Endometrial epithelial cells possess special pattern recognition receptors (PRRs) called Toll-like receptors (TLRs) that recognize "pathogen-associated molecular patterns" (PAMPs) (7). Different TLRs recognize various PAMPs, and their expression is highly tissue specific. TLRs are found in epithelial urogenital tissues, professional antigen-presenting cells (such as macrophages and dendritic cells), and trophoblast-derived tissues such as placenta and amnion (8).

Complement

Complement is a collection of serum proteins that bind pathogens, leading to immediate destruction, opsonization, or chemotaxis. Once activated, factors remain bound to the pathogen (i.e., factor C3b) or released locally for neutrophil chemotaxis (i.e., factor C3a). Complement is activated through multiple mechanisms resulting in the formation of a "C3 convertase" (Fig. 1): (i) it is activated by antibodies present on pathogens through factor C1q (the "classical" pathway); (ii) it binds directly to the pathogen through factor C3b (the "alternative" pathway), or (iii) it is activated by the terminal mannose of bacterial N-acetyl glucosamine through mannose-binding protein (the "lectin" pathway). The presence of C3b then opsonizes organisms for phagocytosis by neutrophils and macrophages. In some cases, such as with *Neisseria* sp., complement also forms a multicomponent membrane attack complex (MAC) that leads to direct perforation and lysis of the organism (9,10).

Maternal complement levels in pregnancy are similar or greater than those of nonpregnant controls (11). Because of the potential of activation of complement by maternal antibodies toward paternal antigens, the trophoblast must have a mechanism in place to inhibit this process. At least three important complement regulatory proteins are expressed by the trophoblast as early as 6 weeks of gestation: decay-accelerating factor (DAF, CD55) (12), membrane cofactor protein (MCP, CD46), and CD59.

DAF inhibits formation and accelerates decay of C3/C5 convertase, which inhibits the alternative pathway. MCP is an intrinsic-acting protein that binds efficiently to C3b attached to other molecules on the cell surface (13). MCP then cleaves the C3b or C4b components of complement to their inactive derivatives, which inhibits the classical complement pathway. Finally, CD59 inhibits the final common component of both complement pathways—the MAC. CD59 is expressed in greater amounts than either DAF or MCP, although the absence of CD59 is compatible with successful pregnancy, indicating that MCP and DAF are able to compensate for a lack of CD59.

Expression of all three proteins occurs on the terminally differentiated syncytiotrophoblast that is in direct contact with maternal blood. Villous cytotrophoblast cells express CD59

Table 1 Commonly Encountered Cytokines		
Cytokine	Origin	Function
IL-1β	Epithelium, macrophages, neutrophils	Stimulates T- and B-lymphocytes; makes B-cells responsive to IL-5 and T-cells responsive to IL-2
IL-2	T-cells	Autocrine stimulation of T-cells
IL-4	T-cells (Th ₂)	Differentiation of naive T-helper cells into Th ₂ cells
IL-5	T-cells (Th ₂)	Stimulates B-cell growth and increases immunoglobulin secretion
IL-6	Epithelium, macrophages, T-cells	Stimulates acute phase response; differentiation of B-cells (IgG1 antibody) and T-cells (cytotoxic and Th ₁₇ types)
IL-10	Activated T-cells and monocytes	Downregulates function of Th ₁ and Th ₂ cells
IL-12	Macrophages and dendritic cells	Induces synthesis of IFNγ, IL-2, and TNF by Th ₁ cells; reduces synthesis of IL-4, IL-5, and IL-10 by Th ₂ cells
IL-13	T-cells (Th ₂)	Induces IgG4 and IgE isotype switching in human B-cells
IL-17A	T-cells (Th ₁₇)	Induces epithelia and macrophages to produce IL-6, IL-8, TNF, and TGFβ
TGFβ	T-cells (Treg)	Inhibits activation of lymphocytes and monocytes, promotes differentiation of Treg cells and Th ₁ cells, causes IgA isotype switching
IFNγ	T-cells (Th ₁), NK cells	Increases MHC class I expression, promotes Th ₁ differentiation, stimulates NK cells
TNF	Epithelium, macrophages, T-cells	Stimulates acute-phase inflammatory response, is neutrophil chemoattractant, is synergistic with IL-6 and IL-1β
Chemokine		
IL-8 (CXCL8)	Epithelium, endothelia, macrophages	Attracts neutrophils
RANTES (CCL5)	Epithelium, T-lymphocytes	Attracts T-cells, eosinophils, basophils
MCP-1 (CCL2)	Macrophages, monocytes, endothelium	Attracts monocytes/macrophages

Figure 1 Complement pathways. All three pathways result in the formation of C3 convertase, which catalyzes C3 to split into C3b (binds pathogens) and C3a (chemotactic for neutrophils). Through the *classical pathway*, component C1q binds to antibodies on the bacterial cell surface, catalyzing C4b and C2 to combine into C3 convertase. Through the *lectin pathway*, mannose-binding lectin (MB lectin) binds mannose on the bacterial surface, catalyzing C4b and C2 to combine into C3 convertase. Through the *alternative pathway*, free factor C3b combines with factor B and factor D to form a C3 convertase.

Table 2 Cells of the Innate and Adaptive Arms of the Immune System

Innate immune system	
Epithelium	Initial barrier to pathogens; present antigen; contain PRRs
Macrophages	Immune sentinel; kill pathogens; present antigen; contain PRRs
Neutrophils	Immune foot soldiers; kill opsonized pathogens
NK cells	Cytotoxic; kills infected cells in similar manner to cytotoxic T-cell
B-1 cells	Hybrid innate/adaptive B-cells; produce poly-reactive antibodies
$\gamma\delta$ T-cells	Hybrid innate/adaptive T-cells; T-cell receptors act like PRRs
Adaptive immune system	
Cytotoxic T-cell	Cytotoxic lymphocyte; directly kills infected cells
T-helper (Th) cells	Cytokine-secreting lymphocytes; direct immune processes
Th ₁	Promotes inflammation; produces IFN γ and IL-2
Th ₂	Promotes antibody responses; produces IL-4, IL-5, and IL-13
Treg	Suppresses inflammation; produces IL-10 and TGF β
Th ₁₇	Promotes inflammation; produces IL-17; recruits neutrophils
B-cell	Antibody-secreting lymphocyte; directed by Th ₂ cells
Dendritic cell	Professional antigen-presenting cell; programs T-lymphocytes

Abbreviations: PRR, pattern recognition receptors; NK, natural killer.

but are largely devoid of MCP and DAF after 8 weeks of gestation. Proliferation of this population to generate invasive cytotrophoblast cell columns is associated with continued expression of CD59 and an increased expression of DAF and MCP (14,15). MCP is also expressed on the preimplantation embryo (16).

Cytokines

Cytokines are intracellular messengers of the immune response, triggering receptors on immune cells and local tissues that lead to downstream events such as cell differentiation, activation, and cytokine secretion. Chemokines—derived from the words *chemotactic cytokines*—are cytokines that play a primary role in chemotaxis. They summon specific immune cell populations into a tissue to engage a pathogenic threat. Cytokines form the communication network for the immune system and are produced and utilized by cells in both arms. A list of commonly encountered cytokines, their cell of origin, and their common function is listed in Table 2.

Macrophages

Macrophages are innate sentinel cells that function as effector cells against certain pathogens. As an innate sentinel, the macrophage detects pathogens using surface receptors such as the mannose receptor, scavenger receptors (which bind many charged ligands), TLRs, and CD14, a TLR-4 co-receptor that recognizes bacterial lipopolysaccharide (LPS). Once activated, macrophages generate large cytoplasmic granules containing oxygen free radicals, antimicrobial peptides, and lysozyme that destroy phagocytized pathogens. They also secrete many important index cytokines and chemokines, such as interleukin (IL)-6, TNF, and IL-8.

The recognition of molecular patterns by sentinel cells should not be confused with antigen-initiated adaptive immune processes. The activation of the innate immune system does not directly lead to the development of immunologic memory. Activated sentinel cells release cytokines and chemokines. These cytokines and chemokines primarily recruit and activate innate effector cells, but they may also influence the process of antigen presentation to initiate adaptive processes (17).

Macrophages increase rapidly in number during early pregnancy, then remain relatively stable throughout gestation, representing 20% to 25% of CD45+ leukocytes and 10% of total decidual cells at the implantation site (18,19). Villous macrophages have been demonstrated to secrete substances that promote the development of multinucleated syncytia from cytotrophoblast cells, which subsequently secrete human placental lactogen and human chorionic gonadotropin (hCG) (20).

Uterine macrophages are capable of presenting alloantigen and have a suppressive effect on mixed lymphocyte reactions and may contribute to protection of the fetus against immunologic rejection (21,22). This may be at least in part due to expression of indoleamine 2,3-dioxygenase (IDO), which is suggested to have an immunosuppressive role in pregnancy. They exhibit lower IL-1 expression when compared with their peripheral counterparts, are capable of inducing interferon (IFN)- γ expression by NK cells, and secrete IL-10 (23,24).

Uterine macrophages may also regulate the population of uterine NK (uNK) cells, influencing differentiation and activation status through the production of IL-15, which is secreted by uterine macrophages isolated from both early and term gestations (24,25).

Neutrophils

Innate effector cells include neutrophils, which are of myelocytic lineage. Neutrophils are hailed by activated macrophages using chemokines such as IL-8 or indirectly by a population of “helper” T-cells through IL-17 secretion (26). Once neutrophils arrive, they rely on antibody binding and/or complement activation on the pathogen surface to direct chemotaxis and bind and phagocytose pathogens. Antibodies produced by B-lymphocytes tag (opsonize) pathogens for destruction. Neutrophils then use CD16, the Fc antibody receptor, to adhere to the opsonized pathogen.

The number of leukocytes in the peripheral blood increases during pregnancy, primarily due to an absolute increase in neutrophils (27). Peripheral neutrophils exhibit decreased lobularity index and myeloperoxidase activity at midgestation of normal pregnancy, suggesting a relative immaturity of the population as numbers increase (28).

Both neutrophils (29,30) and monocytes (31) display reduced chemotaxis, adherence, reactive oxygen metabolite release, phagocytosis, and microbial killing in pregnant compared with nonpregnant women. In seeming contradiction to this, neutrophils in pregnancy circulate in a chronically active state. Although pregnancy neutrophils cannot be fully activated for oxidant production (29), their basal rate of unstimulated oxidant production is the same as that of LPS-treated nonpregnancy neutrophils (30). Thus, while the maximum potential for activation of resting pregnancy neutrophils is suppressed, they circulate in a baseline-activated state.

Neutrophils have also been implicated in the process of cervical ripening and parturition (32,33). Chemotaxis to the cervix and lower uterine segment are actively promoted by myometrial and cervical factors, chiefly by liberation of IL-8 and expression of cell adhesion molecules (34,35). The resulting infiltration of neutrophils leads to a release of local inflammatory cytokines (36,37) and proteolytic enzymes (38) that ripen the cervix and initiate parturition.

NK Cells

Innate effector cells include NK cells, which are of lymphocytic lineage. In contrast to other lymphocytes, NK cells do not possess the CD3 complex or clonally expand in response to antigen stimulation. NK cells do possess many activating and inhibitory receptors of two major structural classes, those of the immunoglobulin superfamily [killer immunoglobulin-like receptors (KIRs) and LIRs] and of the C-type lectin-like family

(Ly49, NKG2D, and CD94/NKG2) (39). These receptors recognize cell surface molecules, such as major histocompatibility complex (MHC)-1 glycoproteins and their structural relatives. The balance between activating and inhibiting signals determines the behavior of the NK cell. If the balance favors activation, the NK cell kills the target cell in much the same way as a cytotoxic T-lymphocyte, by forming an immunologic synapse, perforating the target cell membrane, and infusing granzyme into the cell, which initiates apoptosis of the target cell.

NK cell populations undergo marked changes in pregnancy and can be divided into two distinct subsets (Fig. 2). The majority (90%) have low-density expression of CD56 (CD56 dim) and express high levels of CD16, the immunoglobulin receptor that is responsible for antibody-dependent cellular cytotoxicity. These are considered “peripheral” NK cells. The rest of NK cells (10%), so-called uterine NK cells or large granular lymphocytes, have high-density expression of CD56 (CD56 bright) with low levels of CD16 (CD16 (-)) (40).

Peripheral NK cells are notably decreased in number in the decidua during normal pregnancy (41). Classic circulating CD57+/CD16+ NK cells have a 25% to 30% decrease in cytotoxicity during normal pregnancy (42–48). The decrease can be measured not only by decreases in cytotoxicity assays but also by a decrease in the expression of activation markers CD69, CD25, CD71, and HLA-DR (49). Though baseline cytotoxicity is lower, these peripheral NK cells are able to respond to infection with similar efficacy to nonpregnant controls (50).

Figure 2 Differences between the CD56 dim peripheral NK cell and the CD56 bright uterine NK cell. The CD56 dim peripheral NK cell retains its cytotoxic ability through expression of CD16, a receptor that binds to the antibody heavy chain. By contrast, fewer than 15% of uterine NK cells express this receptor. Uterine NK cells are also highly granulated and produce more cytokines than their peripheral counterparts, suggesting a regulatory function.

Interestingly, peripheral NK cells maintain a nonpregnant phenotype during anembryonic gestations, ectopic pregnancies, and recurrent spontaneous abortions, all of which have been associated with increased NK activity (42,51,52). Thus, classic NK appear to have a differing phenotype in normal versus abnormal pregnancies and could serve as potential effector cells during the elimination of abnormal pregnancy.

uNK cells with the phenotype CD56 bright/CD57-/CD16- are actively recruited to the endometrium and decidua during the late secretory phase of menstruation and early normal pregnancy (53–56) and remain in the decidua if implantation is successful (57). These cells comprise 70% to 80% of decidual leukocytes, but less than 1% of peripheral blood leukocytes, existing side by side at the trophoblast margin with macrophages (20% of leukocytes) and CD3+ T-cells (10% of leukocytes) (58,59). uNK cells possess the receptor for IL-15, which serves to activate them and promote their survival by increasing their expression of *bcl-2* (60–63). IL-15 is expressed predominantly by the perivascular stromal cells surrounding spiral arteries during the mid to late secretory phase of the menstrual cycle and in early pregnancy (64).

uNK cells are considered to be poorly cytotoxic, yet potent cytokine producers, in contrast to classic NK cells that display higher levels of cytotoxicity but are poor cytokine producers. A small fraction of uNK cells (10–15%) contain surface CD16 detectable by flow cytometry (65). CD16 is an antibody receptor, and only CD16+ cells exhibit cytotoxicity, and thus most uNK cells lack cytotoxic capability (66). All uNK cells remain at the implantation site in high numbers during early gestation, decrease after 20 weeks of gestation, and are practically absent in term decidua (67–69).

uNK cells are found in association with extravillous trophoblast in the placental bed (70). It has been suspected by some investigators that interactions between uNK cells and invading endovascular or perivascular trophoblast might promote spiral artery remodeling during human pregnancy. This suspicion is based on the close proximity of these uNK cells with spiral arteries and bolstered by placentation data from murine studies (71). However, in the human, trophoblast invasion along spiral arteries extends deeply into the inner myometrium, where uNK cells do not reside (72), and murine evidence that uNK cell production of IFN γ promotes vascular remodeling remains to be established in the human (73). Thus, the role of uNK cells in the establishment of human hemochorial placentation is unclear.

ADAPTIVE ARM OF THE IMMUNE SYSTEM

The adaptive arm is the immune system's "intelligent" response to specific pathogens. This response is antigen dependent, occurring over weeks rather than minutes as in the innate response. The advantage of this more slowly evolving process is that it has time to "learn" through experience, developing a highly specialized, targeted response to specific antigens that results in the development of immunologic memory. The adaptive immune system consists of antigen-presenting cells, antibody-producing B-lymphocytes, "cytotoxic" CD8+ T-lymphocytes, and a variety of "helper" CD4+ T-lymphocytes. The primary factors determining the developmental fate of naive T- and B-lymphocytes include the type of antigen-presenting cell

and the assortment of cytokines present in the local microenvironment. Cytokines that direct the specific adaptive response are primarily (but not exclusively) produced by T-helper (Th) lymphocytes and referred to as "Th" cytokines.

A core assortment of T-helper cells have been identified based on their cytokine secretion profiles, each "Th" type serving a different immunologic function. The four most commonly described types of T-helper cells are the Th₁, Th₂, Treg, and Th₁₇ lymphocytes (Table 1).

Th₁ lymphocytes promote cytotoxic cellular and antibody-mediated responses through secretion of the Th₁ cytokine IFN γ . IFN γ activates effector cells such as "cytotoxic" T-lymphocytes, NK cells, and macrophages. It also promotes the production of dendritic cell IL-12, which in turn stimulates Th₁ cells to auto-produce IFN γ , reinforcing the phenotype. IFN γ inhibits the Th₂ phenotype by downregulating IL-4 production. IFN γ upregulates MHC class I antigen on target cell surfaces and activates CD8+ cytotoxic T-cells and NK cells, the sum of which promotes the recognition and clearance of intracellular pathogens.

Th₂ lymphocytes promote humoral responses by B-cells through secretion of Th₂ cytokines such as IL-4 and IL-5. These humoral responses result in the development of antibodies that target humoral factors for removal rather than cells for destruction. The presence of other local cytokines promotes antibody isotype switching. For example, IL-13 promotes switching to the IgE antibody class, TGF β promotes switching to the IgA class, and the Th₁ cytokine IFN γ promotes switching to the IgG class.

Regulatory T-lymphocytes (Tregs) have been one of the more recently characterized helper-T-cell subsets. These cells are identified by the presence of a nuclear transcription factor called Forkhead box P3 (FoxP3) and characterized by their suppressive effect on effector T-cells, in part due to secretion of cytokines IL-10 and TGF β . IL-10 antagonizes Th₁ cells and macrophages, while TGF β is a potent suppressor of all other Th responses (Th₁/Th₂/Th₁₇) in the human. Tregs secrete TGF β and/or IL-10 in response to specific antigen and are believed to be an important resident of the maternal–fetal interface necessary for suppressing any adaptive immune responses against the fetus.

Th₁₇ lymphocytes are the most recently characterized class of T-helper cells. Th₁₇ cells secrete cytokines including IL-17A, important for recruiting neutrophils to sites of inflammation, which makes them appear to function similarly to Th₁ cells. Both IFN γ and IL-4 have been shown to negatively regulate Th₁₇ differentiation, while the presence of TGF β and IL-6 together appear to promote this differentiation. Th₁₇ cells appear to play an important role in autoimmune diseases, but if they play a role in inflammatory states during pregnancy, such as preterm labor and pre-eclampsia, this has not yet been defined.

T-Helper (Th) Shift in Pregnancy

Pregnancy has classically been described as having a "Th₂ shift" (74,75). In general terms, the systemic maternal immune response is noted to shift from a cytotoxic (Th₁) to a humoral (Th₂) T-helper paradigm of function. In light of evolving knowledge of T-helper-cell subsets, the Th₁/Th₂ balance paradigm has been recognized as an oversimplification (76,77).

It has become clear that additional regulatory mechanisms play an important role, including those mediated by the regulatory T-cell (Treg). As potent suppressors of inflammation, Tregs appear to be important for the maintenance of normal pregnancy (78).

If the shifting of immune cell subsets to a regulatory phenotype contributes to fetal protection, this may aid in our understanding of the observed maternal tolerance acquired against paternal antigens (79,80). Innate processes also appear to promote local blunting of the adaptive immune system at the maternal fetal interface, including such factors as depletion of tryptophan at the maternal-fetal interface by IDO (81), and the expression of nonclassical placental MHC antigens such as HLA-G. It has been suggested that HLA-G might be an important determinant in the development of Tregs (82,83,84).

Peripheral T-Cells

Pregnancy is accompanied by several unique changes in peripheral and decidual T-cells. Peripheral T-cells demonstrate decreased proliferative responses in serum from pregnant women, detected as a decreased T-cell response to mitogens (85). This may be due to a general state of suppression during pregnancy, as evidenced by a decrease in memory CD4⁺ T-cells and an increase in naive CD4⁺ T-cells, decreased expression of activation markers HLA-DR and CD25, and a decrease in precytotoxic CD8⁺/S6F1⁺ cells with a concomitant increase in regulatory CD8⁺/S6F1⁺-cells (86).

Peripheral blood CD4⁺/CD25⁺ lymphocytes, the putative regulatory T-cell subset, are increased during the first and second trimesters (87).

Uterine T-Cells

Uterine T-cell changes are unique. T-cells comprise only about 10% of decidual lymphocytes (88,89) and decrease in decidua by >60% during pregnancy. This is due primarily to a decrease in CD8⁺ T-cells thereby increasing the CD4⁺/CD8⁺ ratio (90). Of the CD8⁺ T-cells in the decidua only a few express perforin, a suppressive phenotype among CD8⁺ T-cells (91).

Uterine decidual T-cells have been reported to express multiple KIRs including both inhibitory and activating types. When both are expressed in a single T-cell, the inhibitory receptor has been suggested to be preferentially active and may contribute a level of immunosuppression (92).

Uterine decidual T-cells have been characterized as expressing CD25, a chief phenotypic characteristic shared by activated lymphocytes and Treg cells (93,94). Up to 14% of uterine T-cells in the decidua possess a classic Treg phenotype (87). There is evidence for local expansion of decidual Treg cells and a low occurrence of Th₁₇ cells in normal first-trimester decidua (95,96). Furthermore, local moderate Th₁ activity is reported, evidenced by a population of IFN γ -secreting T-cells. Local IFN γ could serve the important purpose of upregulating MHC class II proteins on decidual stromal cells. Decidual stromal cells express ligands (B7-H1 and B7-DC) for the programmed death (PD)-1 receptor, which may play a crucial role by decreasing decidual T-helper cell production of IFN γ , TNF, and IL-2 (97).

During normal and anembryonic pregnancy, but not ectopic pregnancy, CD71 and CD25 increase, signifying

activation of T-cells in response to successful implantation. The response may be augmented by the trophoblast production of IL-2, which, because of the lack of change in ectopic pregnancy, is probably decidua dependent (98,99). Further evidence that T-cells are specifically involved with implantation and placental proliferation is derived from experiments with monoclonal antibodies against CD4 and CD8, which stimulates or inhibits placental proliferation, respectively (100).

$\gamma\delta$ T-Cells

$\gamma\delta$ T-cells are an interesting intermediate cell type that appear to have both innate and adaptive function. They rearrange T-cell receptor (TCR) genes to produce diversity and can develop a memory phenotype. However, various subsets contain a restricted TCR that appears to be used as a PRR (101). These cells recognize not only nonclassical MHC class I molecules (102) but also heat shock proteins, soluble antigen, and carbohydrates (103).

$\gamma\delta$ T-cells appear in the first-trimester decidua (104,105) and increase in the peripheral blood during pregnancy (106). They are also present in second-trimester placental villi (107). $\gamma\delta$ T-cells increase 2.4-fold in the decidua compared with peripheral blood, which is indicative of selective migration (105), and are twice as common as all other T-cells there (108), although the specific mechanism for their selection is unknown.

The specific function of $\gamma\delta$ T-cells is not clearly known. Because of their population kinetics and location, several roles have been proposed. They may protect the mother and fetus from infection, trophoblast from rejection, or limit passage of fetal leukocytes to the maternal circulation (105).

B-Cells

Maternal serum has been found to inhibit priming of B-cells in vitro via a molecule in the IgG fraction of serum, which reduces IL-2 receptor density. This inhibitory action is even more pronounced with retroplacental serum suggesting that it may be concentrated at the maternofetal interface (109).

Peripheral B-cells in pregnancy exhibit decreased synthesis of IgM with increases in IgA and IgE. As IgA and IgE do not cross the placenta, these changes may be a protective mechanism for the fetus. The increase of IgE and IgA (with concomitant decrease in IgM) may be explained, at least in part, by an increase in CD23 (low-affinity IgE receptor) expression on B-cells, which serves as an autocrine growth factor for pre-activated B-cells and is enhanced in the presence of maternal IgG (109).

The importance of these changes is illustrated by the fact that B-cell antibody synthesis can be implicated in pregnancy complications and spontaneous abortions. Antitrophoblastic IgG and IgM, which were better able to fix complement and lyse target cells than in controls, have been demonstrated in significantly higher numbers in patients with recurrent spontaneous abortions (110). Antibodies against fetal endothelial cells have also been demonstrated in patients with recurrent spontaneous abortion (111).

Modulation of B-cells also occurs with regard to B-cell subsets. B-1 (CD5⁺) cells are downregulated during pregnancy while numbers of conventional B-cells (CD5⁻) remain constant. B-1 cells are the main producers of polyreactive

autoantibodies (112) and this antibody production can be enhanced in the presence of estrogen (in mice) (113). This downregulation may thus represent a protective mechanism for the fetus and the mother. During pregnancy, B-cells are generally either absent from or inactive in the uterus and decidua (114,115).

EFFECT OF PREGNANCY ON MATERNAL CELL-MEDIATED IMMUNITY

Cell-mediated immunity is promoted by IFN γ , is carried out by CD8 $^{+}$ T-lymphocytes and NK cells, and results in the programmed cell death (apoptosis) of the foreign cell or infected host cell. Decreased cell-mediated immune function in pregnancy is manifested by a tendency toward reactivation of chronic viral infections, such as cytomegalovirus (116), human papillomavirus (117), and herpes simplex virus (HSV) (118), and by an increased frequency in acquiring new viral infections (119). Circulating NK cells maintain their population size (120), and though they express a general decrease in cytotoxic activity (121–127), they can still respond appropriately to pathogens (128).

Pregnant women are more prone to contract HSV (129), have a longer course of infection (130), and suffer increased morbidity (131,132). Prior to polio vaccine, the risk of paralytic polio was increased in pregnancy (133). Malaria has been shown to have a prolonged course as well as increased morbidity and mortality during pregnancy (134). Varicella pneumonia has also been noted to occur almost exclusively in pregnant females or those otherwise immunosuppressed (135).

Impairment in cell-mediated immune function in pregnancy is associated with improvement in autoimmune diseases such as multiple sclerosis (136,137), rheumatoid arthritis (138), and psoriasis (139).

EFFECT OF PREGNANCY ON MATERNAL HUMORAL IMMUNITY

In contrast to cell-mediated immunity, humoral immunity, promoted by Th $_2$ cytokines such as IL-4 and IL-5, is preserved in pregnancy. Circulating B-cell numbers are unchanged (140,141). T-cell-independent B-cell functions remain intact as manifested by normal IgG stimulation with *Staphylococcus aureus* (142). There is an appropriate antibody response to vaccines (143). Serum complement concentrations remain normal or slightly elevated (11). T-helper cell activity is intact, evidenced by the maintenance of PPD positivity during normal pregnancy (144).

The shift favoring antibody production may help explain the persistence or worsening of immune-complex-mediated autoimmune disease in pregnancy. While the development of a de novo lupus flare during pregnancy may not frequently occur, exacerbation of existing lupus nephritis can be problematic. Grave's disease, seasonal allergies, myasthenia gravis, idiopathic thrombocytopenic purpura, and IgA nephropathy—antibody-dependent diseases—worsen.

The key difference between the pregnant and nonpregnant states is in the development and function of the maternal-placental-fetal unit. Trophoblast-immune cell interactions result in the differentiation of specialized subpopulations of lymphocytes. Moreover, peptide and steroid hormones generated by the placenta have demonstrable effects on immune cells.

INFLUENCE OF PLACENTAL HORMONES ON IMMUNITY

Placental hormones appear to play a role in immune function during pregnancy. The hCG can inhibit mitogen-induced T-cell and T-cell-dependent B-cell responses (145–149). These actions appear to be accomplished directly through T-cell hCG receptors (150), but further delineation of this mechanism is still the subject of ongoing investigation.

Pregnancy induces thymic cortical involution, possibly contributing a mechanistic explanation for altered T-cell function (151,152). The view that such involution represents a quiescence of the gland is in conflict with the data that the medullary portion of the gland actually appears to become more active (153). Murine thymic epithelial cells express the progesterone receptor, and this receptor is necessary for thymic involution to occur in pregnancy in mice (154).

Progesterone appears to be a very important immunoregulatory hormone of pregnancy, but the pathways by which it mediates its effect are still unclear. It is unlikely that specific progesterone receptors on lymphocytes and NK cells exist, as they have not yet been identified (155,156). However, decidual stromal cells have progesterone receptors, and a mechanistic link between these cells and various leukocytes has been suggested (157).

Despite lack of evidence of classic progesterone receptors in these cells, T-lymphocytes and decidual NK cells are reported to produce a peptide called progesterone-induced blocking factor (PIBF) in response to this hormone (158–160). PIBF has been reported to decrease activated lymphocyte production of IL-12 and TNF- α and cause a concomitant increase in IL-10 (161). PIBF is also reported to inhibit perforin liberation from the granules of stimulated NK cells (162), thereby limiting their cytotoxicity. The PIBF receptor has been characterized as joining with the IL-4 receptor α chain to form a novel type of IL-4 receptor (163).

Decreased levels of PIBF have been associated with recurrent spontaneous abortion (164), and monoclonal antibodies against PIBF have been demonstrated to cause decreased IL-10 levels with an associated immune-mediated resorption of pregnancies in mice (165).

Administration of the progesterone receptor antagonist RU486 has been reported to cause a decrease in the production of PIBF (166) and to be associated with at least a threefold increase in NK cytotoxicity (167,168).

TROPHOBLAST DEFENSE: ALTERED MHC EXPRESSION

An interesting mechanism of protection of the fetal allograft from maternal defenses appears to be the altered expression of MHC class I molecules by both syncytiotrophoblast and cytotrophoblast. All trophoblast cells are devoid of "classical" MHC class I molecules, except for the transient expression of HLA-C during early pregnancy. This inhibition of expression of HLA-A and HLA-B is apparently not affected by genomic imprinting, since both maternal and paternal alleles are inducible by IFN γ treatment in vitro (169).

In addition, there is an absence of expression of MHC class II antigens, which appears to be caused by hypermethylation of the IFN γ -responsive promoter that regulates expression of the class II transactivator (CIITA) gene. In vitro introduction of exogenous CIITA can induce cell surface expression of HLA-

DR, -DP, and -DQ, leading to an acquired capacity to present antigen to antigen-specific T-helper cells (170).

Once formation of the cytotrophoblastic shell is complete, the syncytiotrophoblasts and villous cytotrophoblasts remain free of classical MHC class I molecules and downregulate the expression of the nonclassical MHC class I molecules. The invasive cytotrophoblasts, on the other hand, provide the primary contact point for maternal blood and continue to express an assortment of nonclassical MHC class I antigens, which may be helpful in deterring a maternal immune response toward paternal antigens.

Nonclassical MHC molecules that are present throughout pregnancy include HLA-E and HLA-G. Like classical MHC antigens, these molecules appear to be involved in the abrogation of NK-cell-mediated lysis of trophoblast via interactions with inhibitory NK cell receptors (171–173).

Many studies have focused on HLA-G, first discovered in 1987 (174). It is an inhibitory nonclassical MHC class I molecule that is found on both invasive cytotrophoblastic and amniotic epithelial cells (175). Like the classical MHC class I molecules, it comprises an alpha chain associated with $\beta 2$ microglobulin. Unlike the classical MHC class I molecules, HLA-G contains limited polymorphism and a truncated cytoplasmic tail as a result of a stop codon in exon 5/6. It can appear in 6 isoforms: two soluble and four membrane bound.

The membrane-bound isoforms have been shown to inhibit NK cell migration and NK-mediated cell lysis through interactions with various lectin family and immunoglobulin-like receptors on NK cells and macrophages (176–178). HLA-G binds the CD94/NKG2A and p49 receptors, one or both of which are found on all NK cells isolated from maternal decidua during the first trimester (179). It may also bind the ILT2 and ILT4 (immunoglobulin-like transcript) inhibitory receptor on macrophages (180).

Soluble isoforms of HLA-G may serve an immunoregulatory role during pregnancy. Soluble HLA-G appears to induce apoptosis of CD8+ T-cells through the Fas/FasL pathways (181), and a low concentration is detectable in the serum of pregnant women throughout gestation. Although soluble HLA-G is present only in small amounts, it is more than twice as abundant in the serum of pregnant women as in nonpregnant and is likely in even greater concentration at the maternal-fetal interface (182).

HLA-E is not found on the cell surface unless HLA-G is also present. It is co-expressed with HLA-G due to a specific nonapeptide transcribed from the leader sequence of HLA-G, which serves as a ligand for HLA-E to induce its surface expression (183,184). HLA-E appears to have similar characteristics to HLA-G, for example, binding CD94/NKG2A (185,186).

HLA-G and HLA-E have both been demonstrated to influence cytokine production by decidual NK cells. Decidual NK cells cocultured with K-562 leukemia cells lacking classical and nonclassical MHC molecules expressed TNF-alpha, IL-10, and GM-CSF. When the K-562 cells were transfected with HLA-G, these concentrations of these three cytokines were significantly decreased in culture supernatants. When this same cell line was transfected with HLA-E, only IL-10 was significantly decreased (187).

HLA-C has been shown to exist only transiently on trophoblasts in the first trimester. It is recognized by KIRs (killer immunoglobulin-like or inhibitory receptors) on NK cells. Decidual NK cells have a higher expression of KIRs specific for HLA-C than do peripheral NKs. HLA-C is also upregulated in the presence of IFN γ , which may serve as a protective mechanism for trophoblastic cells (188). Expression of HLA-C apart from the pregnant state has been shown to be deleterious in some circumstances, as expression of HLA-Cw4 has been associated with poor prognosis in HIV infection and rapid development of AIDS, suggesting potential immunosuppressive functions (189).

Because of these functional differences from other “classical” MHC class I molecules, some investigators have suggested that, from a conceptual standpoint, HLA-C may be better grouped with the “nonclassical” MHC class I molecules (190).

TROPHOBLAST DEFENSE: OTHER MECHANISMS

In addition to the nonclassical MHC molecules, the trophoblast expresses other antigens that may counter maternal immunosurveillance. The Fas ligand (FasL) binds to Fas expressed on target cells and results in the initiation of the target cell apoptosis pathway. Trophoblast constitutively expresses the FasL, while decidual NK cells express Fas. IFN γ and TNF promote Fas expression and sensitivity, whereas IL-6 and IL-10 increase the resistance of trophoblast cells to Fas-mediated apoptosis (191).

RCAS1 (receptor-binding cancer antigen expressed on SiSo cells), a membrane-associated homodimer, has been recognized to play a role in immune evasion of the tumor cells in a manner similar to the FasL (192). Both RCAS1 and the FasL appear to be expressed concomitantly in uterine endometrial glands and extravillous cytotrophoblasts (193).

IDO is an enzyme that catabolizes tryptophan and is expressed by syncytiotrophoblast in mice (194). In the murine model, it is released by macrophages in response to IFN γ , inhibits T-cell proliferation, and is able to prevent T-cell-mediated rejection of normal pregnancies (194,195). IDO has also been demonstrated in human placental trophoblast cells and decidual macrophages, where its expression is stimulated by IFN γ (196,197). The expression of IDO by syncytiotrophoblast is a likely contributor to decreased serum levels of tryptophan found during pregnancy (198).

THE PLACENTAL SINK

The apical surface of the syncytiotrophoblast contains specialized Fc(γ) receptors (Fc γ R) (199,200). Significant transport of the four classes of maternal IgG begins around 20 weeks of gestation. The placenta may also serve as an immunosorbent tissue to protect the fetus from antibodies directed toward paternal antigens (201).

CONCLUSION

In conclusion, research over the past three decades has identified a host of changes in the maternal immune system and fetal tissues that promote the initiation and maintenance of normal pregnancy. It is daunting to think that what is now known is probably the tip of the iceberg. However, through further study, the immunology of the maternal-fetal interface may hold the secrets of successful and healthy pregnancy.

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