Immunity
Review

Interferons and Proinflammatory Cytokines in Pregnancy and Fetal Development

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Successful pregnancy requires carefully-coordinated communications between the mother and fetus. Immune cells and cytokine signaling pathways participate as mediators of these communications to promote healthy pregnancy. At the same time, certain infections or inflammatory conditions in pregnant mothers cause severe disease and have detrimental impacts on the developing fetus. In this review, we examine evidence for the role of maternal and fetal immune responses affecting pregnancy and fetal development, both under homeostasis and following infection. We discuss immune responses that are necessary to promote healthy pregnancy and those that lead to congenital disorders and pregnancy complications, with a particular emphasis on the role of interferons and cytokines. Understanding the contributions of the immune system in pregnancy and fetal development provides important insights into the pathogenesis underlying maternal and fetal diseases and sheds insights on possible targets for therapy.

Introduction

By the age of 5, approximately 8% of children are diagnosed with some form of birth defects (Moore et al., 2017b). Genetic abnormalities and environmental exposures such as smoking, alcohol, medications, and infections in utero are important causes of birth defects. However, the majority of birth defects (approximately 50%–60%) have no known genetic or environmental causes (Moore et al., 2017b). The rate of failed pregnancies and pregnancies with complications is also remarkably high. The early stages of pregnancy have the high rate of failure of approximately 30% (Wilcox et al., 1988). About half of early pregnancy loss is due to abnormal chromosome numbers caused by meiotic failure, but many have no clear explanations (Moore et al., 2017b). Intrauterine growth restriction (IUGR) and preterm birth, the leading causes of perinatal mortality, are found in nearly 10% of pregnancies, each (Nardozza et al., 2017; Purisch and Gyamfi-Bannerman, 2017).

The immune system evolved to protect the host against invading pathogens. Protection of the developing fetus is critical for the success of a species. In mammals, immune protection of the fetus must be carried out without harming the mother harboring the fetus. Conversely, mothers carrying a semiallogeneic fetus need to tolerate and prevent immune-mediated damage of the fetus while protecting against pathogens. Thus, pregnancy is accompanied by dynamic alterations in the maternal and fetal immune responses dependent on the stage of pregnancy or development—a topic covered by previous reviews (Kollmann et al., 2017; Pazos et al., 2012). For species that spend a long gestational period with each pregnancy, the quality of the fetus must be ensured for its survival and reproductive success. Yet, the checkpoint mechanisms for ensuring quality control for the developing fetus are not well understood.

In this review, we examine the role of the immune system in both promoting successful pregnancy and in mediating congenital disorders and complications. Signaling pathways engaged by cytokines have a powerful ability to rapidly remodel tissue and alter cellular behavior. For example, upon binding to their receptor, the interferons (IFNs) induce hundreds of effectors, or interferon stimulated genes (ISGs), that act to restrict viral infections (Sadler and Williams, 2008). There are three types of IFNs: type I IFNs (including IFN-α, β, ε, τ, and δ), type II IFN (IFN-γ), and type III IFNs (IFN-λ1, λ2 and λ3) (Sadler and Williams, 2008). These IFNs differ in both the cellular source and cellular targets based on receptor expressions (Schneider et al., 2014). Many of these IFNs are employed in normal pregnancy and development, as well as in defense against pathogens. Alterations or aberrant activation of immune responses during pregnancy can lead to pregnancy complications and congenital abnormalities. In this review, we put forth the hypothesis that aberrant expression of cytokines and IFNs is a common and critical mediator of congenital disorders and fetal loss that occurs in the settings of infections, chromosomal abnormalities, and metabolic and autoimmune diseases.

Pregnancy Complications during Implantation and Placental Development

All stages of pregnancy, from implantation to parturition (Figure 1), are susceptible to complications that result from fetal-intrinsic or extrinsic aberrations. Implantation and placental development are key vulnerability points during which pregnancy loss and complications arise. Implantation occurs at about day 8–9 in humans and day 4–5 after conception in mice. Just after hatching from the zona pellucida, the blastocyst, which is surrounded by a layer of trophoectoderm, adheres to the uterine epithelium (Aplin and Ruane, 2017) (Figure 1A). This

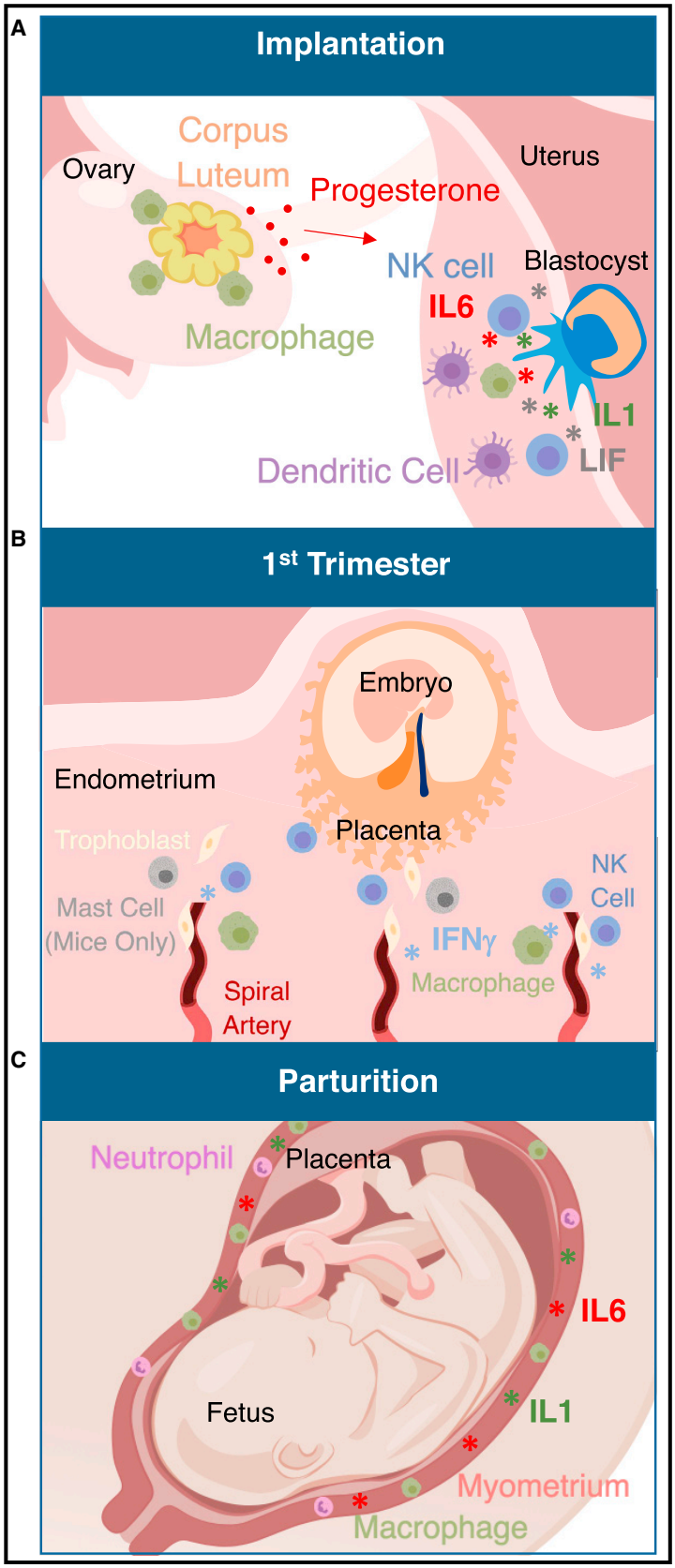

Figure 1. Immune Responses Necessary for Healthy Pregnancy

(A) The blastocyst attaches to and invades the maternal uterine endometrium. This process is accompanied by an evolutionarily conserved inflammatory response including IL-6, IL-1, and LIF. Key cell types necessary for early pregnancy, as demonstrated by mouse models, include dendritic cells, which are essential for decidualization, and macrophages, which are essential for maintenance of the corpus luteum in the ovary. NK cells directly surround the trophoblasts after implantation.

(B) During development of the placenta in the first trimester, immune cells including NK cells and mast cells are necessary for uterine spiral artery remodeling, as demonstrated by mouse models. The cytokine IFN-γ is also necessary for this process in mouse models.

(C) Parturition is mediated by an inflammatory response. Macrophages and neutrophils infiltrate the uterine myometrium. IL-1β is secreted and induces muscle contraction. IL-6 is necessary for on-time parturition in mouse models.

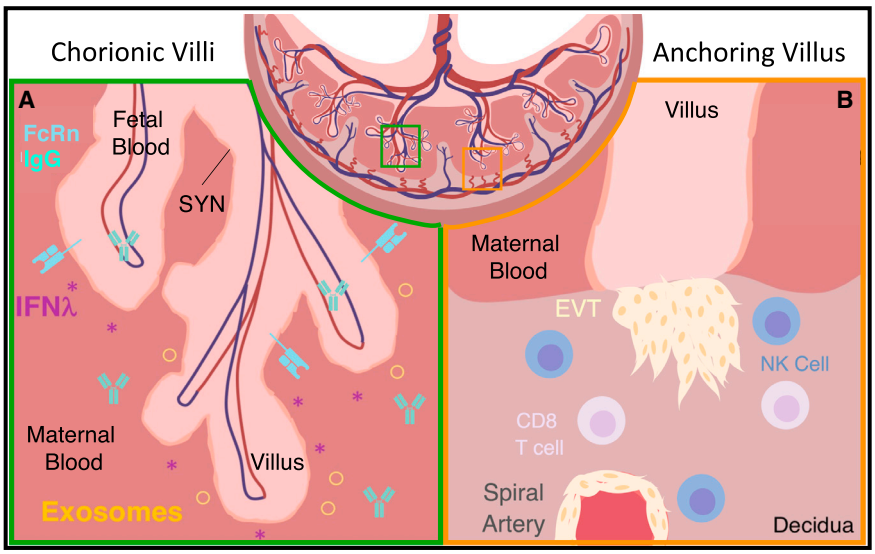

Figure 2. Antimicrobial Protective Mechanisms at the Placenta and Decidua

(A) At the chorionic villi and intervillous space, syncytiotrophoblasts (SYN) constitutively express IFNλ and exosomes, which confer resistance to viruses and other known TORCH pathogens to SYNs and neighboring cells. Maternal IgG is transferred to the fetus using FcRn receptors starting at 13 weeks of gestation in humans.

(B) At the anchoring villi and decidua, NK cells are capable of killing virus-infected cells and are located in close proximity to potential portals of viral entry. NK cells surround extravillous trophoblasts (EVTs) and spiral arteries. Pathogen-specific CD8 T cells are enriched in the human decidua. They have the potential to be cytotoxic upon ex-vivo stimulation.

initial attachment is followed by trophoblast differentiation and invasion of the endometrium. There are high rates of implantation failure, both after natural conception and with *in vitro* fertilization treatments (Aplin and Ruane, 2017), which may be due to genetic abnormalities and failure to hatch, and maternal factors, including endometrial abnormalities, immunological imbalance at the endometrium, and abnormal blood clotting (Simon and Laufer, 2012).

The first trimester is the critical period of placental development, and the origins of many common pregnancy complications can be traced back to abnormal placental development in the first trimester (Kroener et al., 2016). The two key processes of placental development are the villous and extravillous trophoblast formations. The chorionic villi are the site of gas and nutrient exchange between the maternal blood and fetal blood. This exchange occurs at the interface between fetal endothelial cells, which run through the core of the villi, and the maternal blood, in which the villi are bathed (Figure 2A). The villi are covered with a layer of multinucleated fused syncytiotrophoblasts (SYN), which directly contact the maternal blood. Abnormal villous development can lead to early pregnancy loss, IUGR, and preeclampsia (defined clinically as elevated blood pressure and proteinuria or other signs of organ damage including impaired liver function, renal insufficiency, cerebral/ visual symptoms, or thrombocytopenia) (Huppertz et al., 2014).

The fetal extravillous trophoblasts invade the decidua and uterine myometrium, infiltrating the uterine vessels and glands to direct nutrients to the developing fetus (Figure 2B) (Moser and Huppertz, 2017). At the spiral arteries, they remodel the smooth muscles and elastic fibers and ultimately replace the endothelium of the blood vessels (Tessier et al., 2015). By 10–12 weeks, maternal blood is directed to the villous space, whereby nutrient and gas exchange between the mother and fetus occurs. Insufficient maternal artery remodeling can lead to preeclampsia, IUGR, and recurrent pregnancy loss (Tessier et al., 2015). Conversely, excessive placental invasion is associated with maternal anemia and postpartum hemorrhage (Tantbirojn et al., 2008; Tessier et al., 2015). We will discuss how immune cells and immune effectors play an important role in in regulating the extravillous trophoblast invasion and how inflammatory insults such as infections can disrupt placental development.

Mechanisms That Protect the Embryo against Microbial Threats

Despite some of the devastating effects of certain congenital infections, which we will discuss later, most pathogens are not able to reach the fetus (Arora et al., 2017; Robbins and Bakardjiev, 2012). The placenta provides a powerful physical barrier that protects the fetus against infection by pathogens. The SYNs are multinucleated cells that make up the barrier between maternal and fetal blood in the placenta (Arora et al., 2017). Upon differentiation, SYNs become highly resistant to viral infections: they do not express the entry receptors for viral pathogens including herpes simplex virus (HSV) and cytomegalovirus (CMV), and they have a dense cytoskeleton network of actin that help them to physically resist invasion by bacterial such as *Listeria monocytogenes* (Robbins and Bakardjiev, 2012; Zeldovich et al., 2013). SYNs also constitutively produce exosomes and type III IFNs (IFN-λ), which confer antiviral resistance within themselves and in surrounding cells (Figure 2A) (Bayer et al., 2016; Delorme-Axford et al., 2013; Jagger et al., 2017). An alternative route by which pathogens may reach the fetus is from the uterus—infecting the extravillous trophoblasts and invading the anchoring villi (Tabata et al., 2016). Blocking this route of pathogen entry likely requires a different set of immunoprotective mechanisms. Effector-memory $CD8^+$ T cells are present in the human endometrium, and some of these are pathogen-specific (van Egmond et al., 2016). While they are generally less cytotoxic than their peripheral counterparts, decidual natural killer (NK) cells are capable of killing human cytomegalovirus (HCMV)-infected cells, and decidual $CD8^+$ T cells can degranulate and proliferate after *in vitro* activation (Figure 2B) (Siewiera et al., 2013; van der Zwan et al., 2018). The mechanisms by which some pathogens are able to reach the fetus despite these barriers are still poorly understood.

In addition to providing a barrier to infection, the maternal immune response may provide further protection at the fetus.

Maternal IgG antibodies are directly transferred to the fetus by FcRn receptors expressed by SYNs (Jennewein et al., 2017) (Figure 2A). IgG transfer begins around 13 weeks of gestation, the beginning of the second trimester in humans (Palmeira et al., 2012). Whether transfer of innate inflammatory mediators from the mother to the fetus occurs is less well understood. *Ex vivo* studies of term placentas indicate that transplacental transfer of most cytokines does not occur (Aaltonen et al., 2005). However, chronic maternal infection by human immunodeficiency virus 1 (HIV-1) and hepatitis B can lead to higher cytokine concentrations in the cord blood and altered fetal immune responses, indicating that the maternal immune responses can influence the fetus, perhaps due to placental cytokine production (Bunders et al., 2014; Hong et al., 2015). As we will discuss later, maternal IL-17 can directly affect fetal brain development (Choi et al., 2016).

The developing embryo also has cell-intrinsic mechanisms to protect itself from infection. One intriguing demonstration of this is that pluripotent stem cells, including embryonic stem cells, are resistant to viral infection due to constitutive expression of a subset of interferon stimulated genes (ISGs), including IFITM1 and IFITM3 (Wu et al., 2018). The developing embryo must not only protect itself from exogenous pathogens but also against endogenous genomic threats. Transposable elements, which make up 40% of the genome in mice and 44% of the genome in humans, must be actively suppressed to maintain genomic integrity (Rowe and Trono, 2011). The transposable elements can be classified as long terminal repeat (LTR) elements, including endogenous retroviruses (ERVs), and non-LTR elements, including long interspersed nuclear elements (LINEs). Gametes and early embryos are susceptible to transposable elements reactivation as the genome is globally demethylated during genome reprogramming (Rowe and Trono, 2011). PIWI-associated RNAs (piRNAs) are essential for suppressing transcription of transposable elements, particularly in the gonads and embryo (Siomi et al., 2011). piRNAs are 23-30 nucleotide small silencing RNAs that interact with the PIWI proteins, PIWI, AUB, and AGO3 to cleave their target mRNAs and impose transcriptional silencing by DNA methylation (Siomi et al., 2011). Loss of PIWI protein expression results in upregulation of transposable elements, subsequent double-stranded DNA breaks, and a loss of fertility (Klattenhoff et al., 2007; Siomi et al., 2011). In *Drosophila*, PIWI protein expression is required for both oogenesis and spermatogenesis (Lin and Spradling, 1997). However, in mice, PIWI proteins are required for only spermatogenesis, and piRNA expression is low during oogenesis (Carmell et al., 2007). Moreover, expression of piRNAs and PIWI proteins in humans, macaques, and cows indicates that there may be a species-specific role for piRNAs in mammalian oogenesis (Roovers et al., 2015). ERVs are a collection of previously integrated exogenous retroviruses that accumulate over time in the genome of vertebrates. Recent studies identify a class of small RNAs, tRNA-derived fragments (tRFs), as another small RNA-mediated mechanism of suppressing ERV retrotransposition in the mouse pre-implantation embryo (Schorn et al., 2017). Two distinct classes of tRFs block translation and reverse transcription of retroviral RNAs (Schorn et al., 2017). Specific epigenetic silencing mechanisms are employed for ERV silencing during embryogenesis. Embryonic stem cells use ZFP809 to silence retroviral proviral transcription (Wolf and Goff, 2009). Other KRAB-ZFPs are also likely involved specifically during embryonic development in recruiting epigenetic machinery to silence ERV (Wiznerowicz et al., 2007). Thus, ISGs, epigenetic- and small RNA-mediated repression orchestrates intrinsic antiviral control in early stages of embryo development.

Immune Pathways and Cell Types That Promote Normal Pregnancy

Emerging evidence indicates a central role of the immune system in mediating successful pregnancy, from implantation to parturition. We will discuss a few examples of immune-mediated pregnancy processes. Implantation elicits an inflammatory reaction, where upregulation of inflammatory cytokines, including interleukin-6 (IL-6), IL-1, and leukemia inhibitory factor (LIF), are highly conserved across the therian mammals, including placental mammals and marsupials (Griffith et al., 2017) (Figure 1A). LIF expression in the mother is essential for implantation in mice (Stewart et al., 1992). Various leukocytes are found in the decidua, including maternal NK cells, DCs, macrophages, and lymphocytes (Liu et al., 2017). These cells directly interact with trophoblasts of the developing placenta, and deviations in cell numbers and functions are associated with pregnancy loss, preeclampsia, and preterm birth (Zenclussen and Hämmerling, 2015). $CD11b^{+}$ macrophages are necessary for the maintenance of the corpus luteum in the ovary, which maintains early pregnancy by the secretion of progesterone (Figure 1A): depletion of macrophages using CD11b-DTR mice results in failure of early implantation that can be rescued by progesterone (Care et al., 2013). Additionally, *in vitro* evidence shows that macrophages and trophoblasts interact closely and reciprocally regulate each other: macrophages promote trophoblast survival and differentiation, and trophoblasts regulate monocyte migration and cytokine production (Fest et al., 2007; Rozner et al., 2016). Dendritic cells (DCs) are also essential for early events of pregnancy: depletion of these cells using CD11c-DTR in mice leads to embryo resorption due to a failure of the decidua to develop, including impaired angiogenesis and decidual cell proliferation (Plaks et al., 2008). TGFβ and sFlt1 are two factors produced predominately by DCs and may be responsible for the impaired angiogenesis seen in the CD11c-DTR mice. These functions are independent of the immune tolerance function of DCs, as the early implantation failure occurs in syngeneic pregnancy and when T cells are depleted. Thus, mouse models demonstrate that macrophages and DCs play distinct and essential roles in early pregnancy (Figures 1A and 1B). While they are present in human pregnancy, whether they have similar roles in humans is unknown.

Remodeling of the maternal spiral arteries also requires immune cells. NK cells make up the predominant leukocyte population in the human decidua, and the NK cells are located in close proximity to the invading extravillous trophoblasts and surrounding the spiral arteries (Liu et al., 2017) (Figure 1B). Mice that lack NK cells, IFN-γ, IFN-γ receptor (IFNGR), or STAT1 (transcription factor downstream of IFN-γ receptor), do not have spiral artery remodeling, indicating an essential role for NK cells and IFN-γ in this process (Ashkar et al., 2000). Mice lacking type I IFN receptor (IFNAR) also lack spiral artery remodeling, indicating a non-redundant roles of type I and type II IFNs (Murphy et al., 2009).

Despite the abnormal spiral artery remodeling, pups of mice lacking IL-15, NK cells, IFNGR, or IFNAR have only mild growth restriction, but pregnancies are otherwise minimally affected (Barber and Pollard, 2003; Murphy et al., 2009). Uterine NK cells are essential for control of trophoblast invasion and produce a number of angiogenic factors (Hanna et al., 2006). A recent study also shows that a subset of NK cells may directly interact with the developing fetus by secreting growth-promoting factors including peiotrophin, osteoglycin, and osteopontin (Fu et al., 2017). Additionally, the $Kit^{wsh/wsh}$ mice, which are deficient in mast cells, have abnormal implantation sites and lack spiral artery remodeling (Woidacki et al., 2013). NK cells and mast cells are key regulators of uterine spiral artery remodeling, as demonstrated in mouse studies, a process that becomes aberrant in many pregnancy complications.

Interferons play central roles in pregnancy in distinct species. A prime example of this is the role of interferon-τ (IFN-τ), a unique type I IFN that is essential for pregnancy recognition in ungulates (Roberts, 2007). IFN-τ is expressed by the early trophoectoderm and acts as a hormone of pregnancy recognition to rescue the corpus luteum. It is also thought to be important for implantation. While IFN-τ expression is controlled transcriptionally by Ets2 and not by the IRF transcription factors downstream of viral sensors, it binds to IFNAR and has antiviral activity (Ealy et al., 2001). IFN-α exposure of the endometrium in ewes is sufficient to prolong the estrous cycle with similar efficacy as IFN-τ (Green et al., 2005). While no equivalent of IFN-τ exists in humans, some IFNs are upregulated during implantation, indicating that there may be a common role for IFNs in some aspects of implantation (Roberts, 2007).

Post implantation, the maternal-fetal interface undergoes dynamic immunological changes (PrabhuDas et al., 2015). Decidual stromal cells (DSCs) are a defining cell type in species with extended gestational periods and are critical for maintaining the unique immune environment of the decidua: they silence the chemokines CXCL9 and CXCL10, which recruit cytotoxic T cells, and they secrete IL-15 which is responsible for converting decidual NK cells and macrophages to decidual phenotypes, including reduced cytotoxicity and secretion of angiogenic factors (Ashkar et al., 2003; Chavan et al., 2016). Additional mechanisms exist in the uterus to prevent anti-fetal immune responses. DCs in the decidua are restricted from migrating to the lymph node (LN), likely due to their unresponsiveness to CCL21, the chemokine responsible for their migration to the LN (Collins et al., 2009). Meanwhile, regulatory T (Treg) cells expand during pregnancy in both humans and allogeneic mouse models (Aluvihare et al., 2004; Feyaerts et al., 2017). Partial and transient ablation of Treg cells at midgestation is sufficient to lead to expansion of fetus-specific CD4 and CD8 T cells and loss of allogenic fetuses in mice (Rowe et al., 2011). Thus, the specialized local microenvironment of the placenta and developing fetus promotes tolerance to fetal antigens and downregulation of specific chemokines and cytokines.

Parturition is another key event in pregnancy that utilizes the immune system and is associated with a proinflammatory environment (Figure 1C). Parturition during normal term pregnancy is associated with neutrophil and macrophage infiltration into the myometrium, an upregulation of inflammatory cytokines including IL-1β and IL-8 in the maternal-fetal tissues, and transcriptional changes in the decidua including upregulation of TNF signaling pathway, Nod-like receptors, and NF-κB activation (Christiaens et al., 2008; Rinaldi et al., 2017). Cytokines including IL-1β may directly induce smooth muscle contraction in the uterus: *in vitro* studies show that it can induce calcium influx into myometrial smooth muscle, phosphodiesterase activity, and prostaglandin F2a production, all of which can contribute to muscle contraction (Oger et al., 2002; Tribe et al., 2003). Cervical remodeling and dilation are also accompanied by infiltrating leukocytes into the cervix (Yellon, 2017). Immunological changes in the decidua and myometrium may coordinate the timing of parturition, which requires integration of multiple signals from the mother and fetus (Menon et al., 2016). As seen during embryo implantation, uterine artery remodeling, and parturition, leukocytes and cytokines (Table 1) are essential mediators of coordinated tissue remodeling necessary for successful pregnancy.

Host Immune Responses Contribute to Pregnancy Complications Associated with Infections

The "TORCH" pathogens encompass a range of infectious agents that are known to cause congenital defects. They include protozoa (*Toxoplasma gondii*), bacteria (*Listeria monocytogenes* and *Treponema pallidum*), and viruses (rubella, CMV, HSV, varicella zoster virus, HIV, enteroviruses, parvovirus B19, and ZIKV) (Coyne and Lazear, 2016). In addition to congenital defects, which we will discuss later, TORCH infections cause a number of different pregnancy complications including pregnancy loss, IUGR, and preterm birth (Cappelletti et al., 2017a; Goldenberg et al., 2010; Pereira et al., 2014). One of the newest TORCH pathogens, ZIKV, has raised public fear as it spread across the Americas in 2015–2017, resulting in over 3,000 estimated cases of microcephaly, as well as miscarriage and fetal growth restriction (PAHO and WHO, 2017; Simões et al., 2016). Mouse models of ZIKV infection in pregnant dams have shown similar complications, with growth restriction, fetal demise, and placenta damage being most pronounced (Cugola et al., 2016; Miner et al., 2016; Szaba et al., 2018; Yockey et al., 2016). Recent studies in mouse and human tissue explant models indicate that other emerging neurotropic viruses related to ZIKV, including West Nile Virus and Powassan virus, have the capacity to infect the placenta and fetal brain, leading to fetal demise (Platt et al., 2018). Thus, other viruses may have the potential to impact fetal development at an epidemic level.

Animal models of these infections indicate that pregnancy complications might be, at least in part, mediated by the immune response induced by the pathogen. A recent study has shown that type I IFN signaling through IFNAR within the fetus and fetal-derived placenta mediate the severe complications, including fetal demise and severe growth restriction following ZIKV infection of pregnant mice (Yockey et al., 2018). The detrimental effect of IFNAR signaling is mostly due to a block in placental development. Type II IFN, IFN-γ, might play a similar role: fetal resorption induced by *Toxoplasma gondii* infection is less severe in mice that lack IFNGR (Senegas et al., 2009). Infection can also lead to a break in the immune tolerance toward the fetus. In mouse models of *Listeria monocytogenes*, infection is sufficient to recruit fetal-specific $CD8^+$ T cells to the placenta and cause fetal demise (Chaturvedi et al., 2015). Thus, both

Table 1. Physiological and Pathological Roles of Cytokines in Pregnancy

Cytokine	Physiological roles	Citation	Pathological roles	Citation
Type I IFNs	Pregnancy recognition in ungulates (IFN-τ)	(Roberts, 2007)	Block in placenta development after ZIKV infection	(Yockey et al., 2018)
	Mediates uterine artery remodeling in mouse models	(Murphy et al., 2009)	Microcephaly and cranial calcifications after genetic overexpression, possibly viral infection	(Crow et al., 2015)
			Correlates with pregnancy complications in patients with SLE	(Andrade et al., 2015)
IFN-γ	Mediates uterine spiral artery remodeling	(Ashkar et al., 2000)	Prevents implantation and toxic to embryo	(Robertson et al., 2018)
			Induces abnormal cerebellar development when overexpressed in mouse brains	(Wang et al., 2004)
			Mediates placental damage after malaria infection in mouse models	(Niikura et al., 2017)
			Mediates fetal resorption after Toxoplasma infection in mouse models	(Senegas et al., 2009)
IL-1β	Upregulated during implantation in an evolutionary-conserved manner	(Griffith et al., 2017)	Mediates abnormal lung development after peripartum inflammation in mouse models	(Hogmalm et al., 2014)
	Mediator of myometrial contraction during labor	(Oger et al., 2002; Tribe et al., 2003)	Mediates neuronal damage due to inflammatory preterm birth in mouse models	(Leitner et al., 2014)
			Sufficient to induce preterm labor in non-human primate models	(Sadowsky et al., 2006)
IL-6	Upregulated during implantation in an evolutionary-conserved manner	(Griffith et al., 2017)	Induces autism-like phenotype and abnormal brain development in mouse models	(Smith et al., 2007)
IL-15	Required for uNK cell recruitment and uterine spiral artery remodeling in mouse models	(Ashkar et al., 2003)		
IL-17			Induces autism-like phenotype and abnormal brain development in mouse models	(Choi et al., 2016)
LIF	Upregulated during implantation in an evolutionary-conserved manner	(Griffith et al., 2017)		
	Required for successful implantation in mouse models	(Stewart et al., 1992)		
TNF-α			Toxic to early embryo development	(Robertson et al., 2018)
			Sufficient to induce preterm labor in non-human primate models	(Sadowsky et al., 2006)
			Sufficient to induce neural tube defects after systemic maternal injection	(Taubeneck et al., 1995)
			Mediates fetal demise in mouse models of LPS and poly(I:C)-induced fetal resorption.	(Carpentier et al., 2011; Thaxton et al., 2013)

innate and adaptive immune responses can contribute to fetal demise after congenital infection.

Malaria is another prevalent pathogen associated with poor pregnancy outcomes: women infected with *P. falciparum* or *P. vivax* are at an elevated risk of growth restriction and preterm birth (Moore et al., 2017a). Other studies show a correlation between poor pregnancy outcomes and systemic concentrations of cytokines and chemokines including TNF-α, IFN-γ, IL-10, and CXCL9 in women infected with malaria (Fried et al., 2017). Consistent with these findings, mouse models show that TLR4 signaling and IFN-γ signaling are mediators of abnormal development of the placenta labyrinth vasculature and fetal growth restriction caused by malaria infection (Barboza et al., 2017; Niikura et al., 2017). Thus, the inflammatory response to malaria appears to be a key mediator of malaria-related pregnancy complications.

Intrauterine infection and inflammation are important contributors to preterm birth, which is defined by birth before 37 weeks (Romero et al., 2014a). Around 25% of preterm births are associated with intrauterine infection, usually with vaginal microbes, indicating an ascending infection (Romero et al., 2014a). Extrauterine infections in the mother including pneumonia, pyelonephritis, and periodontal disease are also associated with preterm labor (Agrawal and Hirsch, 2012). Whether or not clinically-detectable infection is present, elevated concentrations of cytokines including IL-6, IL-1, IL-8, and TNF in amniotic fluid or in cervicovaginal lavage of patients is predictive of the onset of preterm labor (Agrawal and Hirsch, 2012; Holst et al., 2009). Recent studies have shown that a vaginal microbiome not dominated by *Lactobacillus* is associated with increased risk for preterm labor, but these findings are not consistent across all studies (DiGiulio et al., 2015; Romero et al., 2014b). While the role of viral infections on preterm births are less clear, experimental evidence shows that coinfection with herpes viruses can lead to both ascending bacterial infection and an enhanced inflammatory responses to bacterial stimulation (Cross et al., 2017; Racicot et al., 2013). Collectively, emerging evidence indicates that the host immune response elicited by infection and possibly the vaginal microbiome of the pregnant mother may be an important contributor to the detrimental outcomes of congenital infections.

Innate Immune Activation Is Sufficient to Cause Fetal Loss and Preterm Birth in Animal Models

Mouse models show that innate immune signals, independent of infectious pathogens, are sufficient to cause miscarriage and preterm birth. A number of studies show that injection of PAMPs or recombinant cytokines in pregnant mice leads to fetal demise and preterm birth and has been a tool to study some of the mechanisms underlying pregnancy complications. Injection of poly(I:C), a double-stranded RNA viral mimic, in early pregnancy (E6.5) in mice reveals that uterine NK (uNK) cells induce fetal demise in an NKG2D-dependent manner (Thaxton et al., 2013). Poly(I:C) induces proliferation and activation of uNK cells and expression of the activating ligand, NKG2D, on uterine macrophages, resulting in abnormal trophoblast migration, increased apoptosis of placental cells, and fetal resorption. Of interest, we found that this model of poly(I:C)-induced fetal death is also dependent on IFNAR expression by the mother (Yockey et al., 2018). It is unclear where IFN signaling is acting on this NK-mediated pathway. In contrast, intraperitoneal LPS injection during early pregnancy (E7.0) shows a role for nitric oxide, presumably produced by infiltrating macrophages, in fetal resorption (Ogando et al., 2003). LPS, a component of the cell wall of gram negative bacteria, is recognized by the maternal tissues (via TLR4) to induce TNF-α, which acts on the placenta and/or fetus to induce placenta necrosis in mice (Carpentier et al., 2011). The immunomodulatory cytokine IL-10, on the other hand, plays a protective role in preventing fetal resorption after intraperitoneal injection of LPS or CpG (TLR9 agonist) (Murphy et al., 2005; Thaxton et al., 2009). NK cells or F4/80$^+$ macrophages mediate the fetal resorption after LPS or CpG treatment, respectively, in IL-10-deficient mice, indicating distinct cellular mechanisms based on the type inflammatory of stimulus. Prior to implantation, cytokines may also directly impact the embryo: TNF-α, IFN-γ, and TRAIL, have been shown to be toxic to the early embryo, inducing apoptosis and impaired growth (Robertson et al., 2018).

Microbial ligands or cytokines, used experimentally to mimic infections or conditions found in preterm labor, are sufficient to induce preterm labor when injected later in pregnancy (Agrawal and Hirsch, 2012). Direct intramniotic infusion of IL-1β and TNF-α, but not IL-6 or IL-8, are also sufficient to induce preterm labor in non-human primate models (Sadowsky et al., 2006). In pregnant mice inoculated intravaginally with LPS, complement activation leads to macrophage-mediated remodeling of the cervix and preterm birth (Gonzalez et al., 2011). Mice lacking the complement receptor C5aR are resistant to LPS-induced preterm labor but still deliver at term, indicating that C5aR is not required for term labor (Gonzalez et al., 2013). In this regard, TLR4 and IL-6 appear to be mediators of on-time labor: in addition to being protective of preterm labor, genetic deletion or inhibitors of TLR4 or IL-6 lead to delayed parturition and increased perinatal mortality (Robertson et al., 2010; Wahid et al., 2015). The context in which type I IFN signaling occurs is also critical: blocking signaling through IFNAR or suppressing type I IFNs increases sensitivity to intraperitoneal-challenge LPS-mediated preterm birth (Racicot et al., 2016). Conversely, type I IFNs mediate preterm birth in the case of intraperitoneal poly(I:C) injection and maternal viral infection (Cappelletti et al., 2017b). These animal studies collectively highlight a role for distinct inflammatory cells and pathways that underlie fetal loss and preterm labor.

Chronic Maternal Diseases Leading to Pregnancy Complications

Maternal autoimmune disease is another known risk factor for pregnancy complications. Since many autoimmune diseases affect women of child-bearing age, the effect of these diseases on pregnancy is of high relevance. Two of the commonly recognized autoimmune diseases associated with pregnancy complications are systemic lupus erythematosus (SLE) and antiphospholipid syndrome (APS). SLE is characterized by systemic inflammation, most commonly affecting the skin and kidney. Women with SLE have an increased risk of preeclampsia, preterm delivery, fetal growth restriction, and fetal loss (Bundhun et al., 2017). Children born to mothers with SLE may also have an increased risk of neurodevelopment disorders and congenital heart defects (Vinet et al., 2015a, 2015b). Anti-phospholipid

antibody syndrome (APS) is characterized by presence of one or more of the anti-phospholipid antibodies and episodes of thrombosis or recurrent miscarriage (Schreiber et al., 2018). Many patients with SLE also have antiphospholipid antibodies. In addition to recurrent miscarriages, women with APS have an increased risk of preeclampsia, growth restriction, and still birth (Saccone et al., 2017; Schreiber et al., 2018).

A number of different inflammatory mechanisms have been implicated in the poor pregnancy outcomes in individuals with SLE and APS, beyond hypercoagulability alone. Antibodies against cardiolipin, beta$_2$-glycoprotein, and lupus anticoagulant are the most common antibodies present in APS, and the concentrations of antibodies correlate with the risk of miscarriage (Santos et al., 2017). A number of *in vitro* studies have shown these antibodies can directly affect trophoblast function by decreasing proliferation, inhibiting syncytialization, and decreasing hormone production (Tong et al., 2015). Antibodies against beta$_2$-glycoprotein, which is expressed by trophoblasts, directly induce inflammatory cytokine expression and cell death of trophoblasts *in vitro* (Mulla et al., 2009). Elevated concentrations of complement factors in the serum and deposition of complement in the decidua are also predictive of poor pregnancy outcomes in patients and mediate disease in mouse models of APS (Cohen et al., 2011; Girardi et al., 2003; Kim et al., 2018). These mouse models, which involve induction of fetal demise and growth restriction after passive transfer of human antiphospholipid antibodies, also show a role for neutrophils and TNF-α in mediating fetal demise (Berman et al., 2005; Girardi et al., 2003). In addition to antibody- and complement-mediated mechanisms, interferons may also be mediators of poor outcomes in SLE and APS patients. Elevated type I IFN activity, a signature of SLE, is one of the factors that correlates with development of preeclampsia in SLE patients (Andrade et al., 2015). The authors suggest that this clinical correlation might be due to impaired placental vasculature remodeling in the setting of elevated IFNα concentrations. The high rates of pregnancy complications for individuals with autoimmune disease extends beyond SLE and APS: rheumatoid arthritis is associated with low birth weight, mothers with systemic sclerosis have higher rates of preterm delivery and IUGR, and those with Sjogren's disease have higher rates of miscarriage, preterm delivery, and low birth weight (Gupta and Gupta, 2017; Ostensen and Clowse, 2013).

In addition to classic states of maternal inflammation including infection and autoimmunity, the role of inflammation in metabolic diseases including obesity and diabetes is increasingly being recognized. Obesity leads to a state of chronic low-grade inflammation, which has been shown to contribute to many health consequences including insulin resistance and type II diabetes (Reilly and Saltiel, 2017). Obese individuals have an increased risk of many pregnancy complications including preeclampsia, stillbirth, miscarriage, and pre-term birth (Kalliala et al., 2017). Children of obese mothers are at an increased risk for a number of complications, ranging from macrosomia (above average infant size), neurodevelopmental/psychiatric disorders (including autism spectrum disorder, schizophrenia, attention deficit hyperactivity disorder, and poor cognitive performance), congenital malformations including congenital heart defects, and asthma (Edlow, 2017; Godfrey et al., 2017; Persson et al., 2017). Global transcriptional analyses of placenta of obese women identify inflammation and immune responses among the top dysregulated pathways (Altmäe et al., 2017). Analyses of the placentas of obese women show increased IL-1β and IL-8 expression (Aye et al., 2014; Roberts et al., 2011). Obese women also have reduced numbers of uNK cells, altered gene expression of uNK cell, and delayed uterine artery remodeling during early pregnancy (Perdu et al., 2016). Fetuses of mothers with obesity have increased markers of inflammation in the cord blood including increased C-reactive protein (CRP), IL-6, and TNF-α concentrations (Dosch et al., 2016; Wilson et al., 2015). While, there is a consistent association between maternal body mass index and expression of the inflammatory marker, CRP, there is still no consensus between studies on the changes in systemic cytokine expression during pregnancies in obese women (Pendeloski et al., 2017). Animal studies using mouse and nonhuman primate models support this correlation between obesity, increased inflammatory markers in the mother or placenta, and poor pregnancy outcomes including stillbirth and fetal resorption (Frias et al., 2011; Mahany et al., 2018). More studies are needed to investigate the causal and mechanistic link between increased inflammation in obesity and associated pregnancy complications. Collectively, pregnancy complications and congenital diseases associated with chronic autoimmune and obesity correlate with elevated expression of type I IFNs, IL-6, and IL-1β (Figure 3, Table 1).

Inflammatory Pathways That Disrupt Fetal Brain Development

Fetal development can also be impacted by inflammation. Nervous system development appears to be exquisitely sensitive to inflammatory insults throughout pregnancy. In the case of the "TORCH" infections, some of the common neurological defects seen include microcephaly, cranial calcifications, ventriculomegaly, ocular defects, and sensorineural hearing loss (Adams Waldorf and McAdams, 2013; Coyne and Lazear, 2016). Many of these presentations, including microcephaly, are similar among pathogens including CMV, rubella, rubeola (measles) and varicella zoster, *Toxoplasma*, HSV, and Zika virus (Devakumar et al., 2017). Similar clinical presentation across a range of viral and protozoan pathogens suggests a common underlying mechanism. This possibility is supported by the findings that fetuses with genetic defects leading to type I IFN overproduction can present as if they have a congenital viral infection, a disease referred to as pseudo-TORCH syndrome or Aicardi-Goutieres syndrome (AGS) (Crow and Manel, 2015). Most of the type I interferonopathies are due to defects in genes that are necessary for nucleic acid degradation, recognition and modification, including *TREX1*, *RNASEH2A*, *RNASEH2B*, *RNASEH2C*, *SAMHD1*, *IFIH1*, and *ADAR*; or negative regulation of the IFN pathway in the case of *USP18* (Crow and Manel, 2015; Meuwissen et al., 2016). Infants with AGS suffer from severe encephalopathy with seizures, cortical blindness, spasticity, and psychomotor retardation (Crow et al., 2015). AGS patients have elevated IFN concentrations in their blood and cerebral spinal fluid (CSF) and increased expression of ISGs in their blood, and the concentration of interferon in the CSF predicts disease severity, suggesting a role for elevated IFN in disease pathogenesis (Crow et al., 2015).

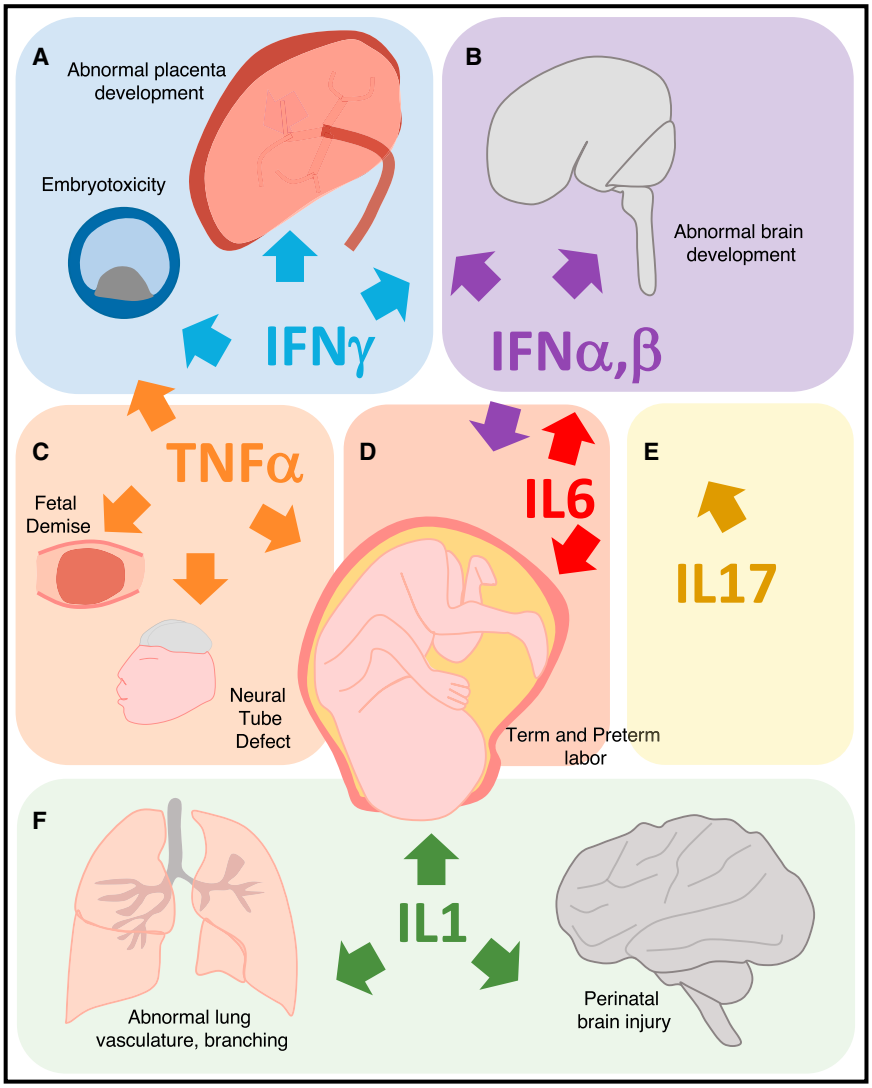

Figure 3. Pathological Effects of Cytokines in Pregnancy

Aberrant expression of IFN-γ, IFN-β, TNF-α, IL-6, IL-17, and IL-1β can lead to developmental failure in multiple organ systems.

(A) Exposure of embryos to IFN-γ in culture is toxic, and systemically elevated IFN-γ at the time of implantation inhibits implantation. Mouse models implicate that IFN-γ responsiveness after malaria and toxoplasma infection mediates some of the placental defects and that IFN-γ overexpression leads to abnormal brain development in mouse models.

(B) Type I IFNs (including IFN-α and IFN-β) mediate abnormal placental development after ZIKV infection and preterm birth after viral infection, as demonstrated by mouse models. Humans with overexpression of type I IFNs due to interferonopathies have abnormal brain development, similar to "TORCH" infections, implicating IFNs as mediators of abnormal brain development.

(C) Exposure of embryos to TNF-α can induce a block in development. TNF-α is a mediator of fetal demise in mouse models of immune stimulation (CpG, LPS, and Poly(I:C)). TNF-α injection in mice can cause neural tube defects. Intraamniotic infusion of TNF-α is sufficient to induce preterm birth in non-human primate models.

(D) IL-6 (upstream of IL-17) induces abnormal brain development and behavior in mouse models of maternal immune activation. IL-6 mediates on time and preterm parturition in mouse models.

(E) IL-17 (downstream of IL6) induces abnormal brain development and behavior in mouse models of maternal immune activation.

(F) IL-1 may induce preterm birth, as amniotic IL-1β administration is sufficient to induce preterm labor in non-human primates. Mouse models reveal that IL-1 may mediate defects associated with peripartum intrauterine inflammation including abnormal lung development associated with bronchopulmonary dysplasia and brain injury.

Recent studies show that in people with Down syndrome, or trisomy 21, many ISGs are overexpressed, likely due to an additional copy of the IFN receptor genes on chromosome 21 (Sullivan et al., 2016). Partial IFNAR and IFNGR deficiency leads to improved growth and neuron viability in a mouse model of trisomy 21, raising the possibility that some of the complications associated with trisomy 21, including developmental delay and growth restriction, may be mediated by IFN (Maroun et al., 2000). Taken together, these findings point toward hyperactive interferon signaling being a potential driver of brain pathology and abnormal brain development after congenital infections and genetic diseases.

IFN-γ is primarily produced by T and NK cells and induces some overlapping effectors with type I IFNs. Mouse models demonstrate a direct role for IFN-γ in altering brain development. Genetic overexpression of IFN-γ in astrocytes leads to abnormal cerebellar development and ataxia in mice (Wang et al., 2004). IFN-γ induces expression of Shh signaling demonstrating a direct interaction with a key neural developmental pathway (Wang et al., 2003). Other studies implicate IFN-γ *in vitro* and *in vivo* in impaired neural progenitor differentiation (Ahn et al., 2015). In these studies, IFN-γ acts by downregulating neurogenin 2, an important regulator of neuronal differentiation and proneural factor (Ahn et al., 2015). Thus, IFN-γ overexpression during development can disrupt developmental pathways and differentiation of neurons.

Systemic maternal immune responses have the potential to be teratogenic: LPS or CpG administration during early pregnancy (starting E8.5 or E6.5 in mice, respectively) lead to neural tube defects, including exencephaly, in mice (Thaxton et al., 2009; Zhao et al., 2008). Excess reactive oxygen species contribute to the LPS-mediated defects, and folic acid administration can protect these mice from neural tube defects (Zhao et al., 2008, 2013). Interestingly, folic acid supplementation reduces the production of IL-1β, TNF-α, and IL-6 made in the response to LPS administration. LPS-induced neural tube defects and resorption were also partially rescued by depletion of NK cells and in mice lacking IL-15 signaling, which lack uterine NK cells (Lee et al., 2013). TNF-α administration alone is sufficient to induce neural tube defects in mice, potentially through its role in altering zinc metabolism (Taubeneck et al., 1995). Animal models demonstrate that a systemic maternal immune response is sufficient

to induce neural tube defects, but the exact mechanisms and the respective contributions of cytokines, oxidative damage, and nutrient imbalances to these phenotypes are still unclear.

In addition to overt structural malformations, maternal immune activation (MIA) during pregnancy is associated with an increased risk of psychiatric diseases including schizophrenia and autism spectrum disorder (Patterson, 2009). One retrospective study estimates that maternal exposure to influenza virus can account for as many as 20% of cases of schizophrenia (Brown et al., 2004). Abnormal behavior analogous to schizophrenia and autism, including inability to inhibit the startle response, has been recapitulated in animals by injection of influenza virus, poly(I:C), LPS, or recombinant IL-6 (Patterson, 2009; Smith et al., 2007). The poly(I:C)-induced autism-like phenotype leads to specific defects in the dysgranular zone of the somatosensory cortex and is mediated by IL-17 (Choi et al., 2016; Shin Yim et al., 2017) (Figure 3). IL-17 produced by maternal T helper-17 (Th17) cells presumably crosses the placenta to trigger IL-17R in the fetal neurons, resulting in cortical and behavioral abnormalities. Maternal gut microbiota, such as segmented filamentous bacteria (SFB), promote the development of Th17 cells and predispose the fetus to neurodevelopmental disorders following poly(I:C) challenge in mice (Kim et al., 2017). Recent studies of healthy human subjects show a correlation between maternal IL-6 concentrations during pregnancy with neonatal brain connectivity and executive memory at 2 years (Rudolph et al., 2018). This indicates that baseline inflammation of the mother may impact brain connectivity even without overt disease. In addition to the direct action of cytokines on the fetal brain, MIA may modulate fetal neurodevelopment through inducing changes in placental tryptophan metabolism and increased serotonin production (Goeden et al., 2016). Thus, during MIA, inflammatory mediators released by the mother may have either a direct or an indirect effect on the fetal brain development.

Perinatal inflammation is also recognized as an important risk factor for brain injury and developmental disorders including cerebral palsy, white matter injury, and autism (Boyle et al., 2017). Elevated cytokines IL-6 and IL-1β in the amniotic fluid and placental inflammation are predictors of brain injury in premature infants (Boyle et al., 2017) (Figure 3). Animal models have helped to confirm this connection and identify some of the inflammatory pathways that contribute to abnormal brain development. Induction of preterm birth by intrauterine LPS exposure leads to abnormal neuronal morphology and decreased dendrites compared to preterm birth induced by progesterone inhibition with RU486 (Burd et al., 2010). Inhibition of IL-1 signaling using an IL-1 receptor antagonist eliminates the abnormal morphology and dendrite numbers (Leitner et al., 2014). IL-1 may act to promote an adaptive immune response: depletion of maternal $CD8^+$ T cells reverses the cortical density and behavioral abnormalities associated with inflammation-induced preterm delivery (Lei et al., 2018). A recent study shows that γδ T cells, which are among the first T cells to develop, may contribute to brain injury: γδ T cell infiltration is observed in postmortem analysis of human fetuses with white matter brain injury, as well as in sheep and mouse models of perinatal brain injury due to hypoxia (Albertsson et al., 2018). Depletion of γδ T cells in mouse models is sufficient to reduce brain injury (Albertsson et al., 2018). Thus, the brain is susceptible to developmental disruption by increased expression of type I immune cytokines including type I and type II IFNs, IL-17, and IL-1β (Figure 3).

Inflammatory Pathways That Disrupt Development of Other Organs

Heart development is also susceptible to disruption by different states of inflammation. While defects in heart development are less common among congenital infections, patients with congenital rubella syndrome have high rates of heart defects including patent ductus arteriosus (PDA), an abnormal connection between the aorta and pulmonary arteries, and pulmonary artery stenosis, a narrowing of the pulmonary artery (Oster et al., 2010). Chorioamnionitis, or infection of the fetal membranes, is also associated with an increased risk for PDA (Park et al., 2015).

A classic example of immune-mediated congenital heart defects is the case of congenital heart block (CHB) that occurs in the fetus of mothers with autoimmune diseases. CHB occurs when the maternal autoimmune antibodies, anti-Ro and anti-La, cross the placental barrier and attack the conduction system of the fetal heart (Brito-Zerón et al., 2015). These autoantibodies commonly occur in mothers with SLE, and 1%–2% of women with anti-Ro antibodies will have babies with CHB. The most common clinical finding of CHB is irreversible atrioventricular node block (Brito-Zerón et al., 2015). The atrioventricular node is the pacemaker of the heart and controls passage of current to the ventricles. The exact mechanism by which the conducting system of the developing fetal heart is specifically damaged by anti-Ro antibody is poorly understood as most of the target antigens are intracellular (Ambrosi et al., 2014).

Lung development spans the entire gestational period, with the formation of alveoli occurring just weeks before birth (Kalikkot Thekkeveedu et al., 2017). Bronchopulmonary dysplasia (BPD) is common in premature infants and results when there is an early block in lung development. While there are genetic susceptibilities, bacterial infection of the amnion and chorion is an important contributor to BPD (Kalikkot Thekkeveedu et al., 2017). Intrauterine LPS administration leads to abnormal lung development, with decreased airway branching and perinatal death, in a macrophage-dependent manner (Blackwell et al., 2011). Constitutive activation of NF-κB in macrophages is sufficient to reproduce these effects. Inhibition of IL-1β and inflammasome activity is sufficient to inhibit the effects of LPS-induced lung development defects (Hogmalm et al., 2014). Interestingly, the cell type in which NF-κB is activated influences the subsequent defects: when NF-κB is constitutively activated in mesenchymal cells, vascular development in the lung is abnormal (McCoy et al., 2017). One of the possible mediators of abnormal lung development after LPS stimulation is inhibition of Shh signaling, which is critical for lung development (Collins et al., 2012). Thus, animal models of BPD have provided insights into the mechanisms of disease: including NF-κB activation and IL-1 expression (Figure 3).

In addition to brain, heart, and lung, other organ systems can be affected by inflammation as well. For example, congenital varicella infection is associated with limb and urogenital

anomalies. Congenital *Treponema pallidum*, or syphilis, infection is associated with abnormal teeth and bone development (Adams Waldorf and McAdams, 2013). Overall, human disease and animal models demonstrate a key role of cytokines, whether induced by infection, inflammation, or genetic abnormalities, in disrupting development of specific organs.

Unanswered Questions and Future Directions

While many questions remain, we highlight a few that might have potential therapeutic benefits. First, a long-standing question has been why some maternal infections, but not others, lead to congenital diseases (Arora et al., 2017). Must the pathogen infect the placenta or the fetus in order to cause developmental defects? What amounts of cytokines, locally or systemically, are required to induce placental insufficiency, IUGR, or abnormal brain development? What are the cellular sources and targets of cytokines in the placenta and the fetus? What are the molecular mechanisms of cytokine-induced dysfunction in target cells?

Second, how might we use our knowledge of toxicity associated with inflammatory cytokines and IFNs to develop therapies to prevent pregnancy complications and birth defects? Is it advantageous to interfere with these inflammatory responses? In the case of congenital infection, blocking type I or type II IFNs might have a detrimental impact on the mother, as the pathogen will replicate and spread to cause severe infection (Racicot et al., 2017). However, if we can understand the ISGs involved in mediating placental insufficiency and abnormal brain development versus those involved in antimicrobial defense, we may be able to selectively target the pathogenic ISGs while leaving the protective ISGs intact. Similarly, it will be important to delineate which aspects of cytotoxic responses to pathogens by NK cells and $CD8^+$ T cells at the maternal-fetal interface control pathogens or contribute to pathology. Since many pregnancy complications and birth defects have no known genetic or environmental causes, identification of common "developmentally-toxic ISGs" that underlie infectious and non-infectious causes of birth defects could serve as targets for future therapy.

Concluding Remarks

Healthy pregnancy requires tightly coordinated immune responses. Cytokines and IFNs are critical mediators of healthy pregnancy, for their ability to drastically alter cellular function, migration, cell-cell communication, proliferation, and gene expression. However, when dysregulated or inappropriately expressed, these have the potential to act as teratogens and disrupt fetal and placental developmental pathways, leading to birth defects and pregnancy complications. Investigating the ways in which different immune signaling pathways impact pregnancy and fetal development could provide important insights into congenital disorders and possible therapeutics to prevent pregnancy complications.

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