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Mechanisms of Immune Regulation by The Placenta: Role of Type I Interferon and Interferon Stimulated Genes Signaling During Pregnancy

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Summary

Pregnancy is a unique condition where the maternal immune system is continuously adapting in response to the stages of fetal development and signals from the environment. The placenta is a key mediator of the fetal/maternal interaction by providing signals that regulate the function of the maternal immune system as well as provides protective mechanisms to prevent the exposure of the fetus to dangerous signals. Bacterial and/or viral infection during pregnancy induce a unique immunological response by the placenta, and type I interferon is one of the crucial signaling pathways in the trophoblast cells. Basal expression of type I interferon-β and downstream ISGs harbors physiological functions to maintain the homeostasis of pregnancy, more importantly, provides the placenta with the adequate awareness to respond to infections. The disruption of type I interferon signaling in the placenta will lead to pregnancy complications and can compromise fetal development. In this review, we focus the important role of placenta derived type I interferon and its downstream ISGs in the regulation of maternal immune homeostasis and protection against viral infection. These studies are helping us to better understand placental immunological functions and provide a new perspective for developing better approaches to protect mother and fetus during infections.

Keywords

Interferon stimulated genes; ISG; placenta; trophoblast; type I interferon; pregnancy

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AUTHOR CONTRIBUTIONS

JD and GM wrote the document and prepared the figures. AM, NA, AH, YY and AL edited and discussed the document.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

1. Introduction

The challenge of managing pregnant women during pandemics and their exclusion from early vaccine clinical trials, has, once more, revealed the importance of understanding the function and the role of the immune system during pregnancy. In the last decade, our knowledge of the adaptational changes occurring to the maternal immune system throughout pregnancy, especially during early pregnancy, has advanced significantly. From being focused on the process of tolerance to paternal antigens [1] and the breach of this tolerance being considered as the main cause of pregnancy loses and other clinical complications; we now have a better comprehension of the immunological functions on reproductive organs and their cellular immune component. We have achieved a better comprehension associated with the specific role of the immune cells present at the implantation site and their critical role in supporting many of the physiological changes that take place at the uterus, which are necessary for implantation, placentation, and fetal growth. In addition, we know that pregnant women can controll viral infections in most cases, and vaccination has beneficial effects to both the mother and the fetus. But pregnancy is not a static process, it is an evolving and continuously changing process; accordingly, the maternal immune system changes in response to the environment and signals originated from the placenta and the fetus. In this review we will discuss first the normal role of the immune system during early pregnancy, its interaction with the fetal/placenta interface; and second, we will review the mechanism by which the placenta provides an immune modulatory function to protect the fetus and the mother against infections.

2. Immune Homeostasis of Pregnancy

Pregnancy is a unique period that requires major adaptational processes that involve complex interactions between fetus and mother. During the different trimesters of pregnancy, the maternal immune system must undergo highly dynamic and regulated transformation and adaptation throughout gestation, as it must avoid rejecting a semiallogeneic fetus and remain competent to fight against infections. In general, pregnancy can be divided into four critical periods that are associated with implantation, placentation, fetal growth, and parturition. In each of these periods the immunological milieu changes in response to the developmental stages of the fetus; or, as discussed below, it can also change in response to environmental factors, primarily infections, which can consequently impact the outcome of the pregnancy.

Embryo implantation is the critical first step for the establishment of pregnancy. Interestingly, inflammation is required for successful implantation. Starting with the apposition and attachment of blastocyst to the endometrial surface epithelium, the uterus must be receptive to embrace the implanting blastocyst during a specific period named the implantation window. Therefore, the uterus is primed to activate pro-inflammatory signals, such as prostaglandin E2 (PGE2) [2] and produce a range of cytokines, including interleukin-6 (IL-6), Leukemia Inhibitory Factor (LIF), IL-15, tumor necrosis factor (TNF), and chemokines, including CXC-chemokine ligand 8 (CXCL8), CXCL10 and CC-chemokine ligand 2 (CCL2), which can be secreted by endometrial stromal cells and immune cells that are recruited to the implantation site [3–6]. For the role of these

pro-inflammatory cytokines, it has been demonstrated that IL-15 and IL-18 can stimulate the activation of uterine natural killer (uNK) cells and regulate the inflammation process during implantation. In addition, TNF-α, IL-1β, IL-1RA, and IL-12 are involved in the extracellular remodeling and trophoblast invasion, which are critical for implantation and placentation [7–9].

Using *in vitro* models of implantation, we demonstrated that TNFα promotes the expression of inflammatory factors from endometrial stroma cells, and these inflammatory factors foster trophoblast differentiation, which grants them the capacity to migrate and invade into the uterine compartment [10]. One of the cytokines induced by TNFα in human endometrial stroma cells (hESC) was IL-17. We found that the IL-17 pathway is enriched in trophoblasts during the time of implantation. IL-17 interacts with trophoblast cells and induces the expression of genes responsible for promoting trophoblast migration and invasion [10] (Figure 1). The findings from this study demonstrated the presence of an inflammatory network led by TNFα that promotes the expression and secretion of pro-inflammatory cytokines, such as IL-17 in hESC.

These *in vitro* findings are supported by clinical observations. In cases of infertility or implantation failure, local injury, as result of endometrial biopsy, before *in vitro* fertilization can significantly increase implantation rates [11,12], which is suggested to be caused by the induction of the pro-inflammatory molecules necessary for implantation [13,14]. Indeed, the mechanism by which the biopsy treatment increases endometrial receptivity demonstrates that the local injury induces an inflammatory response that is characterized by elevated levels of pro-inflammatory cytokines/chemokines, such as macrophage inflammatory protein-1β (MIP-1β), TNFα, growth regulated oncogene α (GROα), osteopontin (OPN) and IL-15 [13]. In addition, there is an increase in the number of innate immune cells, particularly macrophages, dendritic cells (DCs), and a unique population of natural killer (NK) cells with a $CD56^{hi}CD57^{lo}$ phenotype. Moreover, it has been shown that the use of non-steroidal anti-inflammatory drugs around conception is associated with increased risk of miscarriage [15]. Taken together, these findings emphasize the requirement for a pro-inflammatory environment for a successful embryo implantation. However, the localized inflammation during implantation must be tightly controlled, otherwise embryo implantation will be impaired due to the disturbance of the dynamic balance between pro- and anti-inflammatory mediators [16,17].

Interestingly, recent findings from our group have shown that, during early pregnancy the IL-10 to TNFα ratio in normal pregnancies was significantly higher than in patients with pregnancy loss [18]. Furthermore, the early pro-inflammatory profile is followed by a clear shift toward an anti-inflammatory profile immediately after implantation; characterized by an increase in IL-10, decrease in TNFα, and increasing IL-10/ TNFα ratio. Contrary to successful pregnancies, pregnancy loss was associated with a failure in this shift, with no increase in neither IL-10 alone nor in the IL-10/ TNFα ratio. These findings demonstrate that an inflammatory condition is necessary for embryo implantation, however, once implantation is complete, the shift from inflammation to anti-inflammation is necessary for the maintenance of the pregnancy. Furthermore, the role of inflammation during implantation is evolutionary conserved between multiple species. Griffith et al. showed that

inflammation is observed in Marsupials as well as Eutherians [19]. While in the marsupials, the pro-inflammatory process continues after the early implantation leading to detachment from the epithelium of the lumen, in eutherians, there is a shift to anti-inflammatory cytokines that allow the continuation of the pregnancy. The lack of the inflammatory shift observed in the marsupials may be associated with the inadequate trophoblast migration and invasion necessary for placentation [19]. Consequently, although inflammation is essential for embryo attachment and early implantation, the shift towards an anti-inflammatory condition is essential for the successful maintenance of the pregnancy [20]. A major unanswered question is what are the factor(s) regulating or promoting the shift from pro-inflammatory to anti-inflammatory?

The answer to this question may exist in the signals that originate from the fetus; many of which have immune modulatory properties. We postulate that embryo-derived factors need to communicate with stromal and immune cells at the maternal/fetal immune interface, which helps to prevent a continuous inflammatory condition. One of the earliest immune modulatory factors secreted by the embryo is human chorionic gonadotropin (hCG), which can determine the function and differentiation of T cells [21–23], B cells, and dendritic cells [24,25]. hCG has been suggested to induce the immune modulatory changes seen in the phenotype of B-cells and also modulate the function of immune cells either through a direct pathway that involves the direct binding of hCG to its receptor on T and B cells [23,26] or indirect pathways by inducing changes in regulatory cell populations, such as dendritic cells [27–29]. In our study, we observed that endometrial stroma cells are an earlier target of hCG. The stroma initially supports inflammation under the influence of TNFα [10] by the secretion of pro-inflammatory cytokines and chemokines, which are required for blastocyst attachment and early trophoblast invasion [30,31]. As the placenta forms, increasing levels of hCG inhibit the expression of those pro-inflammatory cytokines by endometrial stroma cells and prevents the recruitment of immune cells, such as CD8+ T cells, that could reject the placenta [30].

In addition, macrophages are another important cellular component modulating the inflammatory milieu at the implantation site [32]. During early implantation, macrophages present at the decidua are M1 type [33,34] and produce inflammatory cytokines such as TNFα [35]; necessary for the modulation of cytokines and chemokines produced by the stroma [36]. Consequently, the modification of the type of macrophages present in the second phase of the implantation process is critical for the inflammatory shift. Again, signals derived from the embryo are critical for this shift. We reported that first trimester trophoblast cells secret Interferon Stimulated Genes (ISGs) [37], such as programmed death-ligand 1 (PDL1), which can induce the polarization of M1 into M2 macrophages, consequently decreasing inflammation [38,39] (Figure 1).

The last immunological phase of pregnancy is associated with the process of parturition. The maturing fetus has completed most of its development. Now, fetal signals will promote the switch to a pro-inflammatory in various feto-maternal tissue to ensure proper delivery. Many biochemical and endocrine factors are involved in the parturition event, such as platelet activation factor [40], endothelins [41–43], transforming growth factor [44], and platelet-derived growth factor, which will contribute to the pro-inflammatory environment. Apart from these

factors, fetal membrane senescence and the inflammation induced by this process acts as a paracrine signaling system during parturition, as it has been shown that fetal cell senescence promotes the release of inflammatory senescence-associated secretory phenotype (SASP); a set of inflammatory biomarkers associated with term labor [45,46]. However, the premature activation of fetal membrane senescence is a characteristic observed in preterm birth (PTB) and preterm premature rupture of the fetal membranes (pPROM) [46]. Therefore, parturition is a timed event characterized by the recrudescence of an inflammatory process, which promotes uterine contraction, expulsion of fetus, and rejection of the placenta [5].

In summary, pregnancy is a unique immunologic condition, which requires the precise switching between different immune statuses during the three developmental trimesters, any disturbance to the dynamic balance will be detrimental to pregnancy progression, resulting in poor pregnancy outcomes and complications. Thus, the success of pregnancy greatly depends on the capability of the maternal immune system and the local signals from the maternal-fetal interface to control and regulate the immune response during pregnancy.

3. The Role of the Placenta as an Immune Modulatory Organ

Infections pose a significant threat to pregnancy and to the well-being of the fetus. Bacterial and viral infections are considered as the two types of microorganisms that have been proven to be of major risk for the normal success of the pregnancy. There are strong clinical links between bacterial infection and preterm birth [47–50]. Indeed, infections have been reported to be responsible for up to 40% of preterm birth cases [51,52]. Furthermore, 80% of preterm deliveries occurring at less than 30 weeks of gestation have evidence of some types of infection [49,50]. Various experimental *in vivo* models have demonstrated that delivery of infectious components triggers preterm delivery, fetal damage, and even maternal death [53–55]. Clinical studies have also correlated placental infection and inflammation with prematurity [56,57]. Maternal Immune Activation (MIA) is associated with the higher risk for developmental problems in the offspring, such as autism spectrum disorders (ASD), schizophrenia, and allergies [58], which is supported by many experimental studies [59–63].

Growing literature suggests that the way in which a microorganism can induce a pregnancy complication, such as preterm birth, involves the dysregulation of the innate immune responses towards the pathogen, leading to excessive inflammation and apoptosis at the maternal-fetal interface [64,65]. Meaning the same cells under normal conditions that promote fetal acceptance may initiate a detrimental immune response, triggered by infection, that promote fetal rejection [66–68]. However, a new paradigm is being established in terms of the immunological response of the mother to micro-organisms. Contrary to previous thoughts that would focus only on the maternal immunologic response to the pathogens, it is now evident that the overall response during pregnancy is determined and influenced by a specific and active responses from the fetal/placental unit. In other words, the immunological response to infections during pregnancy is the result of the combination of signals originated from the maternal immune system and the fetal-placental unit, leading to a unique immunological response (Figure 2). Although the fetal immune system can recognize and respond, it is mainly the signals originating from the placenta that will modulate how the maternal immune system will behave in the presence of different pathogens. Therefore, it

is crucial to understand how the placenta responds to dangerous signals and the modulatory role of placental signaling on maternal immune response.

Following implantation and early placentation, the placenta functions as the primary organ to exchange nutrients, gases, and metabolic waste products between maternal and fetal blood. In this stage, there is rapid growth and development of fetus, which requires an undisturbed environment that, otherwise, will impact fetal development. The trophoblast represents the first point of contact between the blastocyst and the maternal decidua and, as discussed above, has an active role in shaping the immunological milieu at the implantation site [69]. Trophoblast cells of human placenta, which are derived from the outer cell mass of the blastocyst, not only serving as the means for nutrient exchange, but also protecting the fetus from foreign pathogen attack. As early as nine days after implantation, the embryo is surrounded by two layers of trophoblast cells: the inner mononuclear cytotrophoblasts (CTBs) and the outer multinucleated syncytiotrophoblasts (STBs) layer. As the outermost layer of human placenta, STBs are highly resistant to infections, including *Listeria monocytogenes*, *Toxoplasma gondii*, HCMV, HSV1, and ZIKV [70–77]. However, when compared to the low susceptibility of STBs, CTBs are more susceptible to infections. For example, STBs of first-trimester chorionic villi are mostly resistant to HCMV infection, while CTBs and other cells of the villous core are more susceptible [73]. Consistently, the primitive trophoblasts, which represent the early phase of trophoblast cell development during implantation, are sensitive to ZIKV infection but become resistant after the formation of syncytium [78]. Therefore, CTBs, which are considered as placental stem cells, are more susceptible to infections when compared with STBs.

Trophoblast cells can attract and educate immune cells, and in addition, respond to signals from the microenvironment in a unique way that supports decidual differentiation, angiogenesis, spiral artery remodeling, placental, and fetal development [3,79–89]. Trophoblast have the ability to sense and respond to their microenvironment through the expression of Pattern Recognition Receptors (PRRs), such as Toll-Like Receptors (TLRs) [62,68,86,90–100] and NOD-like receptors (NLRs) [101–106], which can recognize specific molecular patterns in the microenvironment. These receptors are able to recognize damage-associated molecular patterns (DAMPs) [107,108], as well as, pathogen-associated molecular patterns (PAMPs) from bacteria, viruses, and other microbes [68,93,100,109–111].

The classical response to bacterial lipopolysaccharides (LPS) involves the recognition by TLR4, subsequent activation of nuclear factor-kappa-B (NF-κB) through the myeloid differentiation factor 88 (MyD88) dependent pathway, and finally the production of chemokines and cytokines (e.g. IL-1β and TNFα) [112–120]. A second major group of cytokines that are induced by LPS signals through TLR4 is type I IFN-β and IFN-α, which is mediated by the MyD88 independent pathway via TIR domain-containing adaptor-inducing interferon-β (TRIF) and interferon regulatory factor 3 (IRF3) [121,122]. We found that in the trophoblast, TLR4 ligation by LPS, at low concentrations, is mainly associated with the expression of IFN-β through the MyD88 independent pathway [37,123]. TLR4 ligation induces IFN-β expression by the phosphorylation of tank-binding kinase (TBK) and IRF3, which are the main regulators of type I IFN expression [122,124,125]. Exposure of trophoblast cells to LPS in the presence or absence of the TBK inhibitor BX795 [126,127], prevents

LPS/TLR4-induced IFN-β expression. Furthermore, IFN-β basal levels in the placenta from $Tlr4^{-/-}$ or $Trif^{-/-}$ mice are significantly reduced [37]. These findings emphasize a potential role of commensal bacteria-derived factors maintaining IFN-β basal expression through the TLR4/TBK/IRF3 pathway in trophoblasts. We postulate that this basal IFN-β expression is essential for maintaining immune homeostasis and to prevent viral replication to reach the fetus (Figure 3).

4. Type I Interferon-Beta Protection and Immune Modulation During Pregnancy

Type I IFNs (IFN-α and IFN-β) are polypeptides able to induce an anti-microbial state, modulate innate immune responses, and induce the activation of the adaptive immune system [128,129]. There are three IFN types: type I IFN, type II IFN, and type III IFN. Type I IFN, is the largest IFN class, including IFN-α, IFN-β, IFN-ε, IFN-κ, and IFN-ω. IFN-α and IFN-β are the most well-defined type I IFNs. IFN-β is encoded by a single gene, whereas IFN-α comprises 13 subtypes in human [130,131]. Type I IFN responses can be induced by both viral and bacterial pathogens. These pathogens are detected by TLRs, NLRs, RIG-I-like receptors (RLRs), and cGAS which promote signaling through Stimulator of IFN Genes (STING) [132,133]. Constitutive, baseline expression of type I interferon is very low in most tissues and can rapidly be triggered by viral or bacterial infection [134]. Following secretion from cells, type I IFNs mediate their effects by binding to its cell surface receptor, the type I Interferon associated receptor (IFNAR), and activating members of the janus kinase (JAK) family [135,136]. Activated JAK kinases phosphorylate the signal transducers and activators of transcription (STAT) family of transcription factors that homo-or heterodimerize and form complexes (GAS; ISGF3) with other transcription factors to activate transcription of ISGs (Figure 4A). ISGs are the primary effectors of type I IFN mediated biological responses [128,137], which act as downstream functional proteins of IFN signaling. They exert multiple effects in many different aspects. Depending on cell type, IFN doses and time of treatment, 50–1000 ISGs have been identified by microarrays [138–140]. ISGs profiles induced by three different types of IFN are unique but partially overlapped [141]. However, some ISGs can be directly induced by viral infection independent of IFN production [142].

While identified and named for their ability to interfere with viral replication in infected cells, IFNs, through specific ISGs, have immunomodulatory, cell differentiation, anti-angiogenic, and pro-apoptotic effects [143]. However, in addition to the protective effect, type I IFNs can have deleterious effects and promote complications, such as autoimmune diseases that are associated with excessive or chronic type I IFN responses. Therefore, regulation of their expression and function is critical for an efficient immune response and maintenance of tissue homeostasis.

In the placenta, Type I IFN expression is known to be a characteristic in several species, including humans [71,144–153]; and IFN-β is the predominant class, especially during the first trimester [6,154–161]. In the context of pregnancy, we have shown that loss of IFN-β signaling in the placenta leads to: 1) uncontrolled viral replication and fetal viral infection [123], 2) maternal mortality [123] and 3) hypersensitivity to bacterial products [162]; suggesting a critical

role of IFN-β signaling in the protection of pregnancy. Therefore, it is very important to better understand the function of type I IFN during gestation and the downstream regulatory genes for the development of therapeutic approaches against viral infections during pregnancy.

5. Basal Type I Interferon Signaling

Many cell types produce IFN-β, and due to the widespread expression of IFNAR, JAK1, STAT1, STAT2, and IRF9, type I IFN signaling pathway is inducible in most cell types. Constitutive IFN-β is an essential component in healthy animals, and is necessary for multiple biological functions, including maintenance of the hematopoietic stem cell niche, bone remodeling, and numerous immune cell functions. Disturbance of IFN-β signaling contributes to the pathology of antiviral immunity, autoimmune disease, and cancer [135]. A number of studies suggested that the basal expression of IFN-β under homeostatic conditions partly depends on the commensal microbial flora, which can systemically calibrate type I IFN responses [163] [164] [165,166], and the basal IFN-β production by commensal microbiota might be mediated through TLR signaling [163,167].

Basal IFN-β expression and the attendant tonic IFNAR signaling enables immune cells to rapidly mobilize an anti-microbial response [128]. In macrophages, for example, constitutive IFN-β is important for maintaining their phagocytic potential [168,169], and elimination of endogenous IFN-β impairs bacterial clearance by macrophage [170]. Furthermore, constitutive IFN-β expression shows great importance for NK cell homeostasis and antitumoral function as well. It has been demonstrated that IL-15 expression, which is a type I IFN-regulated gene, is maintained by basal IFN-β expression and is necessary for NK cell proliferation [171–174] as the number of NK cells is significantly lower in IFNAR1$^{-/-}$ or IFNAR2$^{-/-}$ mice compared with wild type mice. In addition, the lack of basal IFN-β secretion and decreased NK activity is associated with increased susceptibility to tumor formation [175]. Thus, these findings highlight the critical role of basal IFN-β signaling as a physiological pathway to maintain cell homeostasis and prime cells to exert a rapid and potent innate and adaptive immune response to pathogenic challenges. Conversely, loss of basal IFN-β signaling results in aberrant immune cell homeostasis and function, bone remodeling, and impaired antiviral and antitumor immunity.

During pregnancy, the normal IFN-β signaling is necessary for the maintenance of a healthy pregnancy, therefore, women with dysregulated type I IFN signaling exhibit adverse pregnancy outcomes, including preeclampsia, preterm birth, and neurodevelopmental defects in the fetus [176–180]. Noteworthy, high levels of type I IFN during pregnancy can be pathogenic, as it has been shown that pregnant lupus patients who have preeclampsia and other fetal complications express high level of ISG expression in their peripheral blood mononuclear cells (PBMCs). Moreover, it has been demonstrated that PAMP-driven activation of type I IFN is sufficient to prime for systemic and uterine proinflammatory cytokine and chemokine production which leads to preterm birth. In response to TLR3 ligation by Poly(I:C) or viral infection in *in vitro* and *in vivo* models, IFN signaling can lead to trophoblast apoptosis and fetal demise [62,68,181,182]. Therefore, these findings suggest the

importance of a balanced state of Type I IFN expression during pregnancy. Noteworthy, this type I IFN priming effects are conserved from mice to nonhuman primates and humans [177].

During pregnancy the placenta is continuously exposed to bacterial products either through the maternal blood or originating from the lower reproductive track. Similar as the data shown for NK or macrophages, we observed that activation of TLR4 in trophoblast cells is associated with the expression of IFN-β in a cyclic manner. Exposure of pregnant mice or trophoblast cells to LPS is characterized by phosphorylation of TBK and IRF3, leading to increased expression of IFN-β and downstream ISGs by the trophoblast (Figure 4A) [155]. Interestingly, shortly after IFN-β exposure, cells enter a state known as "IFN desensitization" that allows cells to recover from IFN signaling.

In the placenta, IFN-β expression is regulated by the expression of Axl receptor tyrosine kinase (Axl) and suppressor of cytokine signaling 1 (SOCS1) protein; two ISGs that can negatively regulate IFN signaling [183,184]. TYRO3, AXL, and MER (TAM) receptors are membrane tyrosine kinase receptors found in high abundance in immune cells and have been reported to regulate innate immune responses by dampening TLR signaling [185]. Loss of TAM receptor signaling has been associated with stages of hypersensitive inflammatory responses implicated in sepsis, chronic inflammatory disease, and autoimmune diseases [183,184,186–189]. SOCS1 has been characterized as a negative feedback loop for type I IFN signaling [188]; however, the induction of SOCS1 proteins by IFNAR activation has been shown to progress through and be contingent on TAM receptor activation [187]. Trophoblast cells express Axl and Mer mRNA, as well as the Axl ligand growth arrest specific 6 (Gas6). Their activation is associated with increased expression of SOCS1 and downregulation of IFN-β expression. Knockdown of Axl receptor in trophoblast cells results in dysregulation of IFN-β expression leading to apoptosis and fetal death [37] (Figure 4B). These findings demonstrate a central role for TAM receptors during pregnancy as negative feedback loop regulators of type I IFN signaling, and their absence is associated with an augmentation of IFN-β/IFNAR signaling. Infections that either suppress IFN-β response or blocks the negative regulatory mechanism leading to exacerbated expression of type I IFN-β will be detrimental for fetal development, the overall outcome of the pregnancy, or even maternal survival.

In conclusion, we ascertain the signals derived from the normal microbiota as positive inducers of basal IFNβ expression that provides an adequate platform to respond to bacterial and/or viral infections, and the TAM receptors as negative inhibitory regulators that prevent a chronic condition characterized by exacerbated expression of type I IFN-β which leads to cell apoptosis (Figure 4).

6. Role of Trophoblasts as an Immunological Barrier during Viral Infections

The immune homeostasis of pregnancy can be disrupted by infections from different pathogens (bacteria, parasites and viruses), leading to the impairment of fetal growth and development [190]. In addition, pregnancy complications, such as miscarriage, preeclampsia, and preterm birth are associated with the disruption of the immunological milieu by either

prolonging the inflammatory state (miscarriage) or shifting to inflammation at an early stage (preterm birth) [36,111,191]. In the long term, maternal infection has been shown to increase the risk for neuropsychiatric disorders including autism spectrum disorders [192] and schizophrenia in the offspring [193,194]. Among those threatening pathogens during pregnancy, the traditional 'TORCH' pathogens, *Toxoplasma gondii*, other, rubella virus, cytomegalovirus (CMV), and herpes simplex virus (HSV), have been considered as major causes of fetal morbidity and mortality. Unexpectedly, the new emerging ZIKA virus (ZIKV) is found to fulfill all the requirements of a 'TORCH' pathogen. It causes mild or absent symptoms in infected mothers but can be transmitted through placenta to fetus, which causes microcephaly and other fetal malformations [195–197]. Therefore, ZIKA virus is recognized as the newest 'TORCH' pathogen [197,198].

As indicated above, the placenta is able to recognize and respond to dangerous signals originating from microorganisms and damaged tissue. One of the outcomes from trophoblast cells responding to TLRs ligands is the recruitment and differentiation of immune cells. Ligation of the TLR3 agonist poly(I:C) and TLR4 ligand LPS induces the expression of chemokines, which in turn promotes monocyte, NK cells, and neutrophil chemotaxis [109]. Moreover, viral single stranded RNA (ssRNA), a TLR8 agonist, triggers restricted pro-inflammatory cytokine response by upregulating the secretion of IL-6, IL-8, and IFN-β [199,200]. Therefore, trophoblasts response against various pathogens is TLR specific, eliciting specific production and secretion of cytokines and chemokines according to the pathogen, which will also exert specific influences on the immune environment during pregnancy (Details on TLR responses have been recently reviewed by Koga et al.) [201]

A critical role of the placenta is to prevent viral vertical transmission, which can be lethal to fetus or can induce major developmental problems. During the first trimester of pregnancy, IFN-β functions as a central modulator for this protection. During early pregnancy, first trimester trophoblast cells can mount a strong type I IFN-β response, which is characterized by the expression of multiple ISGs [37]. This response is characteristic of first trimester trophoblast cells, which differs from third trimester placentas, during which type III interferons are highly expressed [71]. Compared to the constitutive release of type III interferons from full-term human trophoblast cells [71,202], we did not detect IFN-β in the culture media from human first-trimester trophoblast cell line and human primary culture cells [203], however, both the human first-trimester trophoblast cell line and primary culture cells can robustly induce IFN-β signaling when infected with Zika Virus infection. The increase of IFN-β secretion leads to the induction of several anti-viral ISGs [203]. We have found IFN-β protein expression in both human [37] and mouse placenta (unpublished data), suggestive of an evolutionarily conserved trend. Interestingly, although we detect constitutive protein expression at the placenta, we are unable to detect secreted levels in the blood or supernatant of cultured trophoblast cells. Secreted levels are detectable only following viral infection or TLR ligation, such as ZIKV, ligation of the TLR3 agonist poly(I:C) or TLR4 ligand LPS. These findings suggest that IFN-β is stored within first-trimester trophoblast cells, which allows for a rapid and potent response to viral infection. This is critical to prevent the toxicity of high levels of IFN-β to the placenta and fetus [37,182], and this expression pattern is very different from the constitutive release of type III interferons from full-term human trophoblast cells [153].

This differential expression of type I and type III interferon may be associated with the different stages of placenta/trophoblast differentiation and function. Although early studies had suggested that type III interferons were functionally redundant with type I interferons [204], several reports indicate that IFN-λ has specific functions, which differ from type I interferons [205]. Another difference between the type I IFNs and type III IFN pathways is the use of distinct receptors. IFN-λ specifically interact with a heterodimeric receptor composed of two chains: a specific ligand-binding chain IFN-λR1 (or IL-28Rα) and the IL-10R2 (or IL-10Rβ) chain [206]. In contrast, type I interferons are ligands of the IFNAR receptor [207]. The evolutionary adaptation that confers type I IFN-β signaling in the developing placenta may reflect the need for immune regulation and tolerance, which is required for the establishment of the pregnancy [69].

In the animal models, when WT or *Ifnar*$^{-/-}$ pregnant mice are challenged with DNA viruses (MHV68 or HSV-2) or RNA virus (ZIKA virus), there is a significant increase in viral titers in the *Ifnar*$^{-/-}$ placenta and fetus, suggesting that in the absence of overall IFN signaling, there is a lack of adequate defense against viral infection. Compared to the global *Ifnar*$^{-/-}$ mouse model, the importance of placental type I IFN is exemplified by experiments consisting of embryo transfers that distinguish between placental and maternal type I IFN signaling. Breeding *Ifnar*−/− males with *Ifnar*+/− females results in litters with half of the embryos/placentas lacking a functional IFNAR (homozygous *Ifnar*−/−), in a mother with functional IFNAR (*Ifnar*+/−), and half embryos/placenta with a functional IFNAR (heterozygous *Ifnar*+/−), in a heterozygous (*Ifnar*+/−) mother. Pregnant females infected with a DNA virus (MHV68) on E8.5 showed that although the mothers had a functional IFNAR, viral titers were significantly higher in placenta and fetus lacking IFNAR signaling (homozygous *Ifnar*−/−) compared to those with a functional IFNAR (heterozygous *Ifnar*+/−). Therefore, despite sharing the same maternal phenotype (functional IFNAR), the susceptibility to infection was increased in fetal/placenta units lacking a functional IFNAR [123]. Furthermore, when WT embryos (i.e., WT placenta, can produce and respond to type I IFN) were transferred into pseudopregnant *Ifnar*$^{-/-}$ dams (dam can produce type I IFN but can not activate the IFN signaling pathway due to lack of receptor), there were less viral titers in the placenta and absent fetal viral infection compared to mice with *Ifnar*$^{-/-}$ embryo and *Ifnar*$^{-/-}$ dam. Interestingly, the presence of a WT placenta prevented maternal mortality [123].

These results highlight the importance of IFN signaling in the placenta during viral infection, which suggest that: 1) placental type I IFN is critical in the control of viral replication; and 2) in the absence of placental type I IFN signaling, the resulting uncontrolled viral replication can transform the placenta into a viral reservoir with detrimental effects not only to the fetus but to the mother as well. Thus, in the setting of viral infection, placental type I IFN signaling has protective effects to both the mother and fetus.

7. Placenta Derived ISGs-Immune Modulators and Protection Against Virus

The viral life cycle involves multiple steps, including attachment, uncoating, genome replication, transcription, translation, particle assembly, and egress. The final step is to generate more virions that will be released to infect neighboring cells. Every stage of the viral life cycle is a potential target for ISGs. Thus, murine myxovirus resistance 1 (Mx1) targets viral entry by trapping viral components, such as nucleocapsids, and preventing the virus from entering cells [208]. Cholesterol-25-hydroxylase (CH25H), an enzyme that oxidizes cholesterol into 25-hydroxycholesterol (25HC) and can block ZIKV entry providing protection against ZIKV infection in mice and rhesus macaques [209]. The IFN-inducible transmembrane (IFITM) family has been shown to block viral entry as well. In humans, there are four members in the IFITM family: IFITM1, IFITM2, IFITM3 and IFITM5 [210]. They display specific anti-viral effects to different viruses [211]. ISGs that inhibit viral translation, include zinc-finger antiviral protein (ZAP), the IFN-induced protein with tetratricopeptide repeats (IFIT) family, the OAS-RNaseL pathway, protein kinase R (PKR) [212–215], and the exonuclease Interferon stimulated gene 20 (ISG20). ISG20 inhibits HBV replication by directly binding to the epsilon stem-loop structure of viral RNA and degrades the viral RNA. This effect is dependent on its Exo III domain [216]. There are few ISGs shown to inhibit viral assembly and egress. Viperin inhibits HIV-1 and influenza A virus budding at the cell membrane by restraining farnesyl diphosphate synthase (FPPS), an enzyme required for isoprenoid biosynthesis [217,218]. However, Viperin also shows anti-viral effect in early stage of viral life cycle, as it is suggested that Viperin inhibits HCV viral RNA replication [219]. Moreover, Viperin expression decreases ZIKV infection in vitro and this anti-ZIKV activity depends on the C-terminal region [220]. Therefore, these ISGs target at different stages of viral cycle to exhibit their anti-viral effects.

Evaluation of the placental response to SARS-CoV-2 reveled a significant increase in the expression of interferon signaling pathways and ISGs in individuals with COVID-19 compared to healthy individuals [221,222]. Single-cell RNA sequencing of placenta cells revealed significant upregulation of ISG15, a central player in host antiviral responses [222]. Moreover, it was found that ISGs, including IFITM1 and IFITM3, were upregulated in the placenta of pregnant patients with severe disease when compared to asymptomatic/mild COVID-19-positive pregnant women [223]. Interestingly, a recent study reported that maternal SARS-CoV-2 infection was associated with sex-specific alteration in placental ISGs response [224]. In male SARS-CoV-2-exposed placentas, there was a significantly increased expression of the classical ISGs, such as IFI6, CXCL10, CCL2, MX1, and OAS1. This induction was not observed in female SARS-CoV-2-exposed placentas [224]. This data suggests robust interferon signaling and ISGs induction specifically in the male placental infected with SARS-CoV-2. These new findings further strengthen the critical role of IFN signaling and ISGs in placental antiviral response [182,225,226].

During pregnancy, ISGs are important not only for their anti-viral function, but also are essential immune modulators that can influence multiple aspects of endometrial function. ISGs, such as ISG15 [227], MX2, and OAS1, play a crucial role in endometrial cell

differentiation, implantation, and conceptus development during early pregnancy [228]. In the mice uterus, ISG15 mRNA was detected between embryonic-day 3.5 (E3.5) and E9.5 of pregnancy. ISG15 mRNA levels were very low on E3.5 and 4.5 (the start of implantation) but significantly increased (11-fold) on E9.5 [229]. In humans, ISG15 expression was detected in cytotrophoblast progenitor cells in the placental villi and the cell column with a maximum expression levels observed in the first trimester, less in the second trimester, and no expression in the third trimester [230]. ISG20 has also been studied for its role during the implantation window in mice [231]. ISG20 mRNA was present in the uterine luminal and glandular epithelium on E3 and E4, which then decreased rapidly and disappeared completely on E5–6 [231]. This tightly regulated expression pattern of ISG20 during early pregnancy in mice and humans suggest a very specific role of ISG20 during the early stages of implantation and placentation; however, its specific role is still not clearly understood. We described the characterization of ISG20 in first-trimester trophoblast cells in response to ZIKV infection and demonstrated that ISG20 is essential for trophoblast protection again ZIKV replication [203].

In terms of immune regulation, trophoblast cells can modulate macrophage polarization through the secretion of ISGs, such as PDL1. Decidual macrophages have a high degree of plasticity that allows them to change their phenotypes based on the signals present at the implantation site. During the pre-implantation period, macrophages are mainly the M1 phenotype, they then change to M2 phenotype following trophoblast attachment and invasion and then revert to M1 phenotype at the time of delivery [232]. The polarization of M2 macrophages from M1 is mediated in part by the secretion of PD-L1 by trophoblast cells and is regulated by IFNβ [38]. Overall, we know now that trophoblast cells, in response to IFNβ, secrete multiple ISGs that are associated with the regulation of specific immune cells and their local immune functions (Figure 5). Immune cells present at the maternal-fetal interface display unique characteristics necessary for the support of the pregnancy, such as NK cells and macrophages [36]. We postulate that the unique phenotype of these immune cells is determined by trophoblast derived ISGs. Trophoblast derived IL-15 in response to IFNβ modulates NK cell activation and homeostasis [233,234]. Nicotinamide phosphoribosyltransferase (NAMPT), another trophoblast derived ISG, is known to be a key modulator of macrophages differentiation, polarization, and migration [235]. Despite all these observations, the role of ISGs in modulating immune cell functions during pregnancy remains poorly understood and needs further investigation.

8. Conclusion

Type I IFN signaling is critical for the modulation of the immune system and provides protection against viral infection, especially during pregnancy. To achieve a successful pregnancy, the maternal immune system must be tightly controlled and be equipped with the capability to rapidly respond to pathogens. Type I IFN signaling and the derived ISGs are necessary for numerous physiological processes during pregnancy. As the potent effectors of Type I IFN signaling, ISGs have shown various functions, including anti-viral, immunomodulatory, and pro-apoptotic. Unfortunately, the regulation of IFNβ expression and function, as well as the immunomodulatory function of its derived ISGs during pregnancy are still poorly understood. Furthermore, the impact of these ISGs on fetal

development is also unknown. Thus, a better understanding of individual ISG function will facilitate the development of ISG-based therapeutics and identification of ISGs as potential clinical biomarkers.

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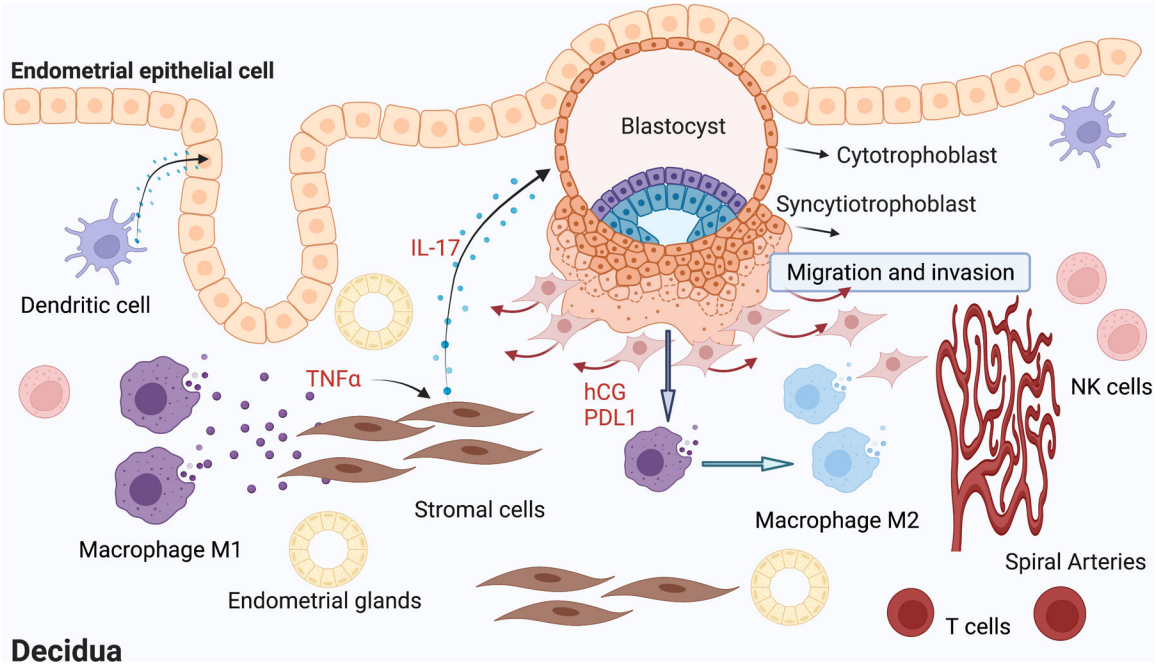

Figure 1. Immune network responsible for embryo implantation and placentation.

During the peri-implantation period, activated macrophages (M1 phenotype) secret TNFα, which induces the expression and secretion of pro-inflammatory cytokines such as IL-17 in human endometrial stroma cells. IL-17 by acting on trophoblast cells promotes the expression of factors necessary for trophoblast migration and invasion. As the trophoblasts invade deeply into the endometrial stroma and form the placenta, increasing levels of hCG inhibit the expression of pro-inflammatory cytokines by endometrial stroma cells and prevents the recruitment of CD8+ T cells, which is necessary for preventing fetal rejection. Moreover, PD-L1 secreted by trophoblast cells promotes the shift of decidual macrophages into M2 phenotype that decreases inflammation and supports tolerance. IL-17, interleukin-17; hCG, human chorionic gonadotropin; TNFα, tumor necrosis factor α; NK, natural killer; PDL1, programmed cell death ligand 1. Figure created with BioRender.com

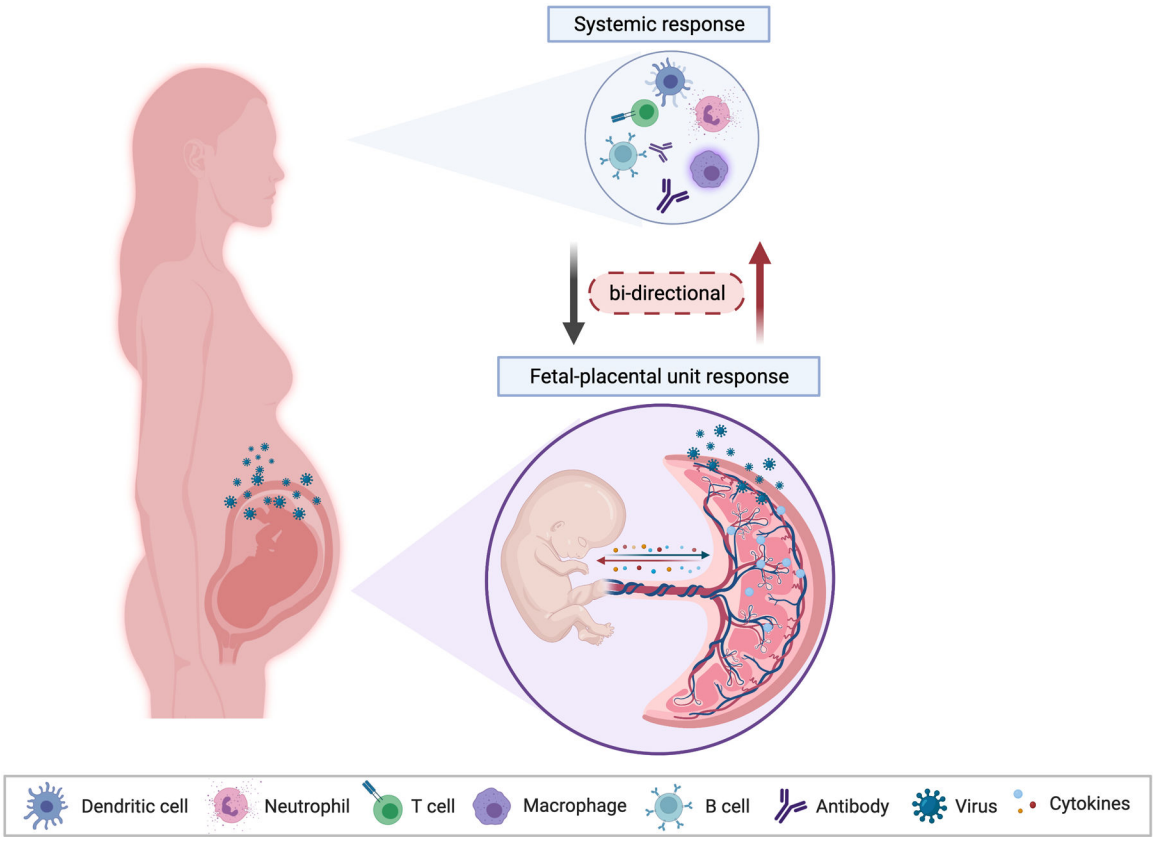

Figure 2. Unique immunological response to infection during pregnancy.

Maternal immunological responses to infection during pregnancy is complex and is strongly influenced by signals originated from the fetus and the placenta. Fetal and placenta signals have a selective effect on the type of immune cells recruited to the site of the infection. In a two-way direction, the maternal immune response will also impact the development of placenta and fetus. Therefore, the immunological response to infections during pregnancy is the result of the combination of signals originated from the maternal immune system and the fetal-placental unit. Figure created with BioRender.com

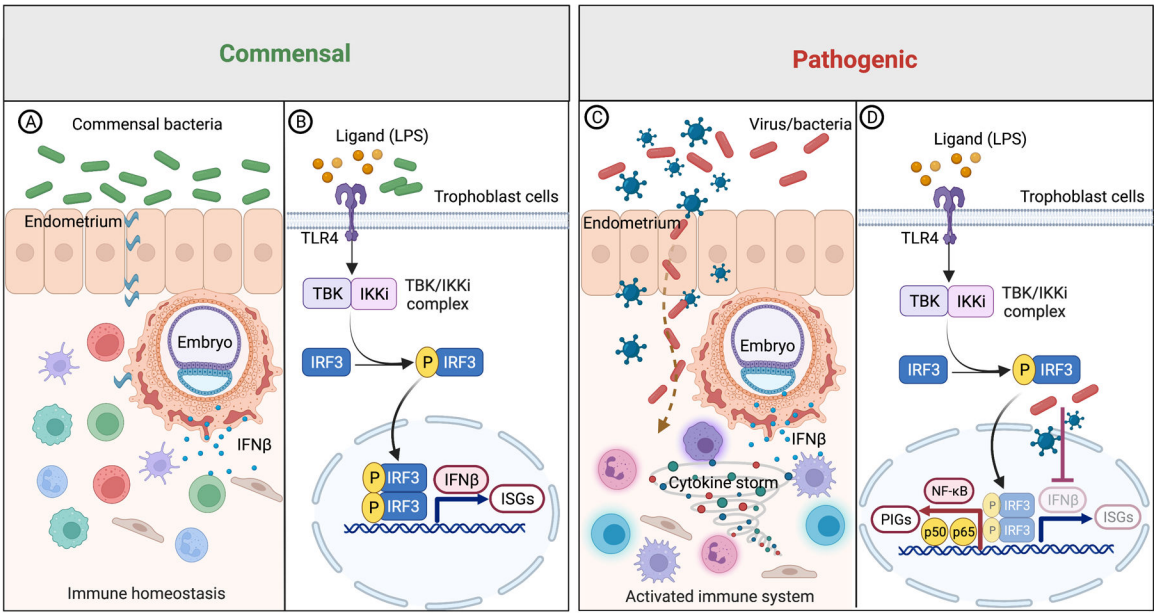

Figure 3. Regulation of IFN-β basal expression through TLR4/TBK/IRF3 pathway

(A-B) Signals derived from commensal bacteria maintains IFN-β basal expression through TLR4/TBK/IRF3 pathway. Basal IFN-β promotes the expression of immune modulatory ISGs, as well as provide awareness and protection against microbial (bacteria & viruses) infections.

(C-D) Disruption of the TLR4/TBK/IRF3 pathway, e.g., viral infections, blocks IFN-β basal expression in trophoblast cells, leading to decreased protection against pathogenic bacteria and a shift towards the NF-κB pathway and induction of a cytokine storm of pro-inflammatory factors such as IL-1β and TNFα.

LPS, lipopolysaccharides; TLR4, toll like receptor 4; TBK1, TANK binding kinase 1; IKKi, inhibitor of nuclear factor kappa B kinase subunit epsilon; IRF, interferon regulatory factor; IFN-β, interferon-β; ISGs, interferon stimulated genes; NF-κB, nuclear factor-kappa-B; PIGs, pro-inflammatory genes. P, phosphorylation. Figure created with BioRender.com

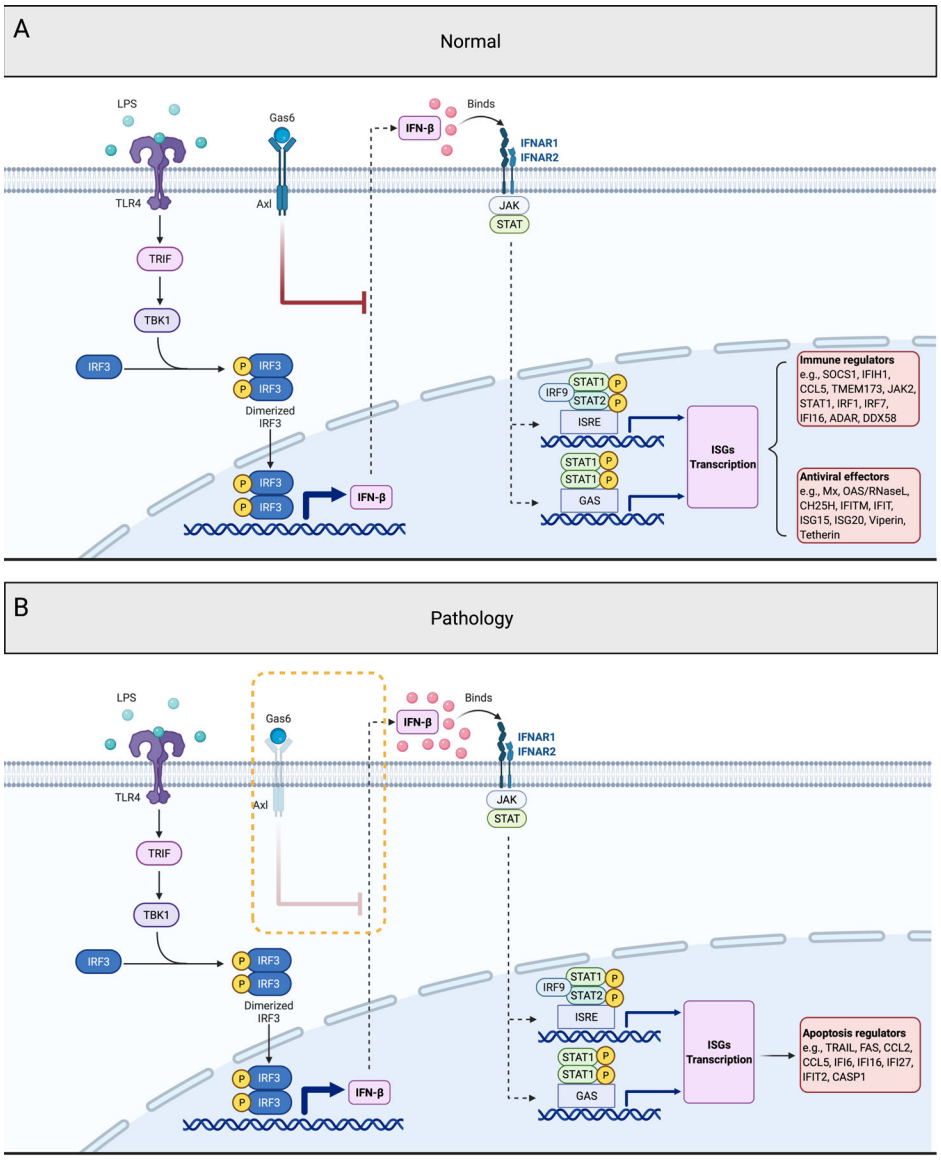

Figure 4. Regulation of IFN-β expression and function in trophoblast cells.

(A) Normal regulation of IFN-β expression and function in trophoblast cells. In normal condition, LPS binds to TLR4 induces IFN-β expression by the phosphorylation of TRIF/TBK1/IRF3, and secreted IFN-β binds to IFNAR and stimulates numerous ISGs expression. These ISGs function as the immune regulators and anti-viral effectors to maintain cellular homeostasis and to inhibit viral replication. Axl and Axl ligand Gas6, inhibits chronic IFN-β expression and its potential toxic effects.

(B) Effect of deletion of Axl on trophoblast function. Lack of Axl expression in trophoblast cells leads to the loss of negative regulation on IFNβ expression, followed by enhanced IFN-β expression and the selective induction of apoptosis related ISGs, such as TRAIL, FAS and CASP1.

LPS, lipopolysaccharides; TLR4, toll like receptor 4; TRIF, TIR-domain-containing adapter-inducing interferon-β; TBK1, TANK binding kinase 1; IRF, interferon regulatory

factor; IFN-β, interferon-β; Gas6, growth arrest specific 6; Axl, AXL receptor tyrosine kinase; IFNAR, interferon alpha and beta receptor subunit; JAK, janus kinase; STAT, signal transducer and activator of transcription; ISRE, interferon-stimulated response element; GAS, gamma-activated sequence; SOCS1, suppressor of cytokine signaling 1; IFIH1, interferon induced with helicase c domain 1; CCL, C-C motif chemokine ligand; TMEM173, transmembrane protein 173; IFI, interferon inducible protein; ADAR, adenosine deaminase RNA specific; DDX58, DExD/H-box helicase 58; Mx, MX dynamin like GTPase; OAS, 2'−5'-oligoadenylate synthetase; CH25H, cholesterol 25-hydroxylase; IFITM, interferon induced transmembrane protein; IFIT, interferon induced protein with tetratricopeptide repeats; ISG20, interferon stimulated exonuclease gene 20; ISG15, ISG15 ubiquitin like modifier; Viperin/RSAD2, radical S-adenosyl methionine domain containing 2; Tetherin/BST2, bone marrow stromal cell antigen 2; TRAIL/TNFSF10, TNF superfamily member 10; FAS, Fas cell surface death receptor; CASP1, caspase 1; P, phosphorylation. Figure created with BioRender.com

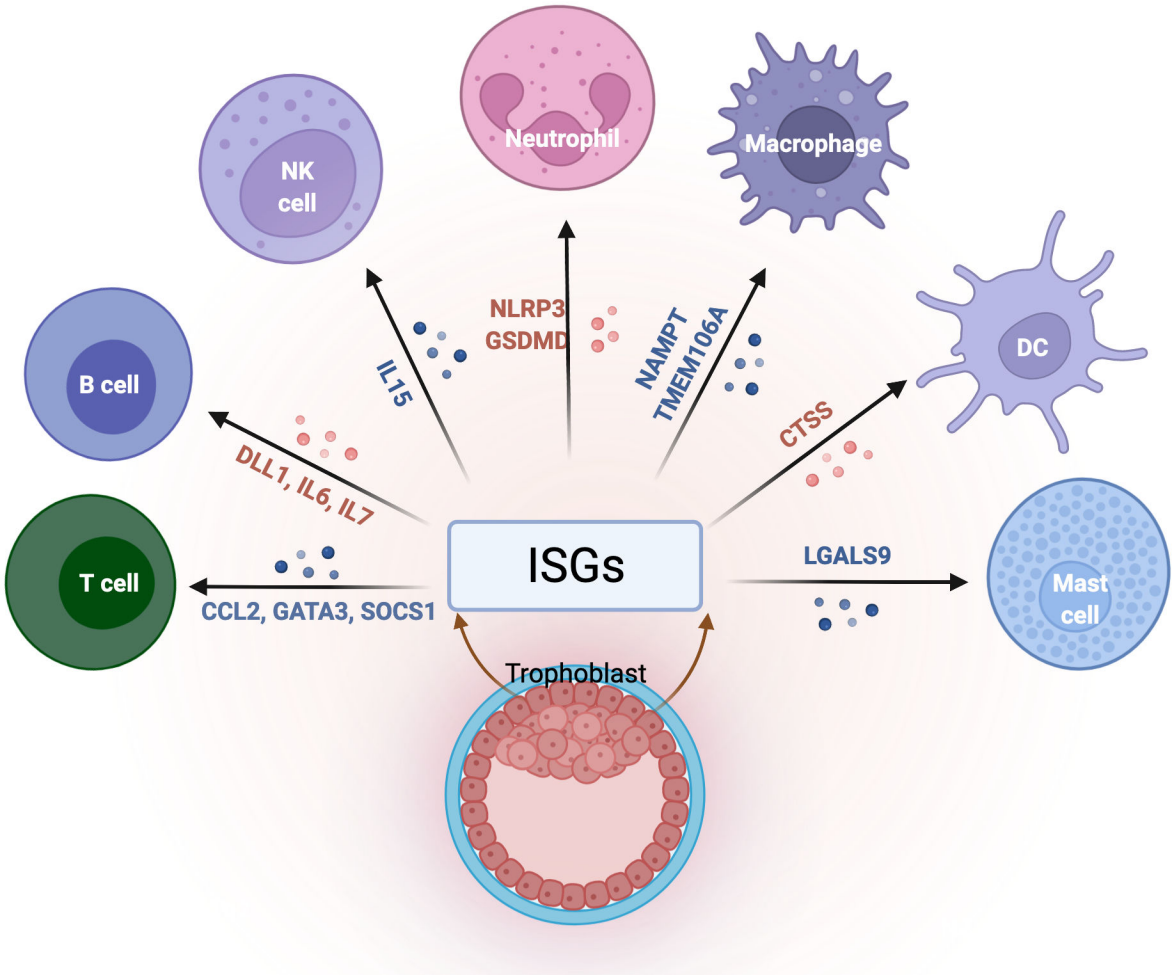

Figure 5. The role of ISGs at the maternal/fetal interface.

Immune cells present at the maternal-fetal interface display unique characteristics necessary for the support of pregnancy, and the trophoblasts plays a critical role in the regulation of their function and differentiation. Trophoblast secreted ISGs modulate immune cells functions and maintains tissue homeostasis at the maternal-fetal interface by preserving tolerance to paternal antigens as well as protection against infections.

Infections that affect ISGs expression in trophoblast cells will disrupt the immunological balance, leading to pregnancy complications. </p/> NK, natural killer; DC, dendritic cells; ISGs, interferon stimulated genes; IL, interleukin; CCL2, C-C motif chemokine ligand 2; GATA3, GATA binding protein 3; SOCS1, suppressor of cytokine signaling 1; DLL1, delta like canonical notch ligand 1; NLRP3, NLR family pyrin domain containing 3; GSDMD, gasdermin D; NAMPT, nicotinamide phosphoribosyltransferase; TMEM106A, transmembrane protein 106A; CTSS, cathepsin S; LGALS9, galectin 9. Figure created with BioRender.com