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Interleukin-10: A Pleiotropic Regulator in Pregnancy

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Abstract

Pregnancy is a unique and well-choreographed physiological process that involves intricate interplay of inflammatory and anti-inflammatory milieu, hormonal changes, and cellular and molecular events at the maternal-fetal interface. IL-10 is a pregnancy compatible cytokine that plays a vital role in maintaining immune tolerance. A wide array of cell types including both immune and non-immune cells secret IL-10 in an autocrine and paracrine manner. IL-10 binds to a specific receptor complex and activates JAK-STAT and PI3K-Akt signaling pathways while inhibiting NF-κB signaling pathway. IL-10 exerts its anti-inflammatory effects mainly by decreasing pro-inflammatory cytokines such as IL-1, IL-6, IL-12, and TNF-α, by inducing heme oxygenase-1, and by inhibiting antigen presentation via blocking major histocompatibility complex (MHC) class II expression. Prior studies from our group and others have shown that IL-10 also functions as a potent protector against vascular dysfunction, and enhancement of IL-10 may serve as an immunotherapeutic intervention to treat adverse pregnancy outcomes. This review seeks to critically evaluate the archetypal functions of IL-10 as an immune suppressive factor as well as its novel functions as a vascular protector and modulator of endoplasmic reticulum (ER) stress and autophagy in the context of normal and adverse pregnancy outcomes.

Keywords

Adverse pregnancy outcomes; Angiogenesis; Preeclampsia; Immune tolerance; Endoplasmic reticulum stress; Autophagy

Introduction

Pregnancy involves immunological modulation in a spatio-temporal manner at the maternal-fetal interface. Survival of the allogeneic fetus in the uterine microenvironment depends on the maintenance of maternal immune tolerance. In fact, the utero-placental tissue produces an array of anti-inflammatory cytokines and other factors that limit immunological aggression towards the fetus.[1–4] Thus, the balance of locally produced pro-inflammatory and anti-inflammatory effectors is essential to a successful pregnancy outcome.[5,6] Among these locally produced factors, interleukin-10 (IL-10) seems to be the most temporal immunosuppressive and anti-inflammatory molecule.[1]

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The IL-10 family of cytokines belongs to the Class II cytokine family and consists of nine members: IL-10, IL-19, IL-20, IL-22, IL-24, IL-26 and the more distantly related IL-28, IL-28B and IL-29 based on their similarities with regard to the structure and location of their encoding genes and their protein structures and receptor complexes (reviewed in Ref 7). IL-10 was originally identified in T helper 2 (Th2) cell clones as a "cytokine synthesis inhibitory factor" that has the ability to inhibit the activity of inflammatory T helper 1 (Th1) type cells.[8] Although originally defined as a product of Th2 cells, this cytokine is now known to be produced by a wide array of cell types, including both immune and non-immune cells.[2,7]

IL-10 works in either autocrine or paracrine manner in response to the inflammatory limb of the immune system to inhibit over-activation of inflammatory signals mainly by inhibiting activities of pro-inflammatory cytokines such as IL-1, IL-6, IL-12, and tumor necrosis factor (TNF)-α.[9–11] IL-10 also inhibits antigen presentation by blocking major histocompatibility complex (MHC) class II expression and co-stimulatory molecules such as CD80/CD86.[3,11] Additionally, IL-10 regulates differentiation and proliferation of several immune cells including T cells, B cells, natural killer (NK) cells, antigen-presenting cells, mast cells and granulocytes.[11,12] Importantly, we and others have identified novel roles for IL-10 as a potent protector against vascular dysfunction that is associated with hypertension and inflammation during pregnancy IL-10.[13–20]

Dysregulation of IL-10 has been shown to be associated not only with cancer, autoimmune and inflammatory diseases, atopic diseases (reviewed in Ref 12), but also with adverse pregnancy complications such as preterm birth, miscarriage, fetal growth restriction and preeclampsia.[3,21–24] Recombinant human IL-10 is currently being tested in clinical trials for treating many diseases including rheumatoid arthritis, inflammatory bowel disease, psoriasis, organ transplantation, and chronic hepatitis C.[12] Interestingly, experimental studies from our laboratory and others have shown that administration of recombinant IL-10 reverses or alleviates symptoms of many adverse pregnancy outcomes in animal models.[20,25–30] Thus, the IL-10/IL-10 receptor (IL-10R) axis may become a new target for therapeutic intervention and treatment of these adverse pregnancy outcomes. In this review, we focus on the archetypal function of IL-10 as an immune suppressive factor as well as its novel functions as a vascular protector and modulator of endoplasmic reticulum (ER) stress and autophagy in the context of normal and adverse pregnancy outcomes (Figure 1).

IL-10 Gene and Expression

Human IL-10 is an acid-sensitive homodimeric protein with a monomeric molecular weight of 18.5 kDa that is encoded on chromosome 1 in both mice and humans. Mouse IL-10 and human IL-10 are fairly conserved in their amino acid sequences sharing ~73% homology and mainly differ in N-glycosylation sites with human IL-10 lacking of this site.[11,12] The gene promoter polymorphisms have been described that influence transcriptional, phenotypic, and functional characteristics of a spectrum of genes.[31,32] Recent reports provide evidence for genetic and epigenetic regulation of IL-10 production.[33–38] The IL-10 gene promoter contains several transcription factor-responsive elements which can be modulated by endotoxin, TNF-α, catecholamines, and cAMP-elevating drugs.[12] Three

linked single nucleotide polymorphisms (SNPs) in the IL-10 gene promoter have been found at −1082(G/A), −819(C/T), and −592(C/A) base pairs upstream from the transcriptional start site.[1,31] GCC, ACC, and ATA, the major haplotypes of the −1082, −819, and −592 SNPs, have been shown to have effect on the expression of IL-10 with the GCC haplotype being associated with high *in vitro* IL-10 production and the ACC and ATA haplotypes with low IL-10 expression.[31] Polymorphic changes in the human IL-10 gene promoter at three well characterized sites, −1082, −819, and −592, are thought to contribute to dysregulated IL-10 production and to the onset and severity of autoimmune, neoplastic, and infectious disorders such as systemic lupus erythematosus and Alzheimer's disease.[1,31,33–37,39,40] Importantly, evidence has also been found for the association of the IL-10 gene promoter polymorphisms with adverse pregnancy outcomes.[31,41] Our laboratory prepared reporter gene promoter constructs containing GCC, ACC, and ATA haplotypes using DNA from recurrent spontaneous abortion patients harboring polymorphic changes at −1082 (G-A), −819 (C-T), and −592 (C-A) sites in the IL-10 promoter.[31] These individual luciferase reporter constructs were transiently transfected into either primary term trophoblasts or THP1monocytic cells. Our results revealed that GCC promoter construct was significantly activated in lipopolysaccharide (LPS)-treated trophoblast cells, but not in monocytic cells, whereas the ACC promoter construct showed weaker activation in both cell types. Importantly, LPS inhibited constitutive activation of ATA promoter in THP1 cells, but not in trophoblasts.[31] Similarly, a more recent study also suggested that the IL-10 T-819 C, but not G-1082A gene promoter polymorphism, can be a major genetic regulator in the pathogenesis of preeclampsia (PE).[41]

Many transcriptional factors have been shown to regulate IL-10 gene expression. A prior study demonstrated that c-Maf is an essential transcription factor for IL-10 gene expression in macrophages activated with LPS.[42] Furthermore, Sharabi et al showed that Twist2 deficient mice when challenged with LPS exhibit a decrease in IL-10 secretion and c-Maf mRNA.[43] It was further suggested that Twist2 could bind to the c-Maf promoter and activate c-Maf transcription, leading to IL-10 expression. In addition, programmed cell death protein 4 (PDCD4), a tumor suppressor, inhibits cap-dependent translation of mRNA via interacting with the eukaryotic translation-initiation factors elF4a and elF4G, which leads to inhibition of translation of many target mRNAs including that encoding IL-10. More recently, van den Bosch et al reported that PDCD4 also interacts with Twist2 and inhibits c-Maf induction via sequestering Twist2, which leads to inhibition of IL-10 expression.[44] This study showed that LPS promotes PDCD4 degradation and subsequently results in dissociation of Twist2 from PDCD4, which induces IL-10 expression via binding of dissociated Twist2 to c-Maf.[44] Additionally, the transcription factor Blimp-1, encoded by *Prdm1*, has been reported to be an important regulator of IL-10 production as IL-10 production in Th1 cells was strictly dependent on Blimp-1 but was further increased by the synergistic function of c-Maf.[45]

IL-10 is expressed by a broad range of cell types in the adaptive immune system, including Th1, Th2, Th17, regulatory T cells (Tregs), CD8+ T cells and B cells, as well as in the innate immune system, including monocytes, macrophages, dendritic cells, natural killer (NK) cells, granulocytes, neutrophils, esinophils, and mast cells. Additionally, IL-10 is

produced by non-immune cells, such as keratinocytes and tumor cells.[9] Numerous studies have indicated that IL-10 expression is regulated by these cell types at different stages of an immune response (reviewed in Ref 9). The maternal-fetal interface is composed of trophoblast cells of fetal origin intermingled with specialized maternal lymphocytes, stromal cells, and endothelial cells that comprise the decidua.[3] IL-10 was detected in the media from human pre-implantation embryo culture, suggesting that pre-implantation embryos secret this cytokine.[46] IL-10 expression has been found in placental villous trophoblasts, uterine NK cells (uNK cells), monocytes, and Tregs in the decidua.[47] IL-10 receptors are localized to placental trophoblasts, decidual stromal cells, macrophages, and uNK cells.[48] Modulation of IL-10 is tightly controlled and programmed at the maternal-fetal interface at different stages of normal pregnancy. In mice, IL-10 is expressed in all three trimesters of gestation and peaks at gestational day 12.[49] The kinetics of IL-10 expression in normal human placental tissue suggests higher levels of IL-10 during first and second trimesters compared to third trimester of pregnancy.[6] IL-10 also undergoes labor-associated changes as its production locally decreases prior to labor and delivery of the fetus and placenta, but increases post labor.[6, 50] We and others have demonstrated in both human and mouse pregnancy models that IL-10 is a critical molecule for a successful pregnancy outcome.[6,13,22–24,31,48,51,52] Moreover, the placental expression of IL-10 is reduced in many adverse pregnancy complications such as spontaneous abortion, preterm birth, and PE with minimum effects in circulating peripheral blood mononuclear cells (PBMCs).[52–54]

Signaling Pathways and Biological Functions

IL-10 exerts its biological effects through binding to IL-10 receptor (IL-10R). Functional IL-10R is a tetramer consisting of two ligand-binding subunits (IL-10R1 or IL-10Rα) and two accessory signaling subunits (IL-10R2 or IL-10Rβ). Expression of IL-10R is reported on hematopoietic as well as nonhematopoietic cells.[11] IL-10R1 is constitutively expressed on placental cytotrophoblasts.[55] IL-10R2$^{-/-}$ mice behave like IL-10$^{-/-}$ mice indicating that the second subunit of the receptor is essential for IL-10 signaling. The most well described IL-10-mediated signaling pathway is the Jak/STAT pathway (reviewed in Ref 56) (Figure 2). Briefly, IL-10R1 and IL-10R2 constitutively associate with Janus kinase 1 (Jak1) and Tyrosine kinase 2 (Tyk2), respectively. Binding of IL-10 to the extracellular domain of IL-10R1 elicits the phosphorylation of the receptor-associated Jak1and Tyk2, both of which, in turn, phosphorylate specific residues (Y446 and Y496) on the cytoplasmic tail of the IL-10R1. Upon phosphorylation, these tyrosine residues and their flanking peptide sequences serve as temporary docking sites for the latent transcription factor, signal transducer and activator of transcription-3 (STAT3).[56] Once binding to these sites, STAT3 is phosphorylated by the receptor-associated Jak1 and then forms homodimers and translocates to the nucleus where it binds to STAT-binding elements (SBE) in the promoters of various IL-10-responsive genes. Notably, as one of these IL-10-responsive genes, suppressor cytokine signaling-3 (SOCS)-3, after induced by the STAT3 complex, blocks phosphorylation of Jak1and subsequently inhibits JAK/STAT-dependent signaling.[56] Through rapidly inducing *de novo* synthesis of SOCS-3, IL-10 has the ability to inhibit the expression of many genes, including endotoxin (e.g., LPS)-inducible cytokine genes (e.g., TNF-α, IL-1, IL-6, IL-8, and IL-12), IFN-γ-inducible genes (e.g., MHC class II molecules,

CD80/CD86, intercellular adhesion molecule-1 and inducible nitric oxide synthase), as well as IL-4-inducible genes (e.g., CD23b and the type-I and type-II IL-1 receptors).[56] Thus, IL-10 exerts anti-inflammatory effects through inhibiting the productions of pro-anti-inflammatory cytokines and preventing antigen presentation via blocking major histocompatibility complex (MHC) class II expression and co-stimulatory molecules such as CD80/CD86 (Figure 2).

Prior studies have suggested the existence of JAK/STAT-independent signaling pathways that mediate anti-inflammatory effects of IL-10.[57] IL-10 induces the expression of heme oxygenase-1 (HO-1), a stress-inducible protein with potential anti-inflammatory effects, through a p38 mitogen-activated protein kinase-dependent pathway (Figure 2). HO-1 is the rate-limiting enzyme involved in the catabolism of heme, which leads to the generation of biliverdin, free iron and carbon monoxide (CO). CO inhibits the expression of LPS-induced pro-inflammatory cytokines and enhances LPS-induced expression of IL-10 in macrophages.[58] Co-treatment of a HO-1 inhibitor or a CO scavenger significantly decreases the inhibitory effects of IL-10 on LPS-induced TNF-α and NO production, as well as the expression of matrix metalloproteinase-9 in macrophages.[57] Collectively, HO-1 and CO play critical roles in mediating the anti-inflammatory effect of IL-10 both *in vitro* and *in vivo*.

In addition to its suppressive effect on inflammation, IL-10 can also activate a major survival pathway consisting of phosphoinositide-3K kinase (PI3K) and its downstream substrates p70 S6-kinase and Akt/protein kinase-B. Through activation of this pathway, IL-10 promotes survival of astrocytes or induces proliferation of mast cells.[59]

IL-10-mediated Modulation at the Maternal-Fetal Interface

Immune tolerance

Local immune tolerance, angiogenesis, cytokine and hormonal balance, cellular and molecular mimicry, genetic and epigenetic as well as environmental cues influence pregnancy outcomes.[4] Successful pregnancy relies on limited inflammation during implantation, immune tolerance (anti-inflammation) during mid-pregnancy, and inflammation again during parturition.[4] Thus, programming of inflammation and anti-inflammation during pregnancy in a spatio-temporal manner is critical to maintenance of maternal immune tolerance for a successful pregnancy (Figure 1). Although the mechanisms underlying the immune tolerance are poorly understood, accumulating data indicate that both maternal innate and adaptive immune responses cross-talk with the fetal-placental unit to maintain a balance between anti- and pro-inflammatory responses. IL-10, a potent immunosuppressive cytokine, has been considered as a pivotal modulator of immune tolerance at the maternal-fetal interface. The generation of mice with IL-10 gene deficiency provided an opportunity for novel approaches to investigate the role of IL-10 in regulating the immune tolerance at the maternal-fetal interface. Pregnant IL-$10^{-/-}$ mice exhibit increases in placental size and maternal blood sinuses[60] and feature susceptibility to low doses of LPS, CpG and polyinosinic:polycytidylic acid (polyI:C) as compared to WT counterparts.[22,48,61] In humans, IL-10 deficiency has been found to be associated with many adverse pregnancy outcomes such as recurrent spontaneous abortion (RSA), preterm birth,

and pre-eclampsia.[53,62–66] Collectively, these data suggest that IL-10 functions as an important protective agent contributing to the regulation of maternal immune tolerance during pregnancy.

Uterine NK (uNK) cells are the major lymphocytes present in the decidua during pregnancy and have the ability to produce and be regulated by IL-10.[22,67–69] Importantly, unlike the primordial immune functions of NK cells, the specialized uNK cells under the influence of pregnancy milieu function to support pregnancy with their unique ability to aid in regulating trophablast invasion and vascular remodeling.[53,70] Fu et al recently reported that decidual NK (dNK) cells posses a unique ability to maintain immune tolerance and successful pregnancy by suppressing inflammatory Th17 cells.[71] Th17 cells are strong inducers of tissue inflammation and represent a lineage of proimflammatory T-helper cells that are involved in autoimmune diseases.[71–76] There is only a small population of Th17 cells that exists in the decidua during the first trimester of normal human pregnancy.[71] Redundant Th17 cells prevent induction of tolerance in transplantation and pregnancy[77,78] and cause fetal loss[71] as well as participate in inflammatory infiltration in women with recurrent spontaneous abortion (RSA). On the other hand, an inflammatory microenvironment induced by IL-1β and IL-6 in the decidua of women with RSA may also promote the expansion and recruitment of Th17 cells. Importantly, observations by Fu et al further showed that the expression levels of IL-10, IL-1 receptor antagonist (IL-1RA) and IFN-γ were significantly decreased in dNK cells from women with RSA. IL-10 has been reported to be the key cytokine responsible for suppressing Th17 cells.[79] These data suggest that IFN-γ, IL-10 and IL-1RA may be synergistically involved in regulating the inhibition of Th17 cells by dNK cells, which contributes to dNK cell-mediated immune tolerance.[71]

Additionally, Treg and DC cells and M2 microphages were also found to exert an immunosuppressive phenotype and mediate the maternal immune tolerance through IL-10.[80–84] Further studies on these intricate interactions are strongly warranted.

IL-10 and Vascular Mediation

While anti-inflammatory role of IL-10 has been well established, impact of IL-10 on vascular biology has only begun to emerge. Increasing evidence has challenged the perception of IL-10 solely as an immunosuppressive factor. The IL-10$^{-/-}$ mice provide a powerful biological approach to investigate the role of this cytokine in the endothelial function and adverse pregnancy outcomes. Prior studies from our group and others have demonstrated that IL-10 also functions as a protector against vascular dysfunction.[13,14–20,84,85] IL-10$^{-/-}$ pregnant mice when challenged with environmental toxicants such as polychlorinated biphenyls (PCBs) exhibit preterm birth, intrauterine growth restriction, increase in amniotic fluid as well as impaired spiral artery remodeling and placental angiogenesis at the maternal-placental interface.[13] Mechanistically, these perturbations were associated with reduced placental protein levels of aquaporin-1 in IL-10$^{-/-}$ mice.[13] Intriguingly, recombinant IL-10 rescued PCBs-induced pregnancy perturbations and restored aquaporin-1 expression to normal pregnancy levels.[13] We have developed a novel *in vitro* model of endovascular activity that recapitulates the interaction between first trimester extravillous trophoblast lacking IL-10 production and endothelial

cells and closely mimics decidual spiral artery remodeling in response to serum from normal pregnancy.[14] Using this model, we have shown that PCBs disrupt the endovascular activity and this disruption can be reversed by exogenous IL-10.[13] Moreover, we have shown that IL-10 deficiency coupled with hypoxia leads to *in vivo* endothelial dysfunction including hypertension and extensive capillary occlusion with swollen cytoplasm in renal glomerulus as well as elevation of anti-angiogenic factors such as soluble fms-like tyrosine kinase-1 (sFlt-1), all of which can be reversed by administration of recombinant IL-10.[20] These results suggest a protective role of IL-10 in maintenance of normal pregnancy and placental angiogenesis. The role of IL-10 as a vascular protector has also been observed in non-pregnant animals. For instance, IL-10 has been shown to function as a key mediator of vascular protection in LPS- or angiotensin II-induced and aging-related endothelial dysfunction and many diseases such as hypertension, diabetes and atherosclerosis.[15–19,84,85]

IL-10 Dysregulation in Adverse Pregnancy Outcomes

Preeclampsia

Preeclampsia (PE) is a multisystem disorder of pregnancy that is characterized by hypertension, proteinurine, edema, and intrauterine growth restriction. It is a leading cause of maternal and fetal morbidity and mortality and affects 5–8% of all pregnancies worldwide. Although the etiology of PE remains poorly understood, it is generally accepted that deficiency in placental perfusion caused by improper trophoblast invasion and poor spiral artery remodeling is the major pathological axis at the maternal-fetal interface.[87–92] As a consequence, placenta-derived flux of inflammatory molecules and anti-angiogenic factors occurs in maternal systemic circulation that leads to maternal endothelial dysfunction and symptoms of hypertension, proteinuria and kidney injury.[87,93] IL-10, as a potent anti-inflammatory factor, has attracted extensive attentions for its roles in normal pregnancy versus PE. We have developed a “humanized” PE model in IL-$10^{-/-}$ mice that faithfully recapitulates most of the features of the human disease. In this model, administration of sera from PE patients into pregnant IL-$10^{-/-}$ mice results in the indication of the key features of PE including development of proteinuria, hypertension, glomerular endotheliosis and fetal growth restriction, as well as elevated levels of anti-angiogenic factors such as sFlt-1 and soluble endoglin (sEng). In contrast, the same serum sample(s) induced a partial PE phenotype in wild type mice. Mechanistically, in the absence of IL-10, these serum samples impaired spiral artery transformation and caused hypoxic injury in uteroplacental tissue. In addition, our laboratory has also generated a hypoxia-induced PE model in IL-$10^{-/-}$ mice. In this model, exposure of IL-$10^{-/-}$ mice to 9.5% oxygen triggered PE-like symptoms and induced trophoblast-specific apoptosis in utero-placental tissue through activation of the proapoptotic cascade of caspase 3. Notably, recombinant IL-10 reversed hypoxia-induced features in pregnant IL-$10^{-/-}$ mice.[20] Similar observations have also been reported suggesting that exogenous IL-10 can normalize blood pressure and endothelial function in pregnancy-induced hypertensive rats.[25] In these studies, the beneficial effects of IL-10 in pregnant deoxycorticosterone/saline-treated rats were associated with decreased plasma levels of endothelin-1, decreased levels of circulating and placental IFN-γ, as well as decreased aortic and placental expression of platelet-endothelial cell adhesion molecule (PECAM) although the effect on placental angiogenesis and spiral artery remodeling effects

remain unclear.[25] Similarly, IL-10 deficiency exacerbates Toll-like receptor 3 (TLR3)-induced PE-like symptoms in mice and exogenous IL-10 treatment confers beneficial effects on endothelial function.[27] Collectively, these experimental studies suggest that IL-10 deficiency may contribute to poor placentation and induction of vasoactive anti-angiogenic factors. This notion is further supported by data from human studies showing reduced production of IL-10 in placental tissues and serum samples from PE women.[61,94–98]

Preterm Birth and Recurrent Spontaneous Abortion

Normal term labor involves an increase in the production of various inflammatory mediators by the fetal membranes and myometrium such as IL-1β, IL-6, IL-8, TNF-α, and PGE2, as well as a decrease in local IL-10 expression.[1,6,99] Recurrent spontaneous abortion (RSA), affecting about 1–3% of women, is defined as the occurrence of three or more spontaneous abortion of clinically diagnosed pregnancies during early weeks of gestation.[1,52] About 50% of RSA cases are of unexplained variety and their etiology remains enigmatic. A major cause of preterm labor is considered to be infection, especially local infection at the maternal-fetal interface. Intrauterine infection may lead to the induction of an overwhelming inflammatory cascade similar to that occurs in normal labor.[1] Likewise, immunological factors have been thought to be responsible for the remaining 50% unexplained RSA. Clinical observations have highlighted IL-10 as a pivotal player in the pathological processes of unexplained RSA and preterm birth as numerous studies showed reduced levels of IL-10 production, IL-10-producing cells, and Th1cytokine/IL-10 ratios in PBMCs, decidual and placental tissues and sera from women with RSA.[53,100–108] All these data support the notion that perturbation in the balance of pro- and anti-inflammatory cytokine expression as well as deregulation of angiogenesis-associated cytokines are associated with RSA and preterm birth (Figure 1).

Using IL-$10^{-/-}$ mice, we developed pre-clinical models for fetal resorption and preterm birth and found that pregnant IL-$10^{-/-}$ mice, when challenged with low doses of LPS or CpG, ligands for TLR4 and TLR9, respectively, experienced fetal resorption or preterm birth depending on the gestational age–dependent exposure.[22,23,48] These adverse pregnancy outcomes were directly associated with activation and amplification of TNF-α–producing uNK cells or macrophages.[22,23,48] In these models, IL-10 had a critical role as a vascular protector and anti-inflammatory cytokine for maintaining pregnancy in response to mild or moderate levels of inflammation.[2,3] Similar observations were also reported in rat models that administration of IL-10 attenuated LPS-mediated fetal dearth rate and fetal growth restriction.[29,30] A recent study provided a supporting evidence for the role of IL-10 in preventing preterm birth as increased IL-10 production occurring via augmented cAMP accumulation contributes to resistance to LPS-induced preterm birth in mice with deficiency in G-protein coupled receptor CB2.[109]

Our prior studies indicated that preterm labor and delivery in IL-$10^{-/-}$ mice were associated with placental infiltration of cytotoxic uNK cells and placental cell death. Depletion of NK cells or TNF-α neutralization in these mice restored term delivery. Furthermore, TNF-alpha neutralization prevented uNK cell infiltration and placental cell apoptosis. These results suggest that the uNK cell-TNF-α-IL-10 axis plays an important role in the genesis of

infection/inflammation-induced preterm labor/delivery.[23] Similarly, injection of TLR9 ligand, CpG on gd 6 or gd 14 resulted in fetal resorption or preterm birth in IL-10$^{-/-}$ mice, but not in its wild type counterparts. Thus, our results clearly indicate that IL-10 deficiency coupled with TLR4 or TLR9 activation induces fetal loss and preterm birth.[48] Consistent with these observations, nonobese diabetic (NOD) mice, known to be deficient in both Treg cells and other IL-10^{+} cells, was found to be sensitive to CpG for induction of pregnancy loss.[120,111] Adaptive transfer of *in vitro* 2-amino-2-[2– (4-octylphenyl)ethyl]propane-1,3-diol-induced Treg cells to NOD mice rescued CpG-mediated pregnancy loss via increasing the numbers of decidual Foxp3+ Treg cells and other IL-10-producing cells.[26] However, our recent study suggests that although IL-10 functions as a pregnancy-compatible cytokine,[48] TLR3-mediated induction of inflammation at the maternal-fetal interface may alter the anti-inflammatory characteristics of this cytokine.[61] In this study, we provided evidence for immune programming of fetal loss in response to polyinosinic:polycytidylic acid (polyI:C), a viral mimic and an inducer of inflammatory milieu. In wild type (WT) mice, poly(I:C) treatment induced expansion of NKG2D^{+} uNK cells and expression of Rae-1 (an NKG2D ligand) on uterine macrophages and led to fetal resorption. In IL-10$^{-/-}$ mice, NKG2D^{-} T cells instead became the source of fetal resorption during the same gestation period. Interestingly, both uterine NK and T cells produced TNF-α as the key cytotoxic factor contributing to fetal loss. Interestingly, polyI:C-treated IL-10$^{-/-}$ mice when supplemented with recombinant IL-10 experienced fetal loss through NKG2D^{+} uNK cells, similar to the response in WT mice. These results indicate that pregnancy-disrupting inflammatory events mimicked by poly(I:C) are regulated by IL-10 and other inflammatory signals.[61]

IL-10, Endoplasmic Reticulum (ER) Stress, and Pregnancy

ER is an essential organelle for protein synthesis, folding, post-translational modification (N-linked glycosylation, disulfide bond formation and oligomerization) and secretion. These processes are intricately programmed and rely on the optimum levels of ATP, Ca^{2+} and an oxidizing environment. Pathological stimuli can interrupt the protein folding process through disturbing metabolic and energy balance, leading to accumulation of misfolded proteins in the ER, a condition termed “ER stress”. These pathological stimuli include factors that cause ER calcium depletion, altered glycocylation, nutrient deprivation, oxidative stress, DNA damage, or energy perturbation.[112,113] In order to remove these misfolded proteins, cells evolve a series of evolutionarily conserved signal transduction pathways, collectively referred to as the unfolded protein response (UPR). Upon aggregation of misfolded proteins, binding immunoglobulin protein (BiP) or glucose-regulated protein 78 (GRP78) binds to these misfolded proteins and dissociates from three membrane-bound ER stress sensors, protein kinase R-like ER kinase (PERK), activating transcription factor 6 (ATF6), and inositol-requiring enzyme 1 (IRE1). Dissociation of BiP from these stress sensors results in sequential activation of PERK-, ATF6- and IRE1-initiated pathways: i) activated PERK blocks protein translation by phosphorylation of eIF2a (eukaryotic translation initiation factor 2a), ii) activated ATF6 acts as a transciption factor to induce expression of ER-resident chaperones such as BiP, and iii) activated IRE1 splices X-box binding protein 1 (XBP1) mRNA. The spliced XBP1 gene product induces the transcription of different genes involved in the ER-associated degradation pathway. Thus, activation of the UPR machinery leads to restoration of protein homeostasis within ER lumen by: i)

inhibiting protein translation to reduce the burden on the folding machinery, ii) generating more ER-resident chaperones to increase the capacity of the UPR machinery, and iii) activating the ER-associated ubiquitin proteasomal degradation pathway to remove accumulated misfolded proteins.[112–117] However, if ER stress is persistent and excessive, and ER homeostasis cannot be re-established, the UPR will initiate the mitochondrial cytochrome c-independent apoptotic pathway to eliminate the stressed cells.[114,115] Thus, the UPR functions as a cell-protective mechanism as well as a cell-destructive terminator. Notably, there is evidence suggesting that chronic UPR activation leads to an activation of NF-κB and the inflammasome, which promote local inflammation.[118]

Deficient placental perfusion induces oxidative stress and triggers release of inflammatory cytokines, anti-angiogenetic factors and placental debris, which lead to placental ER stress.[119,120] Accumulating evidence suggests that placental ER stress is an important contributor to the pathology of many adverse pregnancy outcomes including early pregnancy loss, impaired placental development, intrauterine growth restriction and early-onset form of PE.[121–127] Burton and coworkers recently reported that increased expression levels of many components in the UPR such as phosphorylated IRE1a, ATF6, XBP1 and BiP were observed only in the placenta from the early-onset PE, but not from both the late-onset PE and normotensive controls, suggesting a higher level of the ER stress and UPR activation in the placenta from early-onset PE.[126]

Intriguingly, IL-10 is emerging as a novel modulator of the ER stress (Figure 2).[118,128], Shkoda et al found that intestinal epithelial cells isolated from IL-10$^{-/-}$ mice exhibit increased expression levels of BiP, a prototypic marker for ER stress under conditions of chronic inflammation, suggestive of an increased ER stress in the absence of IL-10.[128] ER stress response protein, BiP, like all heat shock protein 70 family members, depletes cellular ATP via tightly binding ATP, leading to inhibition of protein folding in ER and thereby contributing to ER stress.[128] In addition, accumulating evidence suggests that BiP independently contributes to the initiation and/or perpetuation of chronic inflammatory processes.[128] Further observations revealed that IL-10 inhibited BiP and its miRNA expression via blocking ATF6 nuclear translocation and subsequently preventing ATF6 from binding to the BiP gene promoter.[128] Similar observations have been reported in a recent study suggesting that IL-10 attenuates tunicamycin-induced ER stress through suppression of BiP expression and induction of ER proteins that promote correct protein folding as well as enhancement of ER-associated degradation, which are entirely dependent on the activation of STAT1 and STAT3 signaling pathways, partially dependent on the inhibition of ROS, but independent of NF-κB inhibition.[118] These studies consistently suggest a novel role for IL-10 in suppressing ER stress in addition to the roles as an anti-inflammatory and vascular factor. Accordingly, placental ER stress induced by IL-10 deficiency may provide an additional mechanism by which IL-10 deficiency coupled with other insults such as hypoxia induces PE-like features as reported in our prior studies.[20] Similarly, the mechanism by which exogenous IL-10 rescues LPS- or hypoxia-induced symptoms of adverse pregnancy outcomes observed in our laboratory and others may also be associated with IL-10-mediated alleviation of placental ER stress.[20,29,30] Further experiments, however, are warranted to support these speculations.

IL-10 as a Modulator of Autophagy

Autophagy is a process that involves engulfing of large damaged organelles and protein aggregates into a double membrane vesicle termed the autophagosome, fusion of the autophagosome with the lysosome, and finally degradation by lysosomal resident hydrolases.[129,130] Autophagy serves as a major cell survival mechanism for orchestrating the sequestration and degradation of damaged organelles and regulating energy and nutrient homostasis.[131] A body of evidence has shown that autophagy plays pivotal roles in innate and adaptive immunity both in the direct elimination of intracellular bacteria and in the presentation of endogenously expressed antigens via MHC.[131] Autophagy can be induced by numerous stimuli including nutrient deprivation/amino acid starvation, growth factor withdrawal, ER stress, mitochondrial damage as well as by various immune factors including both host- and pathogen-derived molecules such as toll-like receptor ligands and inflammatory cytokines such as IL-1, IL-2, IL-6, TNF-α and IFN-γ.[131] In contrast, anti-inflammatory cytokines including IL-4, IL-10 and IL-13 inhibit autophagy. In turn, autophagy itself can regulate the production and function of cytokines, including IL-1, IL-18, TNF-α, and Type I IFN.[131] IL-10 has been shown to inhibit autophagy through the PI3K/Akt pathway[132] or through the PI3K/Akt and STAT3 pathways in murine macrophages infected with HIV-1.[133] A more recent study demonstrates that IL-10 inhibits the autophagic flux in the MRC5 lung fibroblast cells via PI3K/Akt signaling pathway that is independent of starvation.[134] Collectively, IL-10 functions as an important negative modulator of autophagy in the context of infection.

Deregulated autophagy has been shown to be associated with brain and cardiac ischemia.[135,136] Interestingly, deregulated autophagy is also implicated in fetal growth restriction and PE.[137–141] However, the claims about whether autophagy is deficient or enhanced in these diseases are highly controversial. Previous studies indicate that autophagy plays a role in extravillous trophoblast cell invasion and vascular remodeling under physiological hypoxia conditions, and that sEng, an anti-angiogenic factor, inhibits activation of autophagy, suggesting that impaired autophagy is involved in poor placentation in PE.[139,140] Incubation of the PBMCs with sera from women with PE or normal pregnancy reveals that autophagy induction increases with gestational age in the cells treated with sera from normotensive women, but not from PE women.[141] These results imply that the autophagy activity is increased in normal pregnancy but decreased in PE. In contrast, an independent study showed that increased expression of microtube-associated protein light chain 3 (LC3, a marker for autophagy) was observed in the placenta from severe PE, but not from normal pregnancy, suggesting that increased autophagic activity in the placenta may be implicated in the pathophysiology of PE.[138] The mechanisms for this controversy remain to be investigated. However, negative effect of IL-10 on the production of pro-inflammatory cytokines that are capable of inducing autophagy should be considered. While the role of IL-10 as a regulator of autophagy has been studied in lymphocytes and fibroblasts, it is not known whether IL-10 plays a role in the regulation of autophagy at the maternal-fetal interface in the context of adverse pregnancy outcomes.

Conclusions

IL-10 functions not only as a potent immunosuppressive agent but also serves as a vascular protector and modulator of ER stress and autophagy at the maternal-fetal interface. IL-10 is a pivotal player involved in the maternal immune tolerance for survival of an allogeneic fetus. Our work using IL-10$^{-/-}$ mice reveals that IL-10 deficiency coupled with other insults such as hypoxia and inflammatory triggers (i.e. LPS, CpG and polyI:C) contributes to the pathologies of adverse pregnancy outcomes including pregnancy loss, preterm birth and preeclampsia, suggesting a link of IL-10 dysregulation to the anomalies of pregnancy. It is possible that uterine immune cells acquire an inflammatory phenotype and produce inflammatory cytokines in the absence of IL-10. Uterine regulatory T cells, NK cells and macrophages are the primary targets for such a dysregulation. These concepts should be pursued to better understand the causative mechanisms for adverse pregnancy outcomes in humans.

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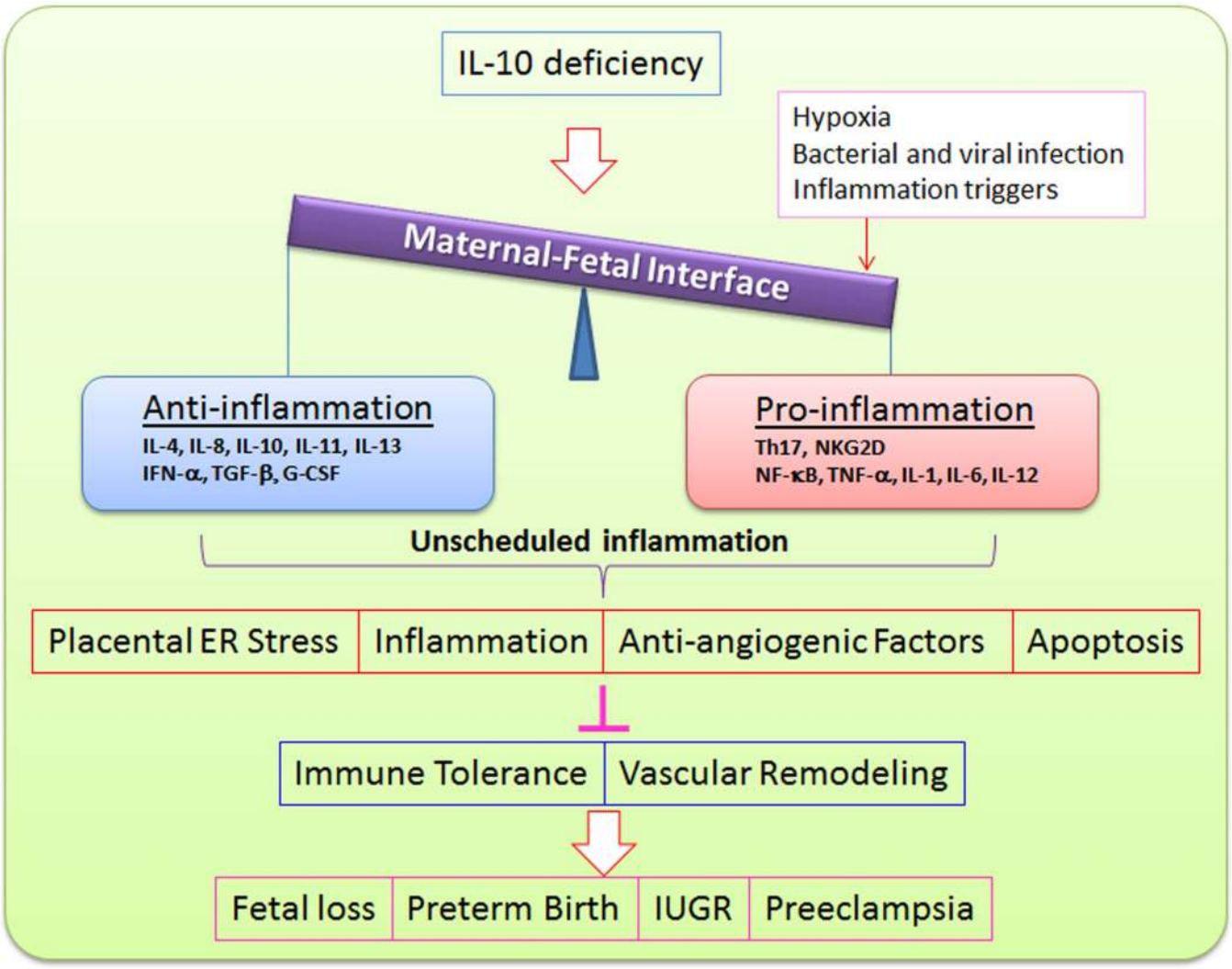

Figure 1.

Role of IL-10 in adverse pregnancy outcomes. IL-10 deficiency coupled with other insults including hypoxia, bacterial and viral infection as well as inflammatory triggers disturbs the balance between anti-inflammation and pro-inflammation at the maternal-fetal interface and consequently results in placental ER stress, inflammation and apoptosis as well as release of anti-angiogenic factors. As a result, maternal immune tolerance and vascular remodeling are perturbed, leading to many adverse pregnancy outcomes.

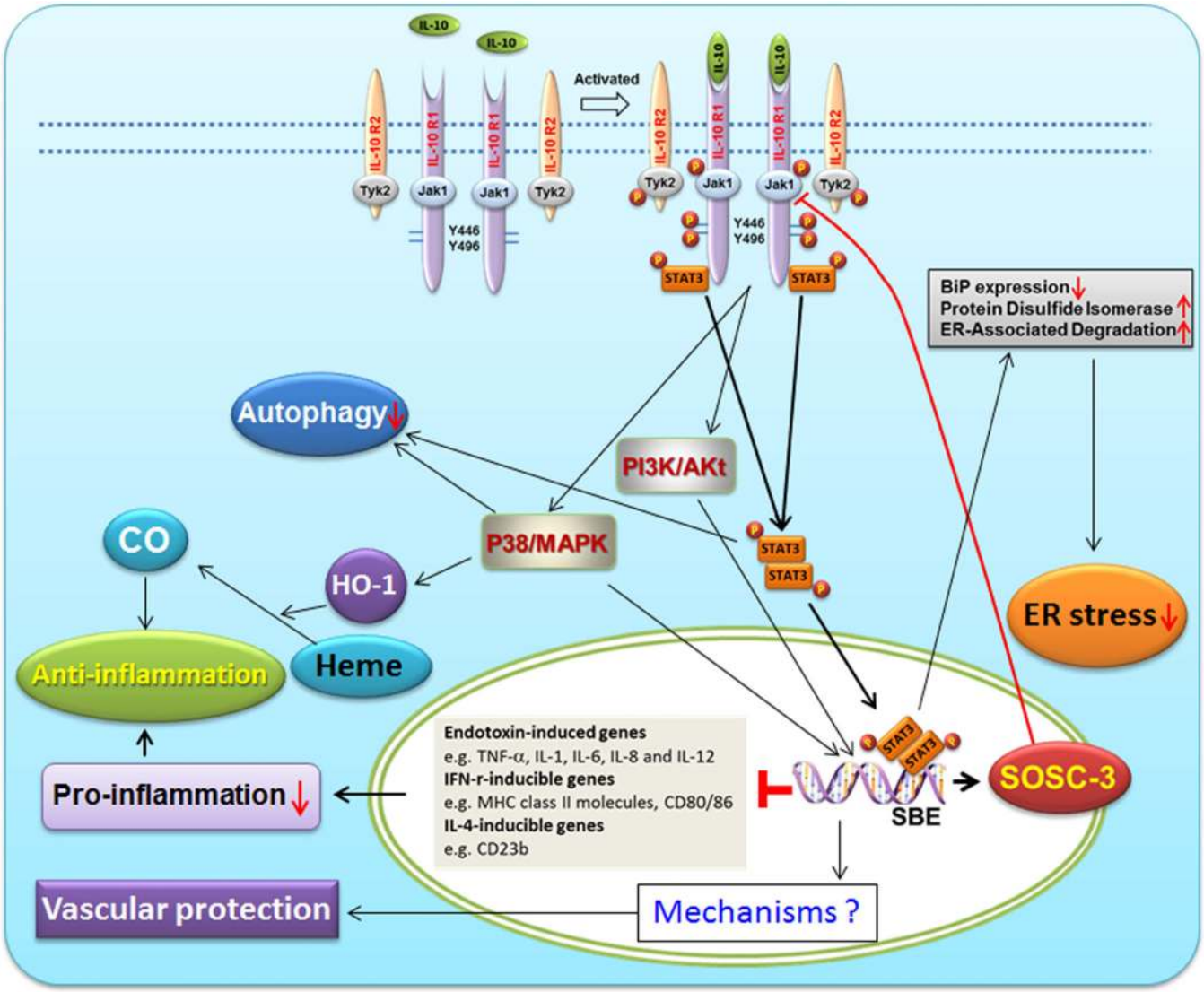

Figure 2.

IL-10 signaling pathways in normal and abnormal conditions. Binding of IL-10 to its specific receptor complex (IL-10R1 and IL-10R2) leads to activation of several signaling pathways, including well-established Jak/STAT pathway, PI3K/Akt- and P38/MAPK-mediated pathways, as well as CO-mediated pathway. Through its signal transduction, IL-10 plays a role in anti-inflammation, vascular protection and inhibition of ER stress and autophagy.