Identifying immune mechanisms mediating the hypertension during preeclampsia

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IN THE UNITED STATE ALONE, preeclampsia (PE) is a common disorder, affecting 5–7% of all pregnancies and accounts for 18% of maternal deaths and is the number one reason for premature births, annually (41). According to the National High Blood Pressure Education Program (73a), a blood pressure of 140/90 mmHg during pregnancy in women who were not previously hypertensive before pregnancy, constitutes a PE pregnancy (75). PE is typically diagnosed past the 20th wk of gestation and worsens with progression of the pregnancy until delivery. While PE remains a significant contributor to maternal vascular remodeling of the placental unit beginning early in the first trimester of a PE pregnancy. As the pregnancy progresses the disease worsens and such factors may also contribute to decreased maternal vascular remodeling of the placental unit beginning early in the first trimester of a PE pregnancy. As the pregnancy progresses the disease worsens and such factors may also contribute to the maternal vascular and renal dysfunction and...
Review

IMMUNE-MEDIATED PATHOPHYSIOLOGY IN A PREECLAMPSIC RAT MODEL

hypertension observed in the later trimesters of PE pregnancy. The shallow trophoblast invasion and lack of vascular remodeling contributes to an increase in uterine artery resistance, reduced placental blood flow, low oxygen and nutrient delivery, and the development of placental ischemia and intrauterine growth restriction of the fetus. The reduction in the supply of oxygenated blood to the uteroplacental unit causes a robust increase in oxidative stress and hypoxia-stimulated factors, such as soluble fms-like tyrosine kinase-1 (sFlt-1) and soluble endoglin (sEng), which also play a role in the development of hypertension (86). Historically, PE has not been classified as an inflammatory disorder; however, new findings suggests that the major shift in immune responses during PE versus normal pregnancies certainly suggests that PE shares many of the unique disease features displayed in autoimmune disorders.

Several studies have shown that changes in the CD4+ T helper population of cells (Th1 vs. Th2) are instrumental in maternal tolerance and overall health of a pregnancy. In fact, previous studies from the Zenclussen lab show that adoptive transfer of Th1-like splenocytes increases mean arterial pressure (MAP), fetal rejection, and inflammatory cytokines when transferred to normal pregnant mice (118). However, more recent analysis of circulating blood collected from PE women has demonstrated a much greater shift in the immunotolerance paradigm than what was previously suggested. Important clinical studies demonstrated a decrease in the proportion of circulating Treg cells and an increase in Th17 cells (27, 60, 81, 85–87). Th17 cells and cytokines such as interleukin (IL)-17, which have been known to be upregulated in autoimmune disorders such as lupus, psoriasis, and multiple sclerosis, play an important role in the host-defense mechanisms against extracellular bacteria by recruiting neutrophils to the site of infection (30). Th17 and neutrophils generate oxidative stress molecules for bactericidal action. Thus, it is hypothesized that the increase in proinflammatory T helper cells and Th17 cells will increase the release of cytokines, recruitment of neutrophils, and production of oxidative stress in the placenta of PE patients (30, 85). Tregs are responsible for suppression of responses in the adaptive and innate immune system and control unwanted immune responses through various mechanisms (40, 46). Loss of Treg function has been shown to lead to autoimmune diseases and other immunopathologies, including maternal loss of tolerance for the fetus during pregnancy (31, 39, 40, 46). Anti-inflammatory cytokines associated with Tregs and Th2 cells help regulate the immune response. Therefore, Tregs and Th2 and their respective cytokines IL-10 and IL-4 play important roles in a normal, successful pregnancy by providing a balance to the immune system (14, 108). The loss of Treg cells and their function could allow for an uncontrolled proinflammatory nature during PE by allowing for the observed increase in Th1 and Th17 cells.

While both innate and adaptive immune cells populate blood vessels under normal conditions, low-grade inflammation has most recently been established as a mechanism contributing to the development of cardiovascular disease (76, 88). During inflammation, leukocyte numbers in the vascular wall greatly increases due to increased adhesion molecule and cytokine expression stimulating migration and proliferation of white blood cells in the vasculature (76). This leads to oxidative stress and increased inflammation, causing impaired vascular function (30). The inflammatory state leads to endothelial cell barrier dysfunction that results in increased vascular permeability (96). Proinflammatory cytokines, such as tumor necrosis factor-α (TNF-α), IL-6, and IL-17 promote cytotoxic and inflammatory responses permeability (26, 29, 49, 59, 62, 120). In the vasculature, increased TNF-α and IL-6 both contribute to endothelial dysfunction, a hallmark feature of PE, and is characterized by increased adhesion molecules and endothelial cell permeability, whereas IL-17 promotes oxidative stress from neutrophils and Th17 cells (20, 50). During PE, increased TNF-α, IL-17, and IL-6 are present in the circulation and in the trophoblast cells of the placenta, whereas IL-10 and IL-4 are decreased (7, 39, 49). Studies have demonstrated that the increased inflammation observed during PE antepartum persists postpartum as well. Vitoratos et al. (103) demonstrated that women with PE remained under inflammatory stress up to 12–14 wk postpartum. A later study by Kvehaugen et al. (56) showed evidence of chronic systemic inflammation and persistent endothelial dysfunction 5–8 yr postpartum and their offspring after PE (56). Furthermore, a preclinical study by Pruthi et al. (81) demonstrated that exposure to experimental PE led to increased vascular damage after injury compared with normal pregnancy in mice. It is possible that the vascular dysfunction observed in PE women postpartum is due to the persistent inflammation after delivery. Nevertheless, such studies suggest that persistent inflammation, postpartum, may play a role in future cardiovascular disease risk in women with PE.

Several studies have reported that in addition to the hypertension and inflammation that occurs during PE, there are also changes in the central nervous system. During pregnancy there is diminished vascular resistance and hyperpermeability in the maternal brain, which increases the risk of neurological complications and cerebral edema; both of which are exacerbated during acute hypertension (13, 24). Women with PE have been reported to have an increased risk of developing stroke, white matter damage, and impaired cerebral autoregulation (97, 121, 122). Cerebral complications such as stroke, structural changes in the brain, cerebrovascular alterations, and tight junction impairments are common in inflammatory-based pathological diseases such as multiple sclerosis, rheumatoid arthritis, and HIV, suggesting that immune mediators in the circulation may have a role in impairing the blood-brain barrier (BBB) (6, 38, 52). Studies by Amburgey et al. (4) demonstrated that circulating factors in plasma from women with PE significantly increases BBB permeability. Furthermore, other studies have reported that inflammatory cytokines such as TNF-α or immune cells like CD4+ T cells are also capable of damaging the BBB (8, 54, 65). It is possible that the inflammatory factors and acute hypertension that is experienced by women with PE during pregnancy damages the vascular endothelium of the BBB, thereby increasing the permeability and entry of inflammatory mediators into the brain, which in turn contribute to neuroinflammation and neurovascular hypertension (68, 113).

Various animal models of placental ischemia exhibit an increase in the production of antiangiogenic factors (sFlt-1), inflammatory cytokines, and immune cells (such as CD4+ T cells), which is associated with the development of hypertension during pregnancy (7, 27, 59, 71, 72, 99, 101, 103, 104, 118, 119). Furthermore, work over recent years has demonstrated a role for these factors to lead to increased vasoconstrictor endothelin-1 (ET-1) and decreased vasodilator, nitric
oxide (NO), oxidative stress, and autoantibodies activating the angiotensin II (ANG II) type I receptor (AT1-AA) and hypertension, all of which are associated with clinical presentation of PE (10, 42, 72, 79, 99, 104–106, 119). However, studies to determine whether inflammatory CD4+ helper T-cell populations and other such factors remain elevated postpartum in preeclamptic women should be performed to determine their role in mediating cardiovascular disease in this patient population later in life.

**Reduced Uterine Perfusion Pressure Model**

The reduced uterine perfusion pressure (RUPP) rat model is the most reproducible animal model of PE. RUPP is used to create placental ischemia and thereby examine mechanisms involved in the pathophysiology resulting in hypertension, which are associated with PE (66, 106). In the RUPP model, a 0.203-mm ID silver clip is placed around the aorta above the iliac bifurcation and two 0.100-mm ID silver clips are placed on the right and left uterine artery arcades on day 14 of gestation. These clips placed on the rats’ blood vessels allows for reduction in uterine flow in the pregnant rat by ~40% causing placental ischemia. Placental ischemia in these rats is associated with an increase in oxidative stress, decreased antioxidant activity similar to what is observed in PE women (89). Placental ischemia in RUPP rats also causes the release of several antiangiogenic factors such as sEng and sFlt-1, an antiangiogenic factor that antagonizes vascular endothelial growth factor (VEGF), and placental growth factor (PIGF) (33, 34). In addition, placenta ischemia stimulates chronic inflammation, plasma IL-6, TNF-α, and IL-17, and AT1-AA (22, 60, 64). RUPP rats display an 13% increase in circulating CD4+ T cells compared with normal pregnant rats and a 47% decrease in Treg cells and increase in Th17 cells in the peripheral circulation compared with normal pregnant rats (106).

**Effect of RUPP CD4+ T Cells to Cause Hypertension During Pregnancy**

Similar to what is seen in women with PE, CD4+ T cells are increased in placental ischemic RUPP rats compared with normal pregnant rats (106). In recapitulation of the idea from the Zenclussen lab, we examined the role of CD4+ T cells from RUPP rats to induce hypertension in normal pregnant rats. Through a series of studies, CD4+ T cells from RUPP rats were adoptively transferred into normal pregnant rats, which not only repeatedly resulted in a significant increase in MAP, but also resulted in an increase in both TNF-α and sFlt-1, both of which have also been demonstrated to contribute to hypertension during pregnancy (59, 69, 106). Even though the mechanisms associated with hypertension during pregnancy have not been fully elucidated, several studies have indicated that increased TNF-α and sFlt-1 during pregnancy mediate hypertension via activation of the AT1-AA, endothelin, and/or reactive oxygen species (ROS) pathways, in addition to the other antiangiogenic or inflammatory effects stimulated by sFlt-1 or TNF-α (59, 73, 99).

Therefore, we performed additional studies to determine the mediator of the hypertension observed in recipients of RUPP CD4+ T cells. We found that there was indeed increased placental and renal production of ET-1. Furthermore, serum from recipient rats significantly increased vascular endothelial cell secretion of ET-1 from human umbilical vein endothelial cells (HUVECs) in culture. Blockade of the ETα receptor by administration of an ETα receptor antagonist significantly decreased the hypertension in normal pregnant recipient rats of RUPP CD4+ T cells (105), suggesting that activation of the endothelin pathway by CD4+ T cells is one mechanism causing hypertension during pregnancy. Additionally, oxidative stress was found to be stimulated in normal pregnant recipients of RUPP CD4+ T cells (104). Reduction of oxidative stress with the antioxidant apocynin, significantly reduced MAP, CD4+ T cells, and placental and cortical ROS in recipients of RUPP CD4+ T cells (104). Subsequent studies demonstrated that adoptive transfer of RUPP CD4+ T cells into NP rats induced AT1-AA and impaired renal function in recipient rats (77). Blockade of the AT1 receptor with losartan attenuated the hypertension in recipients of RUPP CD4+ T cells (77), suggesting that B cell secretion of AT1-AA can be stimulated by placental ischemic CD4+ T cells. Therefore, in a follow-up study we incubated RUPP CD4+ T cells with an antibody to the CD40 ligand (CD40L) before adoptive transfer into normal pregnant rats. One interaction that is essential for long-term B cell activation is between CD40 on B cells and CD40L on T cells. We hypothesized that communication of activated T cells with endogenous immune and/or vascular cells via CD40-CD40L interactions during PE mediate pathophysiology in response to placental ischemia-stimulated CD4+ T cells and is crucial to stimulating production of the AT1-AA. We found that blockade of CD40L on RUPP T cells before adoptive transfer attenuated the AT1-AA from being produced and resulted in less ET-1, placental ROS, and hypertension in normal pregnant recipient rats (15). These data suggest the AT1-AA is produced by a T cell-dependent response dependent on CD40L. Finally, endogenous T cell costimulation was inhibited in normal pregnant rats before the RUPP procedure to determine the effects of CD4+ T cells on placental ischemia (78). In this study, administration of abatacept (Orencia), a fusion molecule of CTLA4 that inhibits T cell costimulation, significantly decreased CD4+ T cells and hypertension, circulating sFlt-1 and TNF-α, and AT1-AA compared with untreated control RUPP rats. Furthermore, when the RUPP procedure was performed in pregnant nude/athymic rats, rats naturally deficient in T cells, there was no change in blood pressure or fetal weights (78). These studies suggested that CD4+ T cells have a direct role in not only contributing to hypertension in pregnancy but also inflammation and the antiangiogenic imbalance that is present during placental ischemia.

**Angiotensin II Type 1 Receptors Autoantibodies Mediate Hypertension During Pregnancy**

In the 1960s, human studies performed by Gant et al. (32) demonstrated that women that went on to develop PE exhibited increased vasoconstriction and blood pressure sensitivity to intravenously infused ANG II than those that went on to have normal pregnancies. However, biochemical assessment indicates PE women have normal plasma renin activity and ANG II levels (32). Several years later in the 1990s Wallukat et al. (107) reported that PE women produce AT1- AA. This AT1- AA binds to and activates the AT1R, thereby increasing chronotropic events in cultured cardiomyocytes, very similarly.
to ANG II, and are suggested to be an important link between placental ischemia and the development of hypertension. AT1-AAs bind with a high affinity to the seven amino acid sequence on the second extracellular loop of the ANG II type 1 receptor (AT1R) and increase AT1 receptor activity, intracellular calcium levels, and activation of intracellular mitogen-activated kinase/ERK kinase pathways (19, 100, 116). AT1-AA's activity on the AT1 receptor was verified by antibody isolation and affinity column antibody purification. Bioactivity was determined analyzing chronotropic events stimulated in cultured neonatal rat cardiomyocytes, which was blocked with losartan, the AT1R antagonist (107). AT1-AA increases tissue factor, ROS production, NADPH oxidase components, and activation of nuclear factor κ-β (NFκ-β) from vascular smooth muscle cells (VSMC) and trophoblast cells (21). AT1-AAs cultured with rat neonatal cardiomyocytes not only increase chronotropic events in cardiomyocytes but later cause apoptosis of cardiomyocytes via a TNF-α-mediated pathway (11, 47), suggesting their role in cellular or tissue necrosis and death.

Although the antigen for the generation of AT1-AA is unknown, we have shown the AT1-AA to be generated in pregnant rats with placental ischemia (RUPP rats) or by infusion of TNF-α, IL-6, IL-17, or by adoptive transfer of RUPP CD4+ T cells into normal pregnant rats (22, 64). We can hypothesize that AT1-AAs are derived from an immunological loss of self-tolerance toward the AT1R, which results in the accumulation of antibodies against the AT1R. However, antibodies can also be generated by molecular mimicry, a process in which a different molecule from a different gene or their protein product can generate autoantibodies due to similarities in structure to the epitope binding region of the antigen of interest (79, 98). For instance, the human parvovirus B19 (PVB19) capsid proteins shares a six amino acid homology with the seven amino acid sequence on the second extracellular loop of the AT1R (42, 98). PVB19 is a single-stranded DNA virus that codes for nonstructural proteins and two capsid proteins (VP1 and VP 2) (42, 98). The PVB19 has a seroprevalence of ~80% of the population and associated with several autoimmune diseases and PE (42, 98). Although this is a proposed mechanism of AT1-AA generation, more research is warranted to determine whether the PVB19 capsid proteins may serve as an antigen for AT1-AA production.

Studies with chronic AT1-AA infusion into pregnant rats increased blood pressure which was associated with increased ROS, ET-1, and sFlt-1 production (80). Furthermore, AT1-AA have been shown in an animal model to result in enhanced sensitivity to ANG II (112) as was observed in PE women by Gant et al. (31). When ANG II along with AT1-AA is administered acutely to rats during pregnancy, there is a 40-mmHg increase in blood pressure above what is observed with ANG II administered alone (10, 112). In addition, chronic ANG II and AT1-AAs administered together not only further increases MAP but also heightens oxidative stress, ET-1 secretion, and renal artery resistive index above ANG II or AT1-AA administered alone (Fig. 1) (10, 112). Studies from our lab have shown that HUVECs incubated 6 h with ANG II (10−7 M) and AT1-AAs exhibited a 100-fold increase in ET-1 (112), which was not observed in HUVECs incubated with ANG II or AT1-AAs alone. These data suggest a synergistic effect among ANG II, AT1-AA, and activation of AT1R (112). One could also extrapolate from these data that there is an enhancement of ANG II signaling when AT1-AAs are present (112).

Although the mechanisms of increased ANG II sensitivity in PE is unknown, we hypothesize that AT1-AAs increase ANG II sensitivity in PE by increasing the AT1R affinity for ANG II when the AT1-AA are present in circulation. One mechanism by which the AT1-AA can increase ANG II sensitivity is by increasing the dimerization of the AT1R (1, 83, 115). When the AT1R heterodimerizes with the vasodepressor bradykinin receptor (B2), an increase in AT1R responsiveness to ANG II occurs (115). AbbAlla et al. showed that women with PE have increased B2 protein amounts and that AT1/B2 heterodimerization is present in the platelets and the omental vessels of PE patients (1, 83, 115). Thus the mechanism by which AT1-AAs increase ANG II sensitivity in PE could be due to AT1R receptor dimerization, however, more studies are needed to verify this hypothesis.

AT1-AAs are not only elevated in women with PE but are also elevated in pregnancies with uterine growth-restricted fetuses, kidney transplant recipients, patients with systemic sclerosis, vasculopathy, tissue fibrosis, hypertension, renovascular disease, and pregnant women with HELLP (hemolysis, elevated liver enzymes, low platelet count) syndrome (23, 25, 28, 67, 119). AT1-AAs appear to be elevated as early as the second trimester of pregnancy (108) and exist up to 1 year postpartum in ~18% of PE patients (44). In addition, AT1-AA are associated with greater severity of the disease and could be an indicator in midgestation of worsening progression of the pregnancy toward PE (94). Most recently, we have shown that AT1-AA may be a causal factor for many of the neurological symptoms associated with PE. Warrington et al. (109) recently demonstrated that hypertension in response to chronic AT1-AA infusion compromised cerebral blood flow. The increase in the AT1-AA during the second trimester coincide with the development of headaches, blurred vision, and other neurological difficulties. With this most recent evidence one...
can infer that the AT1-AAs play a causal role not only in the hypertension but neurological symptoms during PE. Furthermore, one can suggest that the persistence of AT1-AAs after delivery maybe a risk factor for cardiovascular and renal disease and neurological complications that women with PE are likely to suffer from later in life.

**Alterations in Th17 and Tregs Cause Hypertension During Pregnancy**

As described above, PE is associated with a chronic immune activation that leads to an increased production of inflammatory cytokines by proinflammatory T cells, and a decrease in regulatory and anti-inflammatory cytokines, which further promotes an inflammatory state during pregnancy (9, 26, 36, 110). This imbalance between proinflammatory and regulatory cytokines could be in response to the placental ischemia that occurs during a PE pregnancy. This imbalance worsens as the pregnancy continues, which coincides with the worsening of PE symptoms (58).

**IL-17 and Th17 Cells Mediate Hypertension, Oxidative Stress, and AT1-AA During Pregnancy**

Clinical studies show an association between PE and increased Th17 cells and IL-17. The IL-17 family is made up of six cytokines: IL-17A, IL-17B, IL-17C, IL-17D, IL-17E (IL-25), and IL-17F. IL-17A is the prototype member, and IL-17A and IL-17F have similar functions, are genetically linked, and bind to the same heterodimeric receptor, consisting of IL-17 receptor A and C (55, 70). Binding of the IL-17 receptor activates the NFkB and mitogen-activate protein kinase pathways (55) acting in a feedback loop for expansion of Th17s and are therefore key cytokines responsible for proliferation, recruitment, activation, and migration of neutrophils (55, 70, 71, 117). IL-17 stimulates the production of other cytokines by neutrophils for cell-to-cell communication, and more importantly, it stimulates these cells to release antimicrobial substances, such as ROS as a host-defense mechanism used by neutrophils and macrophages against bacterial infection (70, 117). However, a role for Th17 and IL-17 in mediating the pathophysiology of PE had not previously been established. To determine whether increased IL-17 is relevant in the pathology of PE, Dhillon et al. (22) examined the effect of IL-17 infusion on blood pressure. In this study, IL-17 infusion into normal pregnant rats resulted in a significant increase in MAP and oxidative stress as measured by urinary isoprostane and NADPH-stimulated placental ROS, increased circulating Th17 cells, and AT1-AA. Blockade of the AT1 receptor by administration of losartan attenuated the blood pressure response and decreased placental production of ROS in response to chronic IL-17. Additionally, depletion of B cells with rituximab blunted the blood pressure response and decreased circulating Th17 cells in IL-17-infused rats. Finally, administration of the superoxide dismutase mimetic tempol attenuated the hypertension placental production of ROS and circulating AT1-AAs produced in response to IL-17 infusion (22). The effect of tempol on IL-17-induced pathophysiology suggests that the ROS stimulated by Th17s, via IL-17, may be an important signaling molecule for the activation of B cells to produce AT1-AAs.

To support a role for IL-17 in the pathophysiology of PE, we examined the effect of IL-17 blockade in the RUPP rat model. A soluble form of the IL-17 receptor C (IL-17RC) was infused from gestational day 14–19 in RUPP rats to block the IL-17 signaling pathway. This resulted in significant decreases in blood pressure, intraterine growth restriction, oxidative stress, and AT1-AA and lowered circulating Th17 cells. Importantly, infusion of IL-17RC increased pup weight, which was accompanied by increased placental weight and decreased uterine artery resistance index (17). Thus inhibition of this immune pathway could normalize placental inflammation and improve fetal demise as a direct result of decreased placental stress thus serving as a fetal protective mechanism during PE. Therefore, this form of immunosuppression may have an important role to preserve the health in both mother and fetus.

**Effect of Decreased Tregs and IL-10 in Preeclampsia**

Anti-inflammatory cytokines that help regulate the immune response, like IL-10 and IL-4, play important roles in a normal, successful pregnancy by providing a balance to the immune system (111). Along with increased levels of inflammatory cytokines and T cells, regulatory cytokines and T cells are decreased during PE and in response to placental ischemia (RUPP). These cells are identified by the expression of cell surface markers CD4+CD25+ and their specific internal transcription factor forkhead box protein 3 (Foxp3+) (53). Tregs are responsible for suppression of responses in the adaptive and innate immune system and control unwanted immune responses through various mechanisms. Loss of Treg function has been shown to lead to autoimmune diseases and other immunopathology, including maternal loss of tolerance for the fetus during pregnancy (53). Tregs are increased very early in normal pregnancy and reach their highest levels during the second trimester before decreasing back to normal levels (82). In diseases such as PE where Tregs and their secretion of IL-10 and TGF-β are reduced (45), stimulation and proliferation of inflammatory T cells remains unchecked, leading to excess secretion of inflammatory cytokines such as TNF-α, IL-6, and IL-17, which contribute to endothelial dysfunction, oxidative stress, AT1-AA, and the increase in blood pressure during PE.

A number of studies have provided evidence for reduced Tregs to contribute to PE. Circulating and decidual Tregs have been shown to be decreased in women with PE, and the decrease in Tregs is directly proportional to the severity of the disease (87). IL-10 is an important anti-inflammatory cytokine that is secreted by Tregs and also stimulates Tregs from naïve T cells (46, 74, 90). IL-10 inhibits Th1 inflammatory cytokines secretion and inflammation at the fetal-maternal interface. Prolinflammatory cytokines downregulated by IL-10 include IFN-y, IL-2, and TNF-α (35). Levels of IL-10 are increased throughout normal pregnancy and first begin to drop when labor begins (95). In addition to Tregs, villous cytrophoblasts secrete IL-10 during pregnancy. Moreover, the expression of IL-10 (12) and its receptor have been reported on a number of cell types in the decidua, including trophoblasts, stromal cells, macrophages, and uterine natural killer cells. It is not clear how IL-10 may influence trophoblast invasion; however, the presence of IL-10 at the fetal-maternal interface and its strong anti-inflammatory properties are suspected to con-
tribute to allogeneic tolerance of the fetus during a normal pregnancy (39, 48, 57, 71, 84, 101).

Most recent data indicate that Treg cells can be further classified into Helios natural Treg (nTreg) cells and Helios-adaptive Treg (iTreg) cells (43). nTreg cells are generated in the thymus, and iTreg cells are derived from naïve CD4+ T cells in the periphery. Newer evidence indicates that iTreg cell expansion occurs in healthy pregnancy but not in PE, suggesting that this may originate from the decidua, where distinct dendritic antigen presenting cells reside that are especially proficient to cause iTreg cell induction, essential for healthy pregnancy. Therefore, both iTreg cell induction and expansion are impaired in PE thereby allowing for chronic peripheral and placental inflammation, further complicating the pregnancy (43). Induction of iTreg cells may be important for immune tolerance toward the fetus, and if this is missing it becomes instrumental in causing the exacerbated inflammation observed during PE.

Our most recent studies demonstrated that adoptive transfer of Tregs from normal pregnant rats into RUPP rats lowered blood pressure, minimized intraterine growth restriction, reduced the inflammatory response, and significantly decreased ET-1 and placental oxidative stress. Importantly, Tregs attenuated the production of AT1-AA in response to placental ischemia (16). These data further support a role for decreased Tregs in the pathophysiology of PE. In addition we have supplemented IL-10 in RUPP rats, via osmotic mini pumps, to restore the circulating levels IL-10 to that of normal pregnant rats (37). IL-10 supplementation lowered the total population of circulating CD4+ T cells while increasing the population of circulating Tregs to that of normal pregnant rats. In addition to normalizing Tregs, IL-10 supplementation also normalized proinflammatory cytokines TNF-α and IL-6 and, importantly, supplementation of IL-10 to RUPP rats significantly lowered AT1-AA, placental ROS and ET-1, which proved beneficial in decreasing blood pressure (37). It could be that the lower levels of IL-10 during PE would allow for increased T cell activation and differentiation into a proinflammatory phenotype, thus, leading to an increased number of inflammatory T helper cells, proinflammatory cytokines, and possibly B cell stimulation. Furthermore, it could be the decrease in Tregs that results in lower levels of IL-10 during PE. Although adoptive transfer studies may not be feasible for treatment of PE, supplementation with IL-10 could be a beneficial therapeutic to consider.

Perspectives and Significance

While PE is the primary global cause of prematurity and perinatal morbidity/mortality, there is a tremendous need for improved treatment modalities for this disorder, especially to arrest its development and progression when otherwise very preterm delivery would be necessary. Indeed, our recent findings could have profound implications on identifying possible immunotargets for the treatment of PE. However, further studies are necessary to better understand which therapies could be appropriate to add to the management of PE that will provide safe outcomes for both mothers and fetuses.

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AUTHOR CONTRIBUTIONS


DISCLOSURES

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