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Placental ischemia and resultant phenotype in animal models of preeclampsia

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Abstract

Preeclampsia is new onset (or worsening of preexisting) hypertension that occurs during pregnancy. It is accompanied by chronic inflammation, intrauterine growth restriction, elevated anti-angiogenic factors, and can occur with or without proteinuria. Although the exact etiology is unknown, it is thought that preeclampsia begins early in gestation with reduced uterine spiral artery remodeling leading to decreased vasculogenesis of the placenta as the pregnancy progresses. Soluble factors, stimulated by the ischemic placenta, shower the maternal vascular endothelium and are thought to cause endothelial dysfunction and to contribute to the development of hypertension during pregnancy. Due to the difficulty in studying such soluble factors in pregnant women, various animal models have been designed. Studies from these models have contributed to a better understanding of how factors released in response to placental ischemia may lead to increased blood pressure and reduced fetal weight during pregnancy. This review will highlight various animal models and the major findings indicating the importance of placental ischemia to lead to the pathophysiology observed in preeclamptic patients.

Keywords

preeclampsia; animal models; inflammation; pregnancy; hypertension

Introduction

Preeclampsia (PE) is a systemic disease that affects the function and health of multiple organs in both the mother and baby. While there is no cure for preeclampsia, if left untreated, a more severe, convulsive form called eclampsia may occur [1–3]. PE results, in part, from improper placentation and trophoblast invasion during pregnancy, which leads to placental ischemia [4, 5]. Placental ischemia, in turn, promotes a chronic inflammation in the mother that contributes to much of the pathophysiology characterized by increased mean arterial pressure (MAP), endothelial activation and dysfunction, antiangiogenic factors,

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Compliance with Ethics Guidelines

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Conflict of Interest

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activated inflammatory cells secreting autoantibodies and inflammatory cytokines, and increased oxidative stress [6–8]. In order to study the intricate mechanisms by which preeclampsia develops and progresses, animal models that recapitulate the disease are necessary. Knowing that PE may be initiated by placental ischemia with reduction of placental blood flow between 50–70 % [9], animal models with significantly reduced uteroplacental blood flow have been developed [10]. While such animal models of placental ischemia do have their limitations, studies in a variety of species suggest that reduced uterine perfusion pressure (RUPP) models have many features of PE observed in women. These models provide an opportunity for investigators to quantify the relative importance of pathophysiological factors in mediating cardiovascular and renal dysfunction in response to placental ischemia of pregnancy. The models also provide an important tool to test the efficacy of novel therapeutic approaches for the prevention and treatment of preeclampsia.

Preeclampsia is associated with placental ischemia

While the specific mechanisms leading to the development of preeclampsia have yet to be elucidated, it is known that changes in placentation due to poor vascular remodeling in the spiral artery potentially lead to the characteristic pathophysiology of this disease [11–13]. Trophoblasts migrate along the spiral arteries and increase the diameter, leading to a lower resistance in the vessels that allows for proper placental perfusion and blood flow to the fetus and results in a healthy pregnancy for the mother and baby [14–17]. Maternal blood volume, cardiac output, and heart rate are increased early in pregnancy, but blood pressure is normally decreased, starting in the second trimester, as a result of decreased resistance in the peripheral vasculature [18]. Placental oxygen tension is low in the beginning of pregnancy [19], but PO_2 increases around weeks 10–12 of pregnancy as intervillous blood flow increases and supplies the placenta with oxygen and nutrient delivery [20, 21].

The process of trophoblast invasion and spiral artery remodeling during normal pregnancy rely heavily on the maternal immune system [22, 23]. During trophoblast invasion, the decidua, which is the lining of the uterus and forms the maternal portion of the placenta, contains a high number of immune cells that are necessary for the proper physiology of trophoblast migration [24–26].

Macrophages, natural killer (NK) cells, dendritic cells, T cells, and T regulatory cells (Tregs) are all present in the decidua and are required for a normal pregnancy. Uterine NK cells (uNK), macrophages, and dendritic cells all cumulatively play an integral role in trophoblast invasion and decidua formation [27, 28], while regulatory T cells and regulatory cytokines ensure proper control and function of these proinflammatory cells and their actions [26, 29, 30]. Together, the immune cells present in the decidua during pregnancy work to ensure proper implantation of the placenta, and to promote trophoblast invasion that is neither shallow nor overly invasive [22, 23]. This is accomplished through their production of cytokines and angiogenic factors necessary for normal pregnancy. Any imbalance in these local immune responses could potentially result in an altered formation of the placenta, which could lead to complications during pregnancy such as preeclampsia or even less desirable, loss of the pregnancy [5, 31].

Pregnancies affected by PE are associated with an improper immune response and milieu of immune cells and cytokines [32, 33]. Placental ischemia has been shown to produce an imbalance in immune function that leads to a chronic inflammation and presents a state during pregnancy that is similar to an autoimmune disease [5, 34, 35]. This immune imbalance consists of increased pro-inflammatory immune cells and cytokines, and decreased regulatory immune cells and cytokines, which is believed to contribute to the overall pathophysiology of PE, [33, 36–38]. This alteration in immune balance contributes to production of reactive oxygen species [39, 40], increased endothelin-1 expression [41–44], and B-cell production of auto-antibodies to the angiotensin II type 1 (AT1-AA), all of which culminate in the development of hypertension during pregnancy [35, 45–49].

Hypertension in response to placental ischemia; the RUPP model

Early procedures that induce a reduction of the uteroplacental blood flow during pregnancy lead to hypertension associated with placental ischemia in pregnant animals. In 1939, researchers clamped the abdominal aorta of pregnant dogs and found that it led to an approximate 50 % decrease in placental blood flow and increased the blood pressure by 25 mmHg [50]. When the clamp was removed, the blood pressure returned to normal. The same procedure was used in non-pregnant dogs, but there was no increase in blood pressure, demonstrating a pregnancy specific pathophysiology. Others have since performed a similar procedure to induce placental ischemia by decreasing uteroplacental perfusion by 40 %, leading to markedly increased systolic blood pressure in conscious pregnant dogs [51]. Endothelial irregularities and placental infarcts were also noted in these studies. Other methods have been successfully implemented in dogs where ligation or banding of the utero-ovarian arteries before pregnancy resulted in a gradual increase in blood pressure after the dogs had become pregnant, with a subsequent marked increase in blood pressure throughout the second and third trimesters [52].

This method has been employed by many other researchers in many different animal species. Researchers have induced a reduction in placental blood flow that led to hypertension in pregnant rats, rabbits, rhesus monkeys, and baboons. Aortic clamping in rabbits was also linked to preeclampsia complications, such as fetal compromise, kidney injury, platelet activation, and intrauterine growth restriction [53, 54]. In the rhesus monkey, a 30 % increase in blood pressure occurred with aortic clamping, which was accompanied by an approximate 60 % reduction in uteroplacental blood flow and subsequent development of proteinuria, increased fetal demise, and intrauterine growth restriction [55, 56]. Banding of the uterine-ovarian arteries in baboons during pregnancy led to increased blood pressure and caused much of the pathophysiology seen in women with preeclampsia [57].

The reduced uterine perfusion pressure (RUPP) rat model of preeclampsia uses a combination of aortic constriction and occlusion of the uterine-ovarian arteries to decrease blood flow to the uterus and create a state of placental ischemia in pregnant rats [58]. These rats develop much of the same pathophysiology as women with preeclampsia. Mechanical induction of placental ischemia is performed in pregnant Sprague-Dawley rats. On day 14 of gestation, restrictive silver clips are placed on the abdominal aorta above the iliac bifurcation and, in order to prevent compensatory blood flow through the ovaries, silver clips are also

placed on branches of the ovarian arteries [58, 59]. Blood pressures and tissues are collected on day 19 of gestation. This procedure reduces uteroplacental blood flow by approximately 40 % and increases blood pressure by approximately 20–30 mmHg compared to normal pregnant Sprague-Dawley rats [58]. RUPP rats demonstrate much of the same pathophysiology observed in preeclampsia, including endothelial dysfunction [58, 60, 61], decreased pup weights and litter sizes, intrauterine growth restriction [42, 62], and chronic inflammation associated with the agonistic autoantibodies to the AT1 receptor (AT1-AA) [63]. Full characterization of RUPP animals was completed through many studies that demonstrated that the model sufficiently recapitulates preeclampsia [10]. These animals demonstrate characteristics of endothelial dysfunction with a reduction in nitric oxide (NO) [58] and increased contractility of vascular smooth muscle cells [60]. As seen in women with preeclampsia, RUPP rats also have increased production of AT1-AA [63], which leads to activation of the AngII receptor and contributes to the increases in blood pressure. Similarly to women with preeclampsia, this increase in AngII receptor activity also leads to an increased production in endothelin-1(ET-1) in renal cortices, placentas, and in the vascular circulation [61]. Reactive oxygen species (ROS) in both the placenta and in circulation are increased in RUPP rats versus normal pregnant animals [64]. Importantly, anti-angiogenic factors like soluble fms-like tyrosine kinase-(sFlt-1) and soluble endoglin (sEng) are increased in RUPP animals, which leads to further decreases in the vascularization of the placenta and blood delivery to the fetus, and contributes to the development of hypertension [65, 66].

Placental ischemia in preeclamptic patients is associated with increased inflammatory T cells and inflammatory cytokines. In addition, PE is accompanied by decreased regulatory cells and regulatory cytokines. In concert, such alteration will result in a chronic state of inflammation. Similar immune alterations associated with preeclampsia were validated in RUPP rats to demonstrate a role for placental ischemia in causing these same imbalances in the immune repertoire [67]. An increase in inflammatory $CD4^+$ T cells along with a decrease in T regulatory (Tregs) cells is seen in RUPP rats. Increased inflammatory cytokines such as tumor necrosis factor alpha (TNF-α) and interleukin 6 (IL-6), and interleukin 17 (IL-17) are seen in the circulation of RUPP rats, and regulatory cytokines such as interleukin 10 (IL-10) and interleukin 4 (IL-4) are decreased [43, 68]. Table 1 shows a summary of the similarities between the RUPP rat model and women with preeclampsia. The presence of all of these characteristics in this model indicate that the RUPP model can be a valuable tool for the study of mechanisms stimulated by placental ischemia that lead to characteristics of preeclampsia.

T Lymphocytes during Preeclampsia

A state of controlled inflammation that exists during a normal, healthy pregnancy is necessary for proper implantation and placentation to occur. A balance that exists between pro-inflammatory and anti-inflammatory cells and cytokines during pregnancy allows for the control of necessary inflammatory responses while preventing excessive inflammation [69–72]. When this balance is shifted toward pro-inflammatory responses, and inflammation thus occurs it results in characteristics similar to those observed in preeclampsia [73–75].

A role of inflammatory T cells in the pathogenesis of preeclampsia has been established through adoptive transfer studies using Th1-like splenocytes. Zenclussen et al. (2004) demonstrated the importance of inflammatory T cells when they isolated splenocytes from normal pregnant mice, cultured them to promote differentiation into Th-1-like cells that secreted Th-1 specific cytokines [76], and transferred them into normal pregnant mice. Adoptive transfer of these Th-1-like cells provoked symptoms of preeclampsia such as increased blood pressure, alterations in kidney function, and increased inflammatory markers in the decidua. Adoptive transfer of the Th-1-like splenocytes in non-pregnant mice did not result in any changes in immune composition or blood pressure, thus demonstrating that such a response is specific to pregnancy [76].

The Role of CD4+ T cells in Preeclampsia

Later studies further supported a role for Th-1 cells in the development of preeclamptic symptoms. $CD4^+$ T cells from the RUPP rat model of preeclampsia were adoptively transferred into normal pregnant Sprague-Dawley rats. Adoptive transfer of RUPP $CD4^+$ T cells into normal pregnant rats leads to much of the characteristic pathophysiology seen during preeclampsia, such as a significant increase in blood pressure and declines in glomerular filtration, circulating inflammatory cytokines TNF-α, IL-6 and IL-17, anti-angiogenic factor sFlt-1, and AT1-AA compared to normal pregnant recipients of normal pregnant CD4+ T cells, [38], increased ET-1, and oxidative stress. Normal pregnant $CD4^+$ T cells had no effect on blood pressure or circulating factors when injected into normal pregnant rats [38]. Furthermore, the adoptive transfer of RUPP $CD4^+$ T cells into non-pregnant rats did not have any effect on blood pressure or circulating factors. Losartan or Rituximab blocked any AT1-AA-mediated increase of blood pressure in response to inflammatory T cells [77, 78]. These adoptive transfer studies, along with the previously described Th-1-like splenocyte study, indicate a strong role for preeclamptic inflammatory T cells in the development of hypertension during pregnancy, and in promoting the pathophysiology that accompanies the rise in blood pressure.

IL-17 and TH17 cells mediate hypertension, oxidative stress, and AT1-AA during pregnancy

Although clinical studies show an association between preeclampsia and increased T_H17 cells and IL-17, their role in mediating the pathophysiology of preeclampsia had not previously been established. Dhillon et al. examined the effect of IL-17 infusion on blood pressure during pregnancy. This study showed that IL-17 caused hypertension and increased TH17 cells, oxidative stress, and AT1-AA [40]. A blockade of the AT1 receptor with losartan attenuated the blood pressure response and placental ROS. Additionally, the depletion of B-cells with Rituximab blunted hypertension and numbers of T_H17 cells. Administration of the superoxide dismutase mimetic TEMPOL attenuated the hypertension, decreased placental production of ROS, and significantly decreased circulating AT1-AAs [40]. The effect of tempol on IL-17-induced pathophysiology suggests that the ROS may be an important signaling molecule for B-cells to produce AT1-AAs. This data suggests that

IL-17 causes hypertension via placental oxidative stress and activation of the AT1 receptor via the AT1-AA.

Subsequent studies were performed to examine the effect of an IL-17 blockade on the RUPP rat model of PE. 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. The IL17 blockade reduced hypertension, intrauterine growth restriction (IUGR), oxidative stress and AT1-AA, and lowered circulating T_H17 cells. A significant improvement in pup weight was accompanied by increased placental weight and decreased uterine artery resistance index, indicating the importance of this pathway on the uteroplacental environment [79]. Thus, inhibition of this immune pathway could lower rates of fetal demise as a direct result of decreased placental stress serving as a fetal protective mechanism during PE, and could be a novel therapeutic approach to improving the treatment of PE.

The effect of decreased Tregs in preeclampsia

Along with increased levels of inflammatory T cells, regulatory T cells (Tregs) are decreased during preeclampsia in response to placental ischemia. These cells are identified by the expression of cell surface markers $CD4^+$ $CD25^+$ and their specific internal transcription factor forkhead box protein 3 ($Foxp3^+$) [80]. Tregs are responsible for suppression of responses in the adaptive and innate immune system, and they control 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 [80]. Tregs are increased very early in normal pregnancy and reach their highest levels during the second trimester before decreasing back to normal levels [81]. The peak times for Tregs coincide with important processes like vascular remodeling and trophoblast invasion, which are integral to a healthy pregnancy. Evidence for the contribution of reduced Tregs to the pathophysiology of preeclampsia has been provided by many studies. Tregs have shown to be decreased both in the circulation and decidua of women with preeclampsia, and this decrease is directly proportional to the severity of the disease [82]. Decreased circulating Tregs have also been seen in women who have had multiple miscarriages [72]. Studies have shown that decreases in decidual Tregs cause increased apoptosis in trophoblasts, preventing sufficient invasion of the trophoblast [74, 83]. In addition, an abortion-prone mouse model was found to have decreased numbers of $CD4^+$ $CD25^+$ Tregs in the decidua, but adoptive transfer of Tregs from normal pregnant mice decreased spontaneous abortions [84]. Furthermore, the role of Tregs during pregnancy to provide fetal-maternal tolerance has been demonstrated through adoptive transfer studies where Tregs were depleted prior to injection into T-cell-deficient mice. In this study, allogeneic fetuses, but not syngeneic fetuses, were rejected in the absence of Tregs, and additional studies have also demonstrated that Treg depletion during pregnancy decreases the number of pups surviving to term [85].

As with PE patients, RUPP rats exhibit a decrease in Tregs in response to placental ischemia. We recently demonstrated that adoptive transfer of NP Tregs into RUPP rats prior to placental insult results in lower blood pressure, blunts inflammation and Endothelin-1 expression, normalizes tissue oxidative stress, and attenuates AT1-AA production in

response to placental ischemia. We utilized flow cytometry to demonstrate that the adoptive transfer was sufficient to increase circulating Tregs in response to placental ischemia. This suggests that the number of Tregs is important in controlling inflammation and the vasoactive factors that contribute to hypertension during pregnancy, such as oxidative stress, AT1-AA and ET-1. Although no improvement in fetal morbidity was observed with adoptive transfer of NP Tregs into RUPP rats, improving pathophysiology in the mother may indirectly benefit the fetus by increasing time to delivery, thereby giving the fetus more time to develop and mature.

Syncytial knots and PE

Although PE is associated with chronic inflammation, a stimulus for the inflammatory response is unknown. Recent studies suggests that the inflammatory response is triggered by particles, ranging from large deported multinuclear fragments to sub-cellular components, shed from the syncytial surface of the human placenta [86]. Using an in-vitro model, Chamley and co-workers showed that these syncytial knots are shed by an apoptosis-like programmed cell death process, phagocytosed by macrophages, which then establish a tolerogenic response [87]. However, when phagocytosed, necrotic syncytial knots appear to be immunostimulatory. While there is a strong correlation between trophoblast debris and immune activation in preeclampsia, it remains unclear whether these particles could indeed elicit a pathogenic response in vivo. To address this issue, Chamley et al. recently reported that chronic administration of necrotic trophoblast debris increases blood pressure in pregnant rats relative to pregnant controls [88]. This report was the first demonstration that necrotic trophoblast debris can alter blood pressure in vivo and, while the mechanism by which the necrotic trophoblast debris becomes hypertensive remains to be determined, this observation is consistent with the growing body of evidence suggesting that necrotic trophoblast debris can contribute to the hypertension of preeclampsia.

AT1-AA during pregnancy

Angiotensin II type 1 receptor autoantibodies (AT1-AA) are elevated in women with preeclampsia as early as the 2nd trimester of pregnancy, which is when preeclampsia is usually diagnosed. This suggests that AT1-AAs may play a major role in the pathophysiology of preeclampsia. [45, 63]. AT1-AAs remain elevated in postpartum preeclampsia women after 1 year of delivery, indicating they could be a major risk factor for the development of cardiovascular and kidney disease in mothers later in life.[89]. Importantly, in 1973, Gant et al. found that ANGII infusion into pregnant women in their 2nd trimester resulted in a heightened vasoconstrictor and pressor response in women that went on to develop PE compared to those with NP. Due to a lack of research in this area, the mediator of this heightened response remained unknown. With the discovery of AT1-AA several years later, we hypothesized that AT1-AA may be the causal factor for heightened blood pressure and vasoconstrictor response.

To demonstrate a role for AT1-AAs in the pathophysiology of PE, several studies have investigated the treatment of pregnant rodents with the antibody. Isolated human and rodent AT1-AAs administered to rats during pregnancy were shown to increase blood pressure

while causing renal pathology, and led to the elevation in several circulating factors associated with preeclampsia, such as sFlt-1, sEng, oxidative stress, endothelin-1, TNF alpha, and IL-6 and endothelial microparticles [10, 90–93]. Interestingly, when administered simultaneously to pregnant rats, ANGII and AT1-AA exhibit a greater increase in blood pressure than when either one is administered alone [48, 90]. Chronic administration of ANGII and AT-AAs together increases oxidative stress, endothelin-1 secretion, and renal artery resistive index above that seen with ANGII or AT1-AA alone [48, 90]. These data taken together suggest a synergist effect when both AT1-AAs and ANG II are present together during pregnancy, possibly confirming our hypothesis.

The mechanism of increased ANGII sensitivity in preeclampsia is unknown. However, we hypothesize that AT1-AAs increase ANGII by increasing the AT1R affinity for ANG II. One mechanism by which the AT1-AA can increase ANGII sensitivity is by increasing the dimerization of the ATIR to the vasodepressor bradykinin receptor [94] [95, 96]. Others suggest that it may change the conformation of the AT1R in the membrane of a cell, thus allowing for ANGII to bind more readily to the receptor. Therefore, an increase in ANGII sensitivity in preeclampsia could be due to AT1R receptor dimerization or changes in conformation; however, more studies are needed to verify this hypothesis.

Animal models used to study the role of angiogenic factors

Of particular interest for preeclampsia research is the finding that sFlt-1, positively regulated by hypoxia, is produced by both placental trophoblasts and human placental villous explants in response to low oxygen tension, which is thought to occur in response to placental ischemia [97, 98]. sFlt-1 is the soluble receptor for VEGF and has been shown to interfere with VEGF signaling. While sFlt-1 production is regulated by the hypoxia-inducible factor-1, proof of concept studies using animal model RUPP have demonstrated that placental ischemia can cause increased sFlt-1 during pregnancy. Models of RUPP in both non-human primates and rats have shown significant increases in circulating sFlt-1, and concurrent decreases in bioavailable circulating VEGF [65, 99].

Several experimental models have demonstrated a causative role for sFlt-1 in the pathology of preeclampsia. Viral overexpression of sFlt-1 in pregnant rats led to a preeclampsia-like state, with hypertension, glomerular endotheliosis, and proteinuria [100]. In agreement with the viral expression experiments, direct infusion of sFlt-1 into pregnant mice or rats induces preeclamptic-like symptoms, including hypertension and reduced fetal weight [101–104]. Endothelin and oxidative stress are two major effector molecules in sFlt-1 hypertension during pregnancy. Administration of an ET_A receptor antagonist or Tempol completely normalized blood pressure [105].

It does not appear that the pathological manifestations seen in sFlt-1-induced PIH are a direct result of circulating sFlt-1 but rather the loss of VEGF. VEGF administration in rats with placental ischemia restored normal blood pressure, renal function, and vascular activity [106]. These and other data from animal models have led to the hypothesis that the ratio between sFlt-1 and VEGF or PlGF is critical to maintaining healthy endothelial function and normal vascular activity.

Genetic models resulting in placental ischemia

BPH/5 mouse

The BPH/5 mouse model is a substrain derivation of the BPH/2 “borderline hypertensive” mouse, and exhibits mildly elevated blood pressure throughout the adult lifespan of the animal. Davisson et al. demonstrated that the BPH/5 model exhibits elevations in blood pressure (up to ~25mmHg) during pregnancy that resolve immediately following delivery. The increase in blood pressure was accompanied by proteinuria, glomerulosclerosis, intrauterine growth restriction, maternal endothelial dysfunction, and increased fetal mortality [107]. Additionally, the BPH/5 mouse has altered cytotrophoblast invasion and placental abnormalities that coincide with increased uterine artery vascular resistance and placental ischemia. As with other models of placental ischemia, both angiogenic imbalance and oxidative stress are associated with the etiology of BPH/5 gestational hypertension. Importantly, the administration of Tempol or the viral delivery of $VEGF_{121}$ attenuated the hypertension and proteinuria [108, 109]. BPH/5 remains one of the most intriguing models for the identification of new pathogenic factors in a spontaneous animal model.

Genetic modification of the renin/angiotensin system

Though its role in long-term maintenance of blood pressure is well established, the exact pathophysiological role of the RAS in the development of preeclampsia is less clear. During normal pregnancy, plasma renin concentration/activity and ANGII levels are elevated, while vascular sensitivity to ANGII appears to be decreased. In contrast, during preeclampsia a significant increase in ANGII sensitivity is noted, possibly due in part to production of agonistic AT1-AA [110]. To investigate the role of the RAS in PE, several groups have utilized transgenic mouse and rodent strains in which females overexpressing human angiotensinogen (hAGN) are crossed with males overexpressing human renin hREN [111–114]. This model has been shown to exhibit hypertension and proteinuria during pregnancy [111, 112]. The Lavoie laboratory uses a related model in which mice that constitutively overexpress both REN and AGN subsequently develop chronic hypertension and fetal growth restriction; this is considered a model of superimposed preeclampsia [114]. Both of these models have proven to be versatile tools for investigating the role of the RAS in the etiology of PE, and are likely to be of great utility in future studies.

Conclusion

Hypertension in response to placental ischemia begins early in gestation with inadequate remodeling of the uterine spiral arteries, leading to decreased vascularity and blood supply to the growing uteroplacental unit. Much of this remodeling is controlled by close interactions between immune cells and the maternal vasculature and the invading cytotrophoblasts. Some unknown event occurs that changes this interaction into a chronic state of immune activation and decreased vascularity of the uteroplacental unit. Secreted factors cause an increase in blood pressure and a decrease in fetal growth. CD4+Tcells are among the activated immune cells that have been shown to play an instrumental role in stimulating agonistic autoantibodies, inflammatory cytokines and anti-angiogenic factors, all known players in the pathogenicity of preeclampsia. Various animal models have

demonstrated a role for such factors that are not only elevated in preeclampsia, but play an important role in the clinical presentation of the disease. Through knowledge gained from such animal models, we may be able to develop new chemotherapeutic targets to improve treatment of hypertension secondary to placental ischemia in preeclamptic women.

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Table 1

Pathophysiology seen in women with preeclampsia and in response to placental ischemia RUPP Rats

	Normal Pregnant	Preeclampsia	RUPP Rats
Hypertension	− − −	+++	+++
Endothelial dysfunction	− − −	+++	+++
Intrauterine growth restriction	− − −	+++	+++
Inflammation	+	+++	+++
Agonistic autoantibodies to AT1	− − −	+++	+++
Anti-angiogenic factors	− − −	+++	+++