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The role of immune cells and mediators in preeclampsia

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Abstract

Preeclampsia is a hypertensive disorder of major concern in pregnancy than can lead to intrauterine growth restriction, placental abruption and stillbirth. The pathophysiology of preeclampsia is multifactorial, including not only kidney dysfunction but also endothelial dysfunction, as the maternal endothelium becomes exposed to placental factors that are released into the circulation and increase systemic levels of vasoconstrictors, oxidative stress, anti-angiogenic factors and inflammatory mediators. Importantly, inflammation can lead to insufficient placental perfusion and low birthweight in offspring. Various innate and adaptive immune cells and mediators have been implicated in the development of preeclampsia, in which oxidative stress is associated with activation of the maternal inflammatory response. Immune cells such as regulatory T cells, macrophages, natural killer cells, and neutrophils are known to have major causative roles in the pathology of preeclampsia, but the contributions of additional immune cells such as B cells, inflammatory cytokines and anti-angiotensin II type 1 receptor autoantibodies are also now recognized. Immunological interventions, therefore, have therapeutic potential in this disease. Here, we provide an overview of the immune responses that are involved in the pathogenesis of preeclampsia, including the role of innate and adaptive immune cells and mediators.

Introduction

Hypertensive disorders of pregnancy — a broad group that includes pre-existing hypertension, preeclampsia, gestational hypertension and eclampsia — complicate ~10% of pregnancies and are a major contributor to maternal mortality and morbidity[1]. Furthermore, the incidence of hypertensive disorders of pregnancy has increased from 16.3 million

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Competing interests

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in 1990 to 18.08 million in 2019 worldwide[2]. In all types of hypertensive disorder of pregnancy, hypertension (defined as a blood pressure (BP) >140 mm Hg systolic or >90 mm Hg diastolic) is detected during pregnancy. Pre-existing or chronic hypertension complicates 5% of all pregnancies and comprises cases in which hypertension is identified before conception or at <20 weeks' gestation and persists for 12 weeks postpartum. Gestational hypertension occurs in ~6% of pregnancies and is diagnosed in women who develop hypertension before 20 weeks of gestation in the absence of proteinuria; BP typically returns to normotensive levels postpartum[3,4]. However, gestational hypertension is defined as preeclampsia if BP remains ≥140 mmHg after 20 weeks of gestation and one or more of the following are present — proteinuria, maternal organ dysfunction (including kidney, liver or brain dysfunction), abnormal Doppler sonography, or potential fetal growth restriction[1]. Preeclampsia affects 5% of pregnancies worldwide and is associated with worse patient outcomes, including kidney or liver damage, than gestational hypertension[5–7]. Preeclampsia can be classified as early-onset preeclampsia or late-onset preeclampsia, depending on whether if develops before or at 34 weeks of gestation[8]. Although the presenting features of the two conditions are similar, they have different maternal and fetal outcomes, heritability, biochemical marker and clinical features. Another difference between the two is that early-onset preeclampsia is complicated by uterine growth restriction whereas late-onset is not[9]. Eclampsia is a severe life-threatening complication of pregnancy that develops in 0.8% of pregnant women diagnosed with high BP and that causes seizures during and after delivery[10,11]. Haemolysis, elevated liver enzymes and low platelets (HELLP) syndrome is a severe complication of preeclampsia or eclampsia that causes haemolysis, liver dysfunction and thrombocytopenia[4,10]; its incidence is 0.1–0.6% for all pregnancies and 4–12% in patients with preeclampsia[12,13].

The causes of gestational hypertension, preeclampsia, eclampsia or HELLP syndrome remain unknown, but some underlying conditions such as pre-existing hypertension, kidney disease, and diabetes increase the risk of developing preeclampsia or gestational hypertension[14]. Key mechanisms underlying the development of hypertensive disorders of pregnancy include endothelial dysfunction, angiogenesis, impaired `spiral uterine artery remodelling` and inadequate trophoblast invasion[15–17]. Notably, immune dysregulation and inflammation are important contributors to the placental and kidney dysfunction that culminate in maternal hypertension[17,18] (Fig. 1).

In this Review, we outline key immune mechanisms involved in the pathogenesis of preeclampsia, including the role of immune cells and mediators, and examine how these mechanisms contribute to the oxidative stress, endothelial dysfunction and hypertension that characterize this pregnancy disorder. Moreover, we consider the current management of preeclampsia and potential therapeutic strategies for its treatment.

Pathological alterations in preeclampsia

Placentation and formation of the maternal–fetal interface is a complex process that involves careful orchestration by trophoblasts and immune cells. For example, fetal trophoblast invasion of the maternal endometrium is essential to establish the maternal–fetal blood supply in pregnancy[19]. These trophoblasts promote the remodelling of maternal spiral

arteries into low-resistance vessels throughout the pregnancy by replacing the endothelial cells of the spiral arteries[20]; smooth muscle cells and their respective autonomic innervation are also lost, which further reduces vascular resistance[21]. In preeclampsia, the invasion of extravillous trophoblasts into the myometrium is insufficient[22], which leads to the formation of smaller, higher resistance vessels compared with a healthy pregnancy[21]. Moreover, the spiral arteries in preeclampsia fail to maintain adequate perfusion to support the growing fetus, which leads to progressive placental damage owing to ischaemia and hypoxia. The hypoxic placenta releases vasoactive factors such as tumour necrosis factor (TNF), soluble fms-like tyrosine kinase-1 (sFLT-1; also termed vascular endothelial receptor (VEGFR1)), and soluble endoglin (Fig. 2). These factors promote endothelial dysfunction and increased vascular resistance[23,24].

Moreover, preeclampsia is associated with the pathological release of free radicals by the placenta. In a healthy pregnancy, the maternal and fetal oxygen demand increases oxygen metabolism at the mitochondrial level, which generates free radicals, including superoxide ions. Importantly, reactive oxygen species (ROS) control energy metabolism, cell proliferation and apoptosis, intracellular and intercellular signalling pathways, and biochemical reactions through oxidative–reductive processes[25]. Accordingly, placental ROS are present throughout a healthy pregnancy and are necessary for the cellular replication, proliferation and maturation processes that support embryo development and pregnancy maintenance[26]. However, in preeclampsia, impaired uteroplacental blood flow creates an imbalance between the production of ROS and antioxidants, which leads to oxidative stress, inflammation and apoptosis of syncytiotrophoblasts[27] (Fig. 3). This oxidative stress also affects vascular responses, causing inadequate vascular remodelling, smooth muscle hypertrophy and cellular apoptosis[26]. Of note, we have previously shown that lower than normal mitochondrial oxidative stress is also associated with preeclampsia[28].

In a healthy pregnancy, the immune response is balanced to achieve successful implantation while protecting the fetus from immune insults[29]. Chronic immune activation of $CD4^+$ T cells, B cells, natural killer (NK) cells and macrophages, as well as activation of inflammatory pathways that involve the complement system and agonistic anti-angiotensin II type 1 receptor autoantibodies (AT1-AAs) are associated with placental ischaemia and have been implicated in the pathogenesis of preeclampsia. These immune factors are thought to sensitize women with preeclampsia to vasoconstrictors, such as angiotensin II[30] (Box 1). The immune cell profile in pregnancy is dynamic but early spiral artery remodelling, for example, relies on an anti-inflammatory environment to ensure maternal–fetal tolerance. However, in contrast to normal pregnancy, pro-inflammatory cytokines such as TNF, IL-6 and IL-17 are elevated during preeclampsia[31–34] and promote cytotoxic inflammatory responses[35–37]. For example, in decidual tissue from chorionic villus sampling, women who later developed preeclampsia had high levels of *IL6* mRNA[38]. TNF and IL-6 have been implicated in endothelial dysfunction through decreased nitric oxide (NO) production and increased endothelin-1 production[35,39,40], and can also modulate vascular resistance by increasing the production of anti-angiogenic factors[41] such as sFlt-1. (Fig. 2) Chronic infusion of TNF or IL-6 into normal pregnant rats significantly increased BP, impaired renal haemodynamics and stimulated the production of AT1-AAs. Of note, chronic infusion of these pro-inflammatory cytokines did not have similar effects in non-pregnant rats[42]. In

the pregnant rat, TNF infusion administered late in pregnancy increased BP and plasma markers of preeclampsia, such as sFlt-1, soluble endoglin, endothelin-1 and AT1AA[35,43–45]. TNF blockade with etanercept, which acts as a soluble TNF receptor, reduced BP and improved inflammation induced by placental ischaemia in the reduced uteroplacental perfusion pressure (RUPP) rat model of preeclampsia. Moreover, etanercept also lowered endothelin-1 expression in human umbilical vein endothelial cells in vitro following exposure to sera from RUPP-induced preeclampsia[44,46]. Similarly, administration of IL-17 in normal pregnant rats increased BP and caused placental oxidative stress through increases in mitochondrial ROS and AT1-AAs[47] (Box 1). Another study showed that human umbilical vein endothelial cells supplemented with serum from women with preeclampsia had higher levels of endothelial cell respiration and mitochondrial ROS than those exposed to control serum[7].

The maternal vascular endothelium is an important target of preeclampsia-inducing factors, and severe endothelial dysfunction is not only associated with recurrent preeclampsia[48] but also with maternal cardiovascular disease, and poor cardiometabolic and cerebral health in both the mother and the fetus[27]. The primary physiological function of endothelial cells is to maintain vascular function in response to changes in blood composition and provide a physical barrier that regulates the movement of proteins, water, ions and cells from the blood into the vessel wall[48]. Compared with healthy pregnancy, women with preeclampsia have significantly lower `flow-mediated dilation`, which is associated with an increase in endothelial damage[27]. The production and response to vasodilators is also altered in preeclampsia. For example, imaging of umbilical vein endothelium revealed that tissue from patients with preeclampsia failed to respond to ATP with appropriate Ca^{2+} bursts, which was associated with reduced NO production compared with that observed in tissue from healthy pregnancies[49].

Circulating factors, such as sFlt-1 and VEGF contribute to the endothelial dysfunction that is triggered by excessive ROS and oxidative stress in preeclampsia (Fig. 2). VEGF is important for the growth of new blood vessels and the maintenance of endothelial cell health. In a healthy pregnancy, sFlt-1, which acts as a VEGF inhibitor, regulates angiogenesis and vasculogenesis[26]. However, in hypoxic conditions, Flt-1 cleavage increases and the rise in sFlt-1 levels promotes endothelial dysfunction[26]. Women with preeclampsia have increased levels of sFlt-1 compared with normotensive pregnant women[50]. Collectively, the milieu of anti-angiogenic factors, endothelial dysfunction, oxidative stress and chronic inflammation result in the cardiovascular dysfunction and hypertension seen in preeclampsia.

Innate immune system in preeclampsia

The innate immune system — including complement, macrophages, neutrophils and NK cells — not only protects the mother and fetus from infection but also contributes to the establishment of the maternal–fetal interface (Fig. 4). For example, macrophages and uterine NK (uNK) cells help to establish implantation and remodel uterine spiral arteries[51,52]. Innate immune cells also remove apoptotic cells in the uterus in combination with natural antibodies from innate-like B1 cells[53].

Macrophages

In pregnancy, decidual macrophages contribute to spiral artery remodelling by producing angiogenic factors[54]. In a healthy pregnancy, macrophages comprise ~20–30% of decidual leukocytes. Pro-inflammatory macrophages (also termed M1 macrophages) predominate in the first trimester (<12 weeks' gestation) and contribute to embryo implantation, placental formation and embryo development. However, the macrophage population comprises both pro- and anti-inflammatory macrophages (also termed M2 macrophages) during placental formation and trophoblast invasion of the endometrium. After the placenta has fully developed in the second trimester, anti-inflammatory macrophages predominate until labour, at which point pro-inflammatory macrophages become dominant again[55]. In contrast to a healthy pregnancy, preeclampsia is associated with a sustained increase in the M1-to-M2 ratio. Moreover, the number of `Hofbauer cells`, which are placental macrophages of fetal origin, as well as their expression of anti-inflammatory IL-10, are reduced in preeclampsia[56].

In a healthy pregnancy, polarization of macrophages towards an anti-inflammatory phenotype is essential for maintenance of the pregnancy after successful implantation. Accordingly, dysregulated macrophage polarization is associated with inadequate uterine remodelling and deficient trophoblast invasion, which can lead to spontaneous abortion, preterm birth, and preeclampsia[55]. Specifically, M1 macrophages are more abundant in the placenta, decidua and surrounding uterine spiral arteries of women with preeclampsia than in tissues from healthy pregnancies[57,58]. Although the production of pro-inflammatory cytokines (for example, IL-6, TNF and IL-1β) by decidual macrophages has been implicated in recurrent spontaneous abortion[59], the consequences of increased numbers of pro-inflammatory macrophages in preeclampsia have yet not been fully investigated. In addition, immunohistochemistry studies showed lower trophoblast invasion and higher macrophage infiltration in preeclamptic placentas compared with normal placentas in the third trimester[57]. In vitro studies demonstrated that macrophage secretion of TNF induced apoptosis in trophoblast cells, which might underlie the reduced trophoblast invasion and inadequate spiral artery remodelling observed in preeclampsia[60].

Neutrophils

Neutrophils are present in the decidua from the first trimester and increase by 55% throughout a healthy pregnancy in humans[61,62]. However, circulating neutrophil counts are higher in patients with severe preeclampsia than in women with mild preeclampsia or normotensive women[63]. In preeclampsia, the release of placental micro-debris via `syncytiotrophoblasts` contributes to the inflammatory response and neutrophil extracellular traps (NETs) have been implicated in this process[64]. For example, exposure of circulating neutrophils to IL-8 or syncytiotrophoblast microparticles triggered their activation and release of NETs. Moreover, NETs are abundant in the intervillous space of preeclamptic placentae[65]. Compared with normotensive women, levels of plasma neutrophil elastase, which are indicative of neutrophil degranulation, are elevated in women with preeclampsia (matched for gestational age), especially in those with early-onset preeclampsia[66]. In addition to exposure to syncytiotrophoblast microparticles, up-regulation of cellular adhesion molecules on the endothelial surface, hyperlipidaemia-

induced endothelial cell activation and TNF production have all been implicated as factors that can trigger neutrophil activation in preeclampsia[67,68]. Of note, although neutrophil counts seem to associate positively with the severity of preeclampsia, whether neutrophil activation is the cause or consequence of endothelial damage remains unclear.

Importantly, neutrophils also have a regulatory role in normal placental development and fetal tolerance. IL-8, which is a chemokine produced by neutrophils and other immune, epithelial and endothelial cells, contributes to placental development as it is involved in the regulation of angiogenesis, endothelial activation and cell migration or invasion[69]. However, IL-8 also mediates neutrophil transmigration and is associated with endothelial dysfunction, and can therefore contribute to the pathogenesis of preeclampsia by promoting neutrophil extravasation into the vascular wall of tissues and the release of oxidative stress molecules.

Neutrophils also have immunoregulatory functions that affect the production of pro- and anti-inflammatory cytokines, as well as the recruitment and polarization of T cells. For example, neutrophils can inhibit T cell proliferation and activation via their production of ROS and arginase 1 (ARG-1)[61]. Granulocytic myeloid derived suppressor cells can also exert an immunosuppressive effect via ARG-1. Of note, although pregnancy typically induces an increase in the frequency of these regulatory cells, this effect was not observed in women with preeclampsia, who also had lower serum levels of ARG-1 than women with a healthy pregnancy[70].

NK cells

NK cells are granular, innate lymphocytes that represent 5–20% of all circulating lymphocytes[71]. NK cell function is determined by a balance between the signals received through their killer activating receptors (KARs) and killer inhibitory receptors (KIRs); additional signals received through cytokine receptors and CD16 further regulate NK cell activation[72]. Following activation, NK cells degranulate and release lysosomes that contain perforin and granzymes, which induce target cell lysis. Additionally, NK cells produce pro-inflammatory cytokines such as IFNγ and TNF, which promote the activation of neighbouring immune cells.

NK cells are the most abundant type of leukocyte in the decidua[73]. Most human peripheral blood NK cells are $CD16^{+}CD56^{dim}$ whereas uNK cells are predominantly $CD16CD56^{bright}$[74]. These $CD16CD56^{bright}$ uNK cells have a crucial role in trophoblast invasion and spiral artery remodelling through the production of cytokines such as IL-8 and CXC-chemokine ligand 10 (CXCL10; also known as IP10) and angiogenic factors such as VEGF and placental growth factor (PIGF)[75,76]. Of note, compared with NK cells from women with normal remodelling, NK cells from women with impaired spiral artery remodelling had an altered soluble mediator profile, which led to a failure to induce trophoblast chemotaxis and outgrowth in vitro[77,78]. Animal studies support the paradigm that uNK cells regulate trophoblast invasion and spiral artery remodelling[79]. In mice, uNK cell deficiency[80,81] or impaired uNK cell expansion[82] compromised spiral artery remodelling during pregnancy. Similarly, global NK cell deficiency in pregnant rats delayed spiral artery remodelling and reduced trophoblast invasion[83]. Moreover, in contrast to the regulatory and angiogenic factors released by NK cells in a normal pregnancy, in

preeclamptic pregnancies, these cells secrete pro-inflammatory cytokines, such as TNF and IFNγ, which are elevated in circulation of preeclamptic pregnancies compared with healthy pregnancy, and might thus contribute to a loss of immunological tolerance[84]. High INF-γ levels can lead to `fetal resorption`, placental and trophoblast apoptosis and decreased VEGF secretion[79,85,86].

uNK cells are characterized as non-cytolytic owing to differential expression of the inhibitory receptor, NKG2A. Co-engagement of NKG2A on uNK cells antagonizes their secretion of cytolytic granules[87]. uNK cells also recognize human leukocyte antigen (HLA)-C, which is the most polymorphic of the HLA antigens expressed by fetal trophoblasts; this interaction delivers inhibitory signals and promotes immune tolerance[88]. Interestingly, a specific KIR haplotype that can affect uNK cell binding to HLA-C expressed on invading trophoblast cells was associated with the risk of preeclampsia, intrauterine growth restriction, and recurring miscarriage[89]. Pregnant women with hypertension have increased numbers of circulating NK cells with enhanced cytolytic activity compared with normotensive pregnant women[90–93]. In rats, NK cells from placentas of preeclamptic animals also had a 5-fold increase in cytolytic activity compared with sham controls[94]. Moreover, we showed that rat uNK cells exposed to placental ischaemia cause hypertension, fetal growth restriction and an anti-angiogenic factor imbalance when transferred into normal pregnant rats[95].

Complement system

The complement system is an integral component of the innate immunity and, although complement activation increases during normal pregnancy[96], this activation is further enhanced in preeclampsia[97]. Complement can be activated through three pathways: the classical pathway, the lectin pathway, and the alternative pathway[98]. Alternative complement activation in early pregnancy is associated with an increased risk of developing preeclampsia[99,100]. In an animal model of placental ischaemia, inhibition of complement receptor 1 attenuated hypertension, further suggesting that the activation of the classical and alternative complement pathways might be involved in the pathogenesis of hypertension in preeclampsia[101].

Complement activation leads to target opsonization through C3b, recruitment of pro-inflammatory cells through C3a and C5a, and formation of the membrane attack complex (MAC; also known as C5b–9). Soluble C5b–9 levels are significantly higher in women with hypertensive disorders of pregnancy, including preeclampsia, than in women with healthy pregnancies[102]. MAC insertion induces apoptosis in placental cytotrophoblasts, and potentially reduces the effectiveness of trophoblast invasion and spiral artery remodelling[103]. In animal models, inappropriate complement activation causes fetal loss through complement deposition and destruction of the fetoplacental unit[104]. C3a, C5a and MAC are also highly expressed in plasma during preeclampsia[97,99,100,105–107] and patients who develop preeclampsia have high levels of complement factor B (CFB), CFH, and C1q early in pregnancy[108]. By contrast, plasma levels of several proteins involved in the lectin pathway, such as H-ficolin, M-ficolin and mannan-binding lectin serine protease 3 (MASP3) are lower in preeclamptic pregnancies than in healthy pregnancies, which suggests a link

between dysfunction in the lectin pathway and preeclampsia[109]. Of note, polymorphisms that impair the synthesis of MASP1, which is involved in the lectin pathway, have been associated with an increased risk of preeclampsia[110]. Single-nucleotide polymorphisms in genes encoding complement proteins (*C3*), and complement regulatory proteins (*CD46*, *CFI* and *CFH*) have also been linked to preeclampsia[111–113].

Adaptive immune system in preeclampsia

Adaptive immune responses driven by T and B cells can be directed against pathogens but also against allo- and autoantigens, and are characterized by the generation of immune memory that enhances the immune response to subsequent encounters with the same antigens. Of note, preeclampsia is more common in the first than in subsequent pregnancies and the use of barrier contraceptives that prevent exposure to sperm is associated with a higher risk of preeclampsia[114,115]. Similarly, the lack of prior contact with sperm or oocyte donor alloantigens in medically assisted reproduction increased the risk of preeclampsia compared with natural conception; repeated exposure to donor semen reduced the risk associated with sperm donation[115,116]. Collectively, these observations suggest that seminal fluid might induce adaptive immune tolerance to paternal antigens, thereby reducing the risk of preeclampsia. Accordingly, breakdown of tolerance to paternal antigens might result in inappropriate immune activation that leads to inflammation and promotes preeclampsia[3].

Activated T cells can be polarized, depending on the cytokine milieu and activating signals, to adopt a pro-inflammatory (for example, T helper 1 (T_H1) or T_H17) or an anti-inflammatory (for example, T regulatory (T_{reg}) or T_{H2}) phenotype. T_H1 cells and type 1 cytokines, such as IL-2, TNF and IFNγ, are central to cell-mediated immunity, whereas T_H2 cells and type 2 cytokines, such as IL-4, IL-5, IL-6 and IL-13, have major roles in humoral immunity and control antibody production[117]. Imbalances between pro- and anti-inflammatory T cells seem to contribute to the pathogenesis of gestational hypertension and preeclampsia[118] (Fig. 5). In a healthy pregnancy, progesterone production from the placenta promotes T_H cell differentiation towards anti-inflammatory T_H2 and T_{reg} cell phenotypes, but in preeclampsia this differentiation is skewed towards pro-inflammatory T_H1 and T_H17 cell phenotypes[119]. This imbalance is also observed in other disorders of pregnancy, such as recurrent spontaneous abortion[120]. Furthermore, levels of the immunosuppressive cytokine IL-10, which contributes to fetal tolerance, are low in preeclampsia[117,121].

Regulatory T cells

T_{reg} cells, which are characterized by the expression of CD4, CD25 and the transcription factor FOXP3, are key regulators of immune tolerance during pregnancy[122]. T_{reg} cells regulate pro-inflammatory T_H cells by suppressing their proliferation, for example, through the production of anti-inflammatory cytokines, by consuming IL-2 and by inhibiting antigen-presenting cell activity[123], for example via cytotoxic T lymphocyte antigen 4. Interestingly, mismatching between maternal and fetal HLA-C is associated with polarization of $CD4^+$ T cells to a T_{reg} cell phenotype[115,124]. Furthermore, T_{reg} cells can contribute to the maintenance of an anti-inflammatory microenvironment by modulating the activity of dendritic and NK cells[125,126]. Accordingly, T_{reg} cells have a crucial role in

maintaining an anti-inflammatory decidual milieu, and regulate implantation and placental development by controlling the decidual leukocyte network that facilitates cytotrophoblast development and trophoblast invasion[126]. In a healthy pregnancy, dendritic cells that phagocytose trophoblast debris secrete immunosuppressive cytokines such as IL-10 and transforming growth factor β (TGFβ), which promote T_{reg} cell activity, help to regulate the numbers of NK cells and neutrophils, and inhibit the activation of pro-inflammatory T_H cells[117,125]. By contrast, dendritic cell phagocytosis of necrotic trophoblasts, which are more abundant in preeclampsia owing to oxidative stress and/or hypoxic conditions, induces the release of pro-inflammatory cytokines such as TNF, IFNγ and IL-12.

Two studies reported that the frequency of circulating T_{reg} cells was lower in preeclamptic pregnancies than in healthy pregnancies[127] and the frequency of T_{reg} cells in placental bed biopsy samples was also lower in preeclampsia than in healthy pregnancies[128]. Moreover, reduced expansion of T_{reg} cells has been reported in preeclampsia and proposed to contribute to loss of tolerance to paternally derived fetal antigens[129]. Further insights were obtained using the rat RUPP model, which recapitulates some features of preeclampsia, including an increase in BP, enhanced inflammation (for example, high levels of TNF, IL-6, IL-17 and sFlt-1 in the circulation) and oxidative stress, and AT1-AA production coupled with reduced fetal and placental weight[28,130,131]. Importantly, adoptive transfer of T_{reg} cells from rats with a normal pregnancy into RUPP rats reduced hypertension, suggesting that T_{reg} cells have the capacity to attenuate preeclampsia[132]. Conversely, T_{reg} cell depletion in early pregnancy under normal conditions increased uterine artery vascular resistance, indicating that these cells have a role in regulating uterine artery function[133].

Helper T cells

Effector $CD4^+$ T helper cells include T_H1, T_H2 and T_H17 cells, which have distinct cytokine profiles and effector functions. RUPP rats have significantly higher circulating $CD4^+$ T cell than controls[134]. The adoptive transfer of $CD4^+$ T cells from female RUPP rats into healthy pregnant rats induces changes characteristic of preeclampsia, including an increase in BP and mitochondrial ROS (mtROS) levels[134,135]. Moreover, T cell-deficient nude rats develop preeclampsia-like symptoms following adoptive transfer of placental $CD4^+$ T cells from women with preeclampsia[131], which supports a role for T cell populations in the pathogenesis of preeclampsia. Our previous studies have shown that $CD4^+$ T cells isolated from the placentas of patients with preeclampsia secrete TNF, IL-6, IL-17 and the anti-angiogenic factor sFlt-1, both in culture and following adoptive transfer into pregnant nude athymic rats[131]. Placental $CD4^+$ T cells have also been implicated in the activation of B cells that secrete AT1-AA[136] (Box 1) which contributes to increased circulating inflammatory cytokines, the antiangiogenic factor sFlt-1 and the vasoconstrictor endothelin 1 (ET-1)[6,121,134,137].

In a healthy pregnancy, T_H2 cells increase in the circulation, whereas they decrease in preeclamptic pregnancies[125]. This dysregulation is typically observed in the first month of preeclamptic pregnancies and is accompanied by an increase in the numbers of circulating and placental $CD4^+$ T_H1 cells, pro-inflammatory cytokine levels, autoantibody production and oxidative stress[121].

$CD4^+$ T_H17 cells are pro-inflammatory and secrete IL-17, IL-23 and IL-22 (ref. [138]). Although these cells are typically involved in the immune response to extracellular pathogen, they have also been implicated in the pathogenesis of many autoimmune diseases and inflammatory disorders[139]. Th1-type immunity in preeclampsia increases levels of cytokines such as IL-6 and IL-1β, which further promotes the differentiation of T_H17 cells[140,141]. In preeclampsia, the numbers of circulating and placental T_H17 cells increase compared with those observed in women with a healthy pregnancy. In the RUPP model, BP, inflammation, oxidative stress and AT1-AA production increases, whereas fetal and placental weight are lower than in normal controls. These effects in RUPP animals can be replicated in normal pregnant rats through the adoptive transfer of RUPP-induced T_H17 cells[142]. IL-17 has been implicated in vascular dysfunction owing to its activation of Rho-kinase, which disrupts the production of endothelial nitric oxide synthase (eNOS) by phosphorylating the inhibitory site Thr495, and leads to an increase in vascular tone[143,144]. Moreover, eNOS inhibition increases leukocyte adhesion to the vasculature, which promotes vascular inflammation and hypertension[145]. Blockade of IL-17 signalling with an IL-17 receptor C antibody significantly decreased T_H17 cell number, BP, ROS and AT1-AA production, as well as improving placenta and pup weight in the RUPP rat model[146]. Soluble endoglin acts as an inhibitor of TGFβ receptor signalling and therefore compromises T_{reg} cell differentiation and FOXP3 expression[141]. Since FOXP3 induction restrains the differentiation of T_H17 cells, higher expression of endoglin might promote an increase in T_H17 cell populations in preeclampsia[147].

B cells

During a normal pregnancy, B cells promote a fetus-tolerant immune environment. However, these lymphocytes can also produce antibodies against paternal antigens, as well as autoantibodies, which can lead to pregnancy complications. B cells comprise not only classical B2 B cells but also innate-like B1 B cells, which are associated with T cell-independent antibody responses and produce ‘natural’ low-specificity antibodies, which are typically of the IgM class and specific for lipid antigens[148,149]. B2 cells are derived from common lymphoid progenitor cells and represent the dominant, classical B cells that are associated with T cell-dependent antibody responses. By contrast, B1 cells develop from progenitor cells in the fetal liver and are only predominant in early life.

B1 cells can be categorized according to their expression of CD5. B1a cells are $CD5^+$ and have been implicated in autoimmunity and autoantibody production in preeclampsia, whereas B1b cells are $CD5^-$ and are associated with the production of natural anti-pathogen antibodies[150]. B1a cell frequency in the placenta decreases as normal pregnancy progresses but is elevated in late preeclamptic pregnancy[151]. Moreover, one study reported that $CD19^+CD5^+$ B cells isolated from women with preeclampsia produced AT1-AA (Box 1) in vitro[151]. Several other autoantibodies have been detected in preeclampsia, including antibodies specific for the α1 adrenergic receptor, the anticoagulation proteins C and S, and thyroid antigens[152–154], but these autoantibodies have not been specifically linked to B1 or B2 cells.

AT1-AAs (Box 1) have been identified in circulation up to 7 years postpartum in women with preeclamptic pregnancies[155,156]. This finding suggests the presence of long-lived memory B cells in preeclampsia, which implicates the involvement of T cell-dependent antibody responses and B2 cells. Of note, the frequency of T_{reg} cells correlated negatively with the frequency of memory B cells in women with preeclampsia but not in those with a healthy pregnancy[157]. Interestingly, adoptive transfer of $CD4^+$ T cells from the RUPP model of preeclampsia induces the secretion of AT1-AAs in pregnant control rats[130] but blockade of CD40L on $CD4^+$ T cells, which is a key mediator of T cell–B cell interactions, or B cell depletion, prevents the development of hypertension and AT1-AA production in this model[158]. Adoptive transfer of placental $CD4^+$ T cells from women with preeclampsia women into nude athymic pregnant rats also results in hypertension and AT1-AA formation, which are associated with inflammatory cytokine production and low birthweight[136].

Therapeutic strategies for preeclampsia

Traditional screening approaches to identify women at risk of preeclampsia rely on the assessment of clinical risk factors such as age, BMI and underlying renal or cardiovascular disorders early in pregnancy. These risk factors are treated independently without an assessment of the level of risk, including the presence of additional factors that can increase the risk of developing preeclampsia. Although this approach is simple, the detection rates for preterm preeclampsia (~40%) and term preeclampsia (~35%) are low[8]. In addition to the traditional clinical parameters of high BP and increased uterine artery resistance, laboratory and ultrasound findings are used to predict early-onset preeclampsia and intrauterine growth restriction. Commonly used laboratory tests include the measurement of circulating markers of inflammation, angiogenesis, lipid metabolism, coagulation, fetoplacental endocrine function, cardiac function, kidney function and oxidative stress. These markers, coupled with the aforementioned clinical risk factors, BP, PlGF levels and uterine artery resistance index are useful in diagnosing and assessing the risk of preeclampsia in women at 11–14 weeks of gestation[8]. Additional risk factors, such as obesity, can also be used to predict the risk of preeclampsia[8]. Of note, obesity has been implicated in late-onset preeclampsia[159] and reducing gestational weight gain was associated with a lower risk of developing preeclampsia[160].

Currently, delivery of the fetal–placental unit is the only available intervention in cases of preeclampsia. Angiotensin receptor blockers, although useful to decrease BP, improve kidney function and decrease levels of anti-angiogenic factors[161–163], are contraindicated in pregnancy owing to their teratogenic effects[164]. An alternative strategy for treating preeclampsia might be to target AT1-AAs. A seven amino acid sequence peptide (7AA) that binds to AT1-AAs and prevents them from binding to the AT1 receptor[165,166] improved growth restriction, placental apoptosis, calcium mobilization, proteinuria, hypertension, NO bio-availability, NK cell activation, placental mitochondrial respiration, renal mitochondrial respiration, mtROS and cerebrovascular function in the RUPP rat model of preeclampsia and in an AT1-AA-induced rat model of preeclampsia; positive results were also obtained in cell culture studies[167–173].

Rituximab, which is used to treat autoimmune disorders and B cell cancers, represents another approach to targeting AT1-AA in preeclampsia[174–176]. In a rat model of preeclampsia, rituximab decreased total B cell numbers, and circulating levels of AT1-AAs and TNF, tissue ET-1 levels and maternal BP[177]. However, despite the beneficial effects of rituximab in animal models, maternal B cell depletion probably poses risks to the mother and the fetus. Currently, there are no indications that rituximab exposure during pregnancy increases fetal malformations or other adverse events beyond those reported in other conditions treated with rituximab[178–180]. For example, loss of maternal antibodies and exposure to rituximab in fetal life increases the risk of infection in the mother and neonate. In one reported case of neonatal exposure to rituximab, the child had no B cells at birth but cell numbers had normalized by 4 months of age and the child was able to receive standard vaccinations[181].

Targeting complement might be beneficial in some women with severe preeclampsia or HELLP syndrome, in whom alternative complement activation is enhanced[182]. Supplementing sera collected from these patients with the complement inhibitor eculizumab reduced complement-mediated killing of target cells[182]. Moreover, a patient with severe preeclampsia and HELLP syndrome who developed atypical haemolytic uraemic syndrome (aHUS) requiring kidney replacement therapy responded to treatment with eculizumab[183–185]. Of note, in a study of two mothers treated with eculizumab during pregnancy, levels of eculizumab–C5 complexes were minimal in fetal plasma and complement activation was unaffected in the newborns[184]. Urinary C5b-9 levels might help to identify patients with severe preeclampsia and enhanced complement activation[185].

Additionally, anti-inflammatory therapeutics might be effective in preeclampsia. For example, statins might correct pathophysiological pathways underlying the development of preeclampsia and reduce inflammation[186]. In particular, pravastatin has been used in preclinical studies and in the clinical setting to reverse the pregnancy-specific angiogenic imbalance, restore endothelial health, and prevent oxidative and inflammatory injury[186,187]. Furthermore, treatment with a low dose of aspirin in women at a high risk of preterm preeclampsia lowered the incidence of preeclampsia up to 36 weeks' gestation[188], potentially owing to its anti-inflammatory effects.

Immunomodulatory therapies targeting $CD4^+$ T cells and NK cells, such as NK cell depletion and inhibition of T cell activation have been investigated in rat models of preeclampsia and have the potential to decrease the production of pro-inflammatory mediators such as TNF and cytolytic NK cell activity, while stimulating T_H2 cell differentiation. Of note, 17-orthohydroxyprogesteron caproate (17-OHPC), which is effective in preventing preterm labour[189] also lowered hypertension, pro-inflammatory immune cell numbers and cytokine levels in the RUPP rat model of preeclampsia compared with controls[190].

Conclusion

Immune cells are crucial to successful implantation and establishment of the maternal–fetal interface. However, immune dysregulation and inflammation have also been implicated

in preeclampsia. Several types of immune cell are present in the decidua, including different T cell subsets, B cells, NK cells and macrophages. In healthy pregnancies, these cells are regulated to enable fetal tolerance but they can also become dysregulated and instead promote inflammation, oxidative stress and endothelial dysfunction, as observed in preeclampsia. Although the pathophysiology of preeclampsia is multifactorial, interventions that target the immune system have therapeutic potential. Understanding how the innate and adaptive immune systems work together to ensure fetal–maternal tolerance is therefore crucial to enable the development of new therapeutic approaches for hypertensive disorders of pregnancy.

Glossary

Fetal resorption
The disintegration and absorption of one or more fetuses in the uterus after the completion of organogenesis.

Flow-mediated dilation
A vascular function test traditionally performed in the brachial artery, which measures the change in artery diameter in response to reactive hyperaemia.

Hofbauer cells
A diverse population of fetal macrophages that reside within placental tissue (in the chorionic villus); they are present as early as 18 days post-conception and persist throughout pregnancy.

Spiral uterine artery remodeling
An adaptive process in pregnancy that allows placental blood flow volume to increase while blood flow resistance decreases.

Syncytiotrophoblasts
A specialized, continuous layer of epithelial cells that cover the surface of embryonic placental villi and are in direct contact with maternal blood.

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Key points

- Endothelial dysfunction, angiogenesis, spiral uterine artery remodelling and inadequate trophoblast invasion are key contributors to the genesis of hypertensive disorders during pregnancy.
- An altered immune response might have a pivotal role in the development of preeclampsia, eclampsia and haemolysis, elevated liver enzymes and low platelets syndrome.
- Insufficient or inadequate regulation of the immune system, activation of innate immune cells and imbalanced differentiation of T helper cell subsets create a cytotoxic environment that results in oxidative stress, endothelial dysfunction and intrauterine growth restriction.
- T helper cells facilitate the activation of B cells that secrete anti-angiotensin II type 1 receptor autoantibodies, which can cause hypertension, cerebral dysfunction, kidney dysfunction and intrauterine growth restriction in response to placental ischaemia.
- New therapeutics that target the pro-inflammatory response during preeclampsia have potential to attenuate the effects of the systemic factors that promote the development of this hypertensive disorder of pregnancy.

Box 1

AT1-AAs in preeclampsia

Healthy pregnancies are associated with increased activation of the renin–angiotensin–aldosterone system, combined with reduced responsiveness to the vasoconstrictive effects of angiotensin II (Ang II)[192]. Although levels of AngII are lower in women with preeclampsia than in women with healthy pregnancies, their sensitivity to AngII is enhanced[192,193] and this effect is probably due to the presence of anti-Ang II type 1 receptor autoantibodies (AT1-AAs) in patients with preeclampsia[152].

AT1-AAs activate the AT1 receptor by binding to a specific sequence on its second extracellular loop. This binding seems to enhance, rather than compete with, Ang II binding and its downstream signalling cascade, suggesting that AT1-AAs are allosteric AT1 ligands[166,170,194,195] (Fig. 3). From a therapeutic perspective, small molecules that can bind this allosteric site might be able to block the effects of AT1-AAs or attenuate the effects of Ang II binding[196].

Infusing AT1-AAs into pregnant rats and mice induces a preeclamptic phenotype[197–199]. Furthermore, in rats, AT1-AA treatment increased mRNA levels of preproendothelin (PPET-1), which is a precursor of vasoconstrictive endothelin-1, in the placenta and kidneys[171]. AT1-AAs might also contribute to the rise in soluble fms-like tyrosine kinase 1 (sFlt-1) and soluble endoglin levels observed in patients with preeclampsia compared with those observed in healthy pregnancies[167,200]. For example, AngII or IgG isolated from patients with preeclampsia stimulate sFlt-1 production in human trophoblast cells, placental explants and pregnant mice[201,202]. Soluble endoglin is also elevated in pregnant mice or rats infused with AT1-AAs[200,203]. Additionally, AT1-AAs have been implicated in the preeclampsia-associated increases in reactive oxygen species levels in the placenta, kidney and endothelial progenitor cells[198,204–206].

AT1-AA inhibition with n7AAc not only attenuated hypertension in the reduced uteroplacental perfusion pressure (RUPP) rat model but also improved placental and kidney respiration compared with controls[172]. Moreover, human umbilical vein endothelial cells exposed to sera from RUPP rats treated with n7AAc produced less mitochondrial reactive oxygen species (ROS) than cells exposed to sera from untreated animals[207].

Notably, AT1-AA infusion decreases glomerular filtration rate, either through an increase in renal vascular resistance or through a decrease in renal blood flow in pregnant rats; combined infusion of AT1-AAs and Ang II enhanced these deleterious effects[170,194]. For example, AT1-AA infusion in pregnant rats reduced the vasodilatory response of kidney vessels to acetylcholine[208].

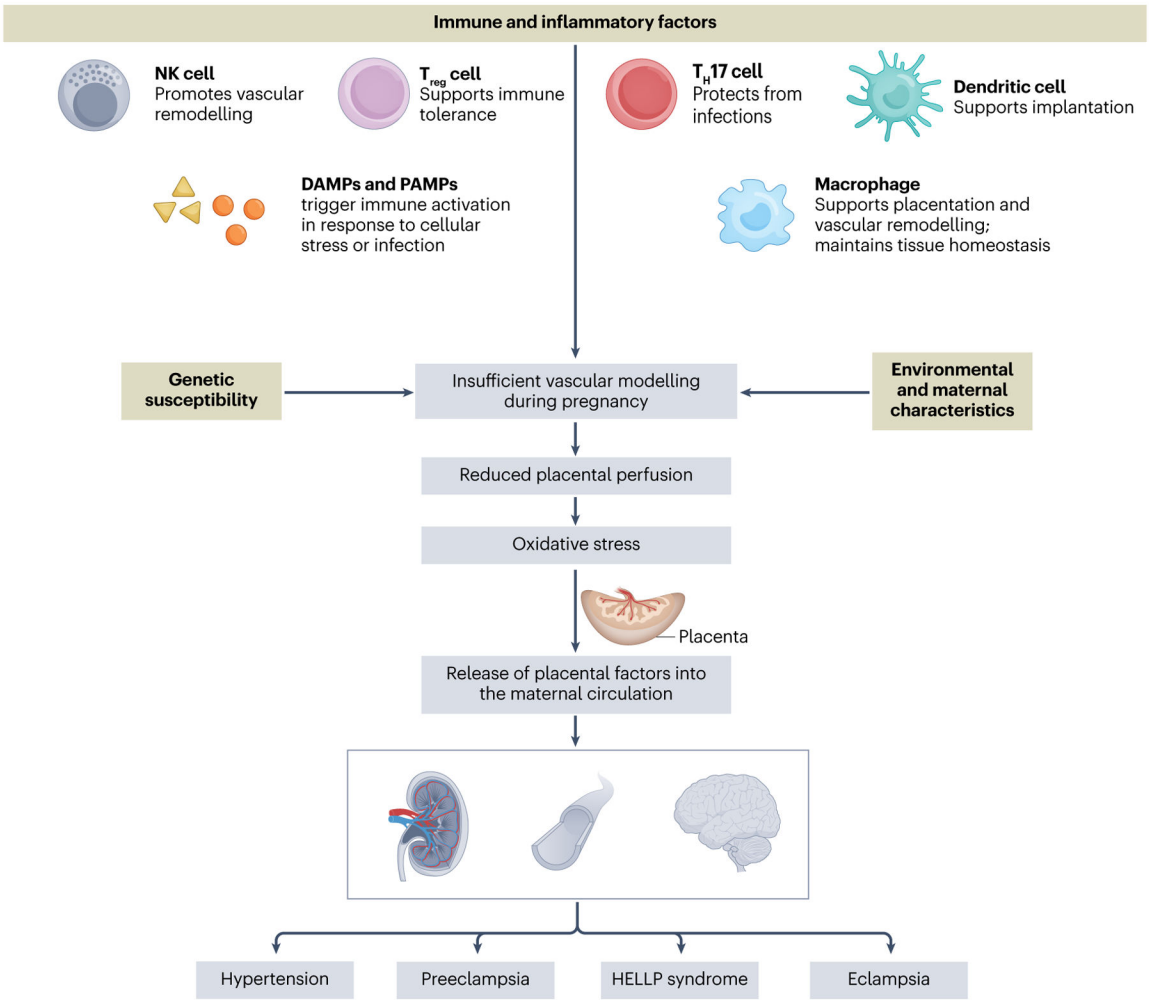

Fig. 1 |. Pathophysiology of hypertensive disorders during pregnancy.

Hypertensive disorders of pregnancy include gestational hypertension, preeclampsia, haemolysis, elevated liver enzymes and low platelets (HELLP) syndrome and eclampsia, which complicate up to 10% of pregnancies and represent a substantial cause of maternal and fetal morbidity and mortality. Genetic susceptibility, environmental or maternal characteristics, and loss of immune tolerance can all contribute to inadequate placentation and can compromise the maternal–fetal interface. Poor placental perfusion causes tissue damage owing to ischaemia and hypoxia, and can impair fetal growth. These effects trigger the release of placental factors that promote widespread immune activation and organ dysfunction.

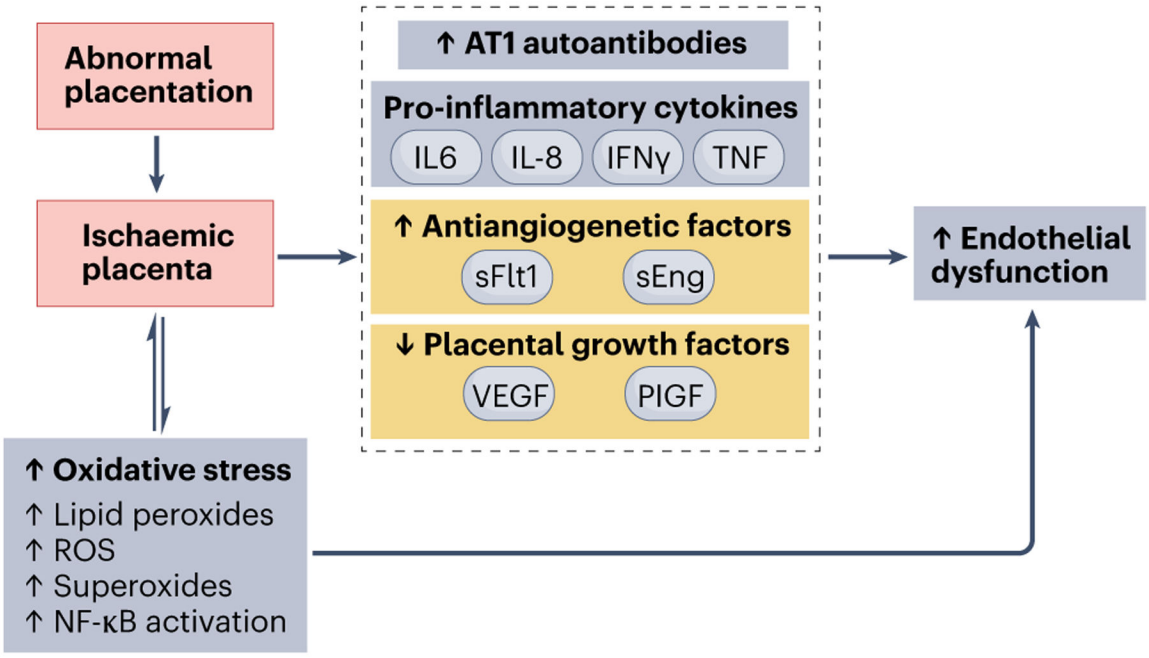

Fig. 2 |. Mechanisms of endothelial dysfunction in preeclampsia.

Abnormal placentation triggers a cascade of events that activates the release of circulating factors, such as cytokines (for example, tumour necrosis factor (TNF) and IL-6), soluble fms-like tyrosine kinase 1 (sFlt-1) and angiotensin II type 1 receptor (AT1) autoantibodies that promote inflammation, create an angiogenic imbalance and induce oxidative stress. Collectively, these alterations result in endothelial dysfunction and hypertension, as well as kidney dysfunction during pregnancy. NF-κB, nuclear factor-κB; PIGF, placental growth factor; ROS, reactive oxygen species; sEng, soluble endoglin; VEGF, vascular endothelial growth factor.

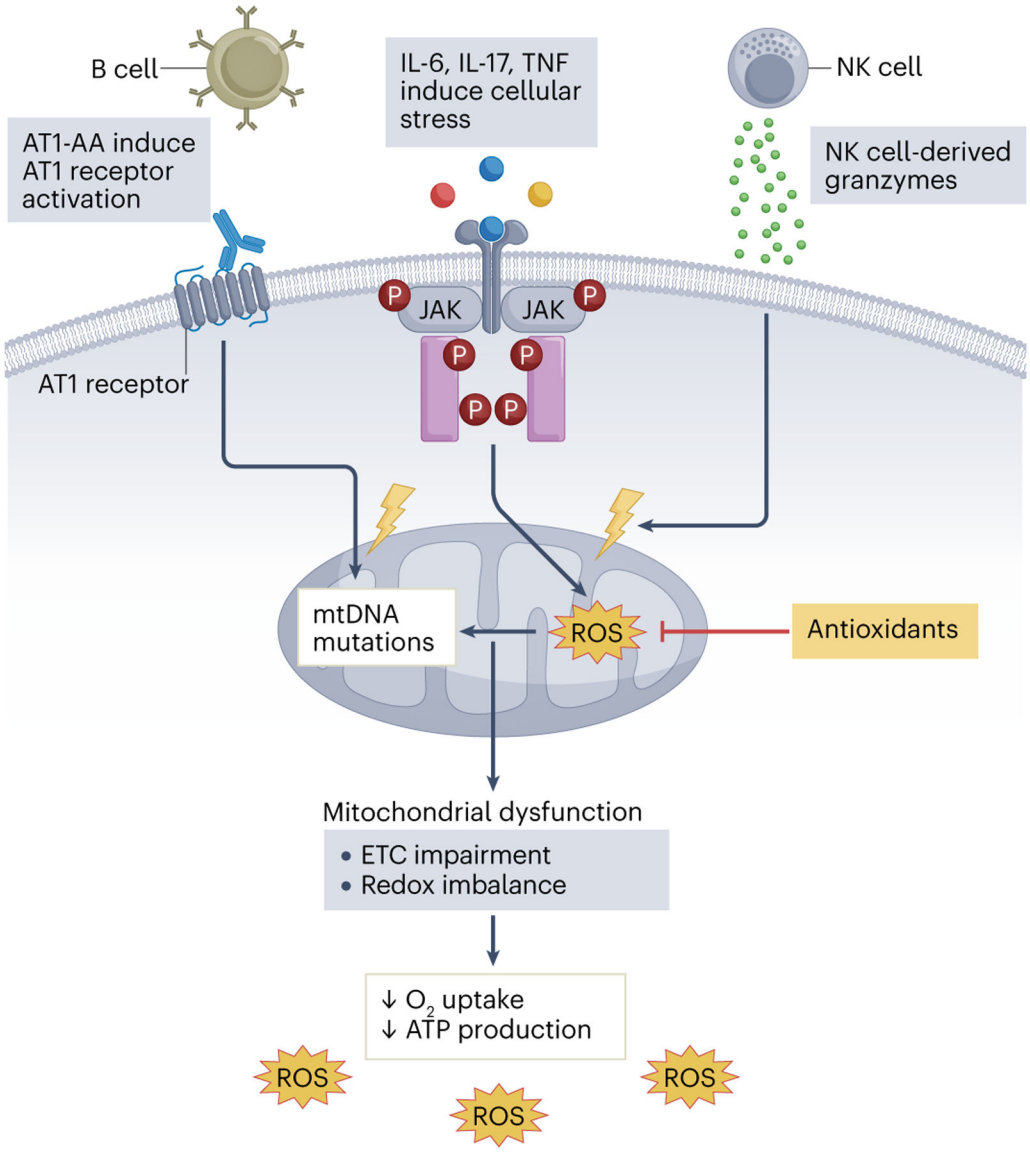

Fig. 3 |. Mitochondrial dysfunction and the pathogenesis of preeclampsia.

Immune alterations characteristic of preeclampsia, such as the production of angiotensin II type 1 receptor autoantibodies (AT1-AAs), increased secretion of pro-inflammatory cytokines (including IL-6, IL-17 and tumour necrosis factor (TNF)) and enhanced natural killer (NK) cell cytolytic activity, induce cellular stress and mitochondrial DNA damage in the placenta. Accumulation of mitochondrial reactive oxygen species (mtROS) leads to DNA damage and affects ATP production, for example, through impairment in the electron transport chain (ETC). ROS and the pro-inflammatory mediators that are produced during this process contribute to the systemic inflammation observed during preeclampsia. JAK, Janus kinase.

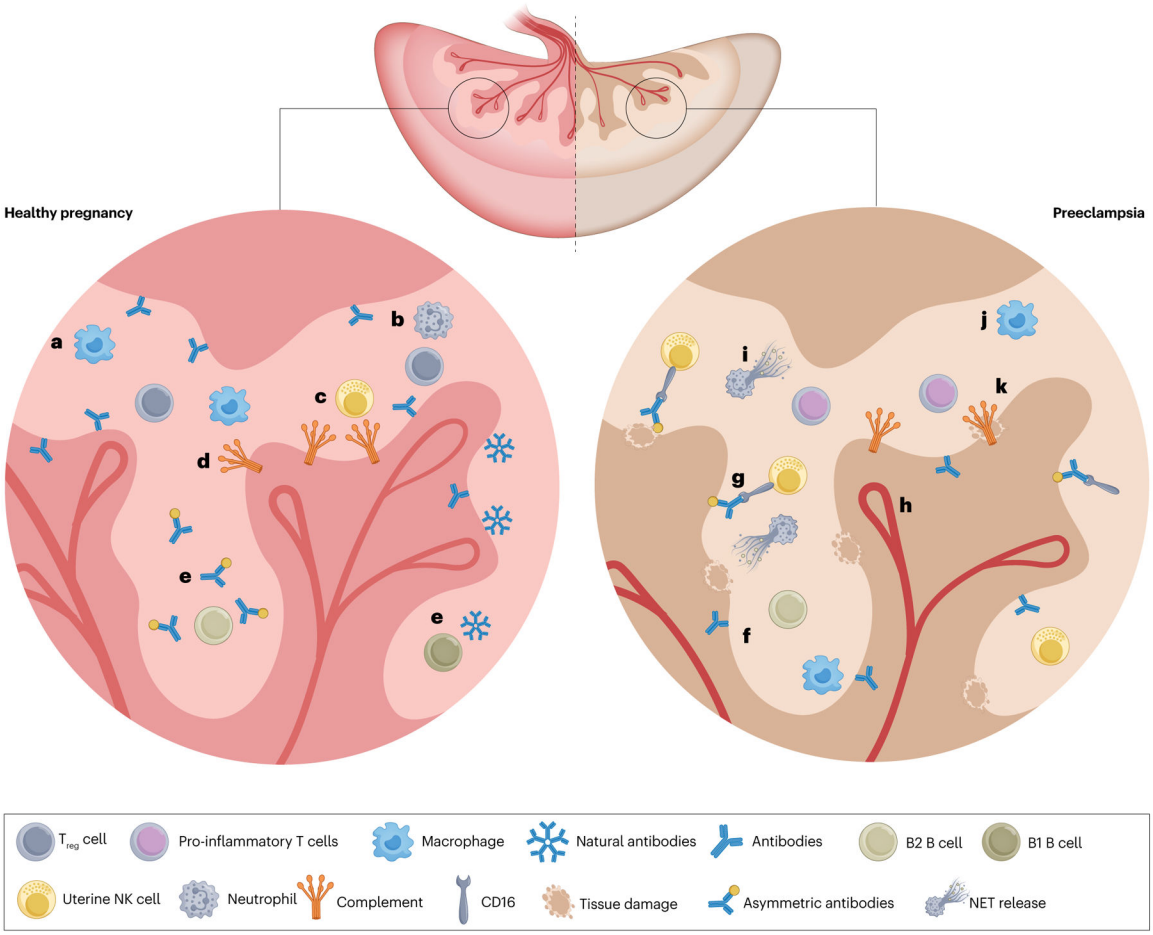

Fig. 4 |. Immune alterations in preeclampsia.

The innate immune system is crucial to the formation of fetal vessels in healthy pregnancy, but can also contribute to inflammation and cell death in preeclampsia. **a**, Macrophages clear cellular debris in the remodelling uterus while also producing proteases to help to establish the fetal blood supply. **b**, The role of neutrophils in healthy pregnancy has not been fully elucidated but these cells can also clear cellular debris. **c**, Uterine natural killer (uNK) cells are very active in healthy pregnancies as they produce vascular endothelial growth factor (VEGF) and proteases that promote spiral artery remodelling; these cells also promote cell turnover in the rapidly changing uterus. **d**, Complement proteins are present in the uterine environment and seem to also contribute to cell turnover. C1q deficiency is associated with decreased fetal viability and improper placentation[191], suggesting that complement is integral to placentation. **e**, B1 B cells spontaneously produce natural antibodies that contribute to maternal immunity and B2 B cells secrete asymmetric antibodies that shield fetal antigens from maternal killer cells. **f**, In preeclampsia, B cells produce anti-angiotensin II type 1 receptor autoantibodies (AT1-AAs), which contribute to immune activation and AT1 receptor activation, resulting in cardiovascular dysfunction. **g**, NK cells become activated through activating signals downstream of CD16 bound by antibodies in preeclampsia and contribute to cellular death. NK cells are also activated by cytokines that promote a cytolytic phenotype. **h**, Cytolytic NK cells can produce

anti-angiogenic factors and inhibit vascularization of the placenta, therefore contributing to preeclampsia. **i**, Neutrophils produce more neutrophil extracellular traps (NETs) in preeclampsia than in healthy pregnancy. NETs can contribute to vascular fibrosis and cell death in the placenta. **j**, The abundance of pro-inflammatory macrophages, which produce tumour necrosis factor (TNF) and IL-6, increases in preeclampsia at stages in which anti-inflammatory macrophages would be dominant in a healthy pregnancy. **k**, Complement activation is also observed in the placentas of women with preeclampsia, where it promotes immune cell recruitment and tissue damage.

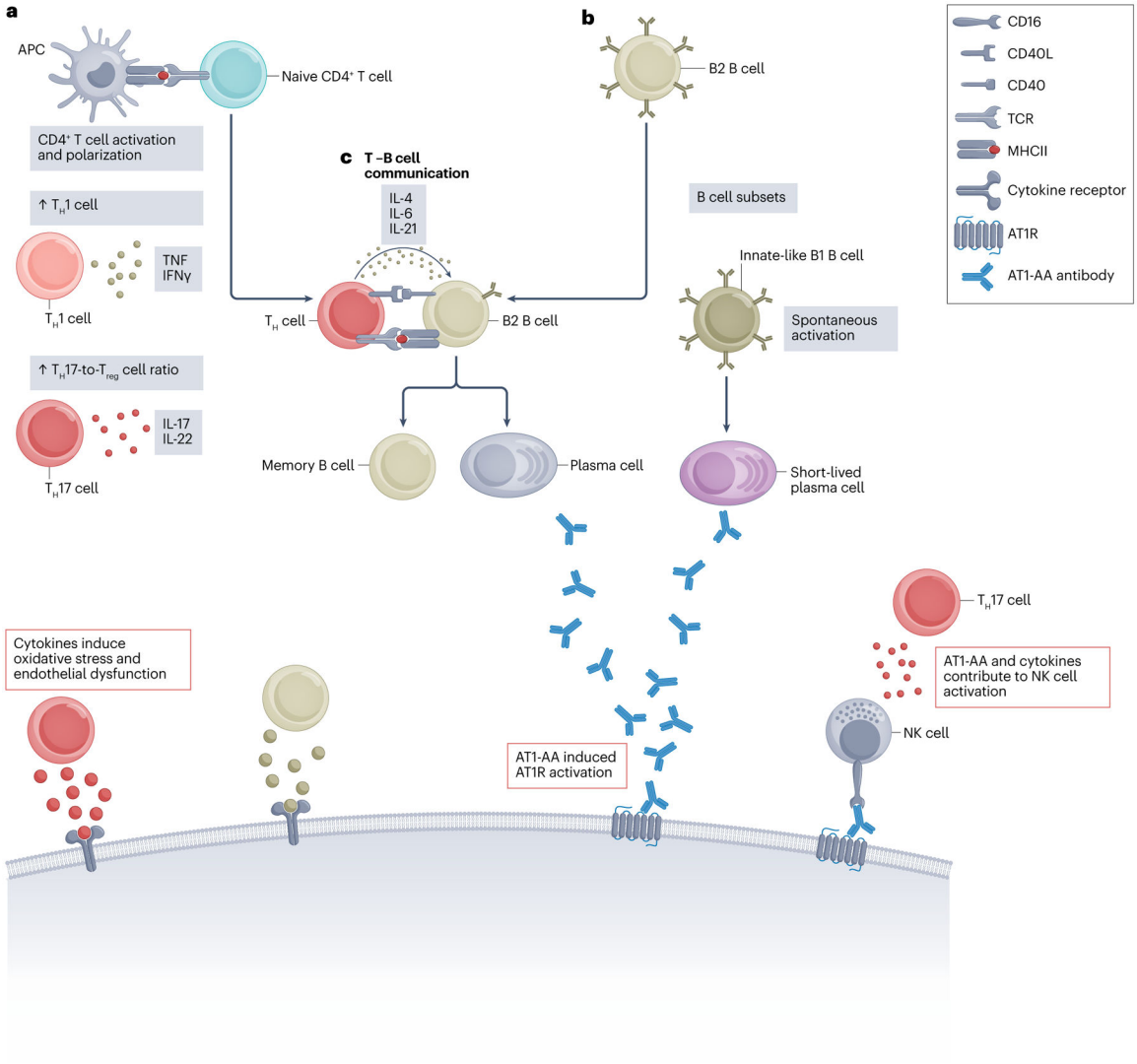

Fig. 5 |. The roles of T and B cells in preeclampsia.

a, Antigen-presenting cells (APCs) activate and polarize $CD4^+$ T helper (T_H) cells. In preeclampsia, T_H cells are polarized towards inflammatory T_H1 or T_H17 cell profiles. T_H1 cells produce pro-inflammatory cytokines, such as IFN-γ and tumour necrosis factor (TNF), which are both increased in preeclampsia. TNF activates various immune cells and endothelial cells, whereas IFNγ is a potent activator of cytotoxic immune cells and promotes B cell activation. T_H17 cells are important producers of pro-inflammatory IL-17, which is linked to immune dysregulation in multiple autoimmune disorders. **b**, B cells are divided into two main subsets: B1 B cells and B2 B cells. B1 cells are innate-like B cells that are associated with spontaneous activation and natural antibody production. B2 cells are classical B cells that require T_H cell help to induce antigen-specific antibody production. **c**, The interaction between B2 B cells and T_H cells involves co-stimulatory molecules such as CD40 and its ligand CD40L. T cell help enables B2 cell differentiation into plasma cells and long-lived memory B cells, which might contribute to long-term, anti-angiotensin II type 1 receptor autoantibodies (AT1-AAs) production postpartum. Similar to angiotensin

II, AT1-AAs activate the AT1 receptor (AT1R), in addition to contributing to immune activation through antibody-dependent cellular cytotoxicity and, potentially, complement system activation. Moreover, T cell-derived pro-inflammatory cytokines not only induce activation of other pro-inflammatory leukocytes but also contribute to the oxidative stress and endothelial dysfunction that is observed in preeclampsia. T_{reg}, regulatory T.