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Themed Section: Immune Targets in Hypertension

REVIEW ARTICLE

Inflammatory mediators: a causal link to hypertension during preeclampsia

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Preeclampsia (PE) is a hypertensive disorder that occurs after 20 weeks of gestation, implicating the placenta as a key offender. PE is associated with an imbalance among B lymphocytes, $CD4^+$ T lymphocytes, NK cells and increased inflammatory cytokines. During early onset PE, trophoblast invasion and placentation are impaired, leading to reduced blood flow to the fetus. In all spectrums of this disorder, a shift towards a pro-inflammatory state where regulatory cells and cytokines are decreased occurs. Specifically, inflammatory $CD4^+$ T-cells and inflammatory cytokines are increased while $CD4^+$ T regulatory cells (Tregs) and immunosuppressive cytokines such as IL-4 and IL-10 are decreased resulting in B cell activation, production of autoantibodies, endothelial dysfunction and hypertension associated with PE. However, the stimulus for these imbalances is unknown and need to be fully understood so that effective treatments that target the pathogenesis of the disease can be designed. Therefore, this review will focus on the pathways involving $CD4^+$, TH1, TH2, Tregs, TH17s, B cells, and NK cells in the pathophysiology of PE.

LINKED ARTICLES

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Abbreviations

PE, preeclampsia; AT_1-AA, agonistic autoantibodies to the angiotensin II AT_1 receptor; TH, T helper; Tregs, T regulatory cells; NCRs, natural cytotoxicity receptors; dNK cells, decidual NK cells; RUPP, reduced uterine perfusion pressure; NP, normal pregnant

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Introduction

The hypertensive disorders of pregnancy complicate 6 to 11% of all pregnancies (Creasy *et al.*, n.d.; Duley, 1992; Berg *et al.*, 2003; Chang *et al.*, 2003). They are a leading cause of iatrogenic preterm birth and significant contributors to maternal and perinatal morbidity and mortality (Duley, 1992; World Health Organization, 1995). The spectrum of disorders includes preeclampsia (PE)–eclampsia, PE superimposed on chronic hypertension and gestational hypertension (transient hypertension of pregnancy or chronic hypertension identified in the latter half of pregnancy (Mammaro *et al.*, 2009). The clinical complications of these disorders include fetal growth restriction, preterm birth, placental abruption, cardiovascular disease and end-organ damage (Creasy *et al.*, n.d.). While advances have been made in our understanding of the pathophysiology of the hypertensive disorders of pregnancy, the treatment has not changed in 50 years with delivery remaining the only known definitive cure (Noris *et al.*, 2005). Although the recent Aspirin for Evidence-Based Preeclampsia Prevention trial demonstrated that daily low-dose aspirin significantly decreased the incidence of PE in high-risk pregnancies (Rolnik *et al.*, 2017), aspirin was not proven to improve management or outcomes of women who go on to develop PE or others hypertensive disorders of pregnancy (Poon *et al.*, 2017).

The precipitating cause during pregnancy of new onset hypertension or exacerbation of previously existing hypertension has yet to be fully elucidated. It is postulated that maternal endothelial dysfunction most often incites or exacerbates the clinical signs used for diagnostic purposes. This maternal endothelial dysfunction, manifesting as placental ischaemia, results from improper vascular remodelling due to insufficient trophoblast invasion, which is tightly regulated by immune cells in the decidua during a normal pregnancy (Cornelius, 2018). Placental ischaemia is believed to be the inciting event resulting from a hindrance of proper trophoblast invasion and placentation that leads to reduced blood flow to the fetus and a resulting shift in immune function towards a proinflammatory state characterized by increased pro-inflammatory immune cells and cytokines and decreased regulatory cells and anti-inflammatory cytokines (Saito *et al.*, 1999; Lamarca, 2010; Saito *et al.*, 2010; Tam Tam *et al.*, 2011).

Shifts in immune cell populations

The normal cellular milieu of pregnancy involves both pro-inflammatory and anti-inflammatory components from the innate and adaptive immune arms (Granger, 2004; Noris *et al.*, 2005; Redman and Sargent, 2005; LaMarca *et al.*, 2007; Gilbert *et al.*, 2008; Toldi *et al.*, 2008; Prins *et al.*, 2009; Lamarca, 2010; Matsubara *et al.*, 2010). On the cellular level, normal pregnancy displays increases in innate immune cells compared to the non-pregnant state. In the circulation, there is an increase in monocytes and granulocytes, as well as an increase in the activation of monocytes (Faas and de Vos, 2017) in normal pregnancy, compared to non-pregnant women. Furthermore, an increase in decidual macrophages and NK cells are also observed during normal pregnancy versus non-pregnancy in order to facilitate trophoblast invasion and uterine spiral artery remodelling (Faas *et al.*, 2014). On a molecular level, the hypertensive disorders of pregnancy are marked by decreased vasodilators, significantly increased inflammatory cytokines, agonistic autoantibodies to the angiotensin II AT_1 receptor (AT_1-AA) and chronic immune activation (Conrad and Benyo, 1997; Schlembach, 2003; Granger, 2004; Noris *et al.*, 2005; Redman and Sargent, 2005; LaMarca *et al.*, 2007; Matsubara *et al.*, 2010). Specifically, women who develop PE exhibit elevated circulating and placental levels of **TNF-α** and **IL-6** (Conrad and Benyo, 1997; Lam *et al.*, 2005). Anti-inflammatory cytokines also play a pivotal role in maintaining a normal, successful pregnancy by providing balance to the immune system (Piccinni and Romagnani, 1996; Hambartsoumian, 1998; Chatterjee *et al.*, 2014). During PE, there is evidence of increased AT_1-AA, inflammatory $CD4^+$ T-cells and inflammatory cytokines such as TNF-α, IL-6 and **TGF-β**. Previously, our laboratory have demonstrated that normal pregnant (NP) rats receiving either TNF-α or IL-6, developed signs of PE such as hypertension, oxidative stress and impaired endothelial function (Murphy *et al.*, 2010; Amaral *et al.*, 2014b). Furthermore, we have reported that AT_1-AA infusion into NP rats mediates the pathophysiology of PE (LaMarca *et al.*, 2012).

Immunosuppressive cytokines such as **IL-4** and **IL-10**, which are present at the fetal–maternal interface and should regulate and control inflammation, are decreased resulting in hypertension and other clinical complications (Conrad and Benyo, 1997; Granger, 2004; LaMarca *et al.*, 2007; Toldi *et al.*, 2008; Prins *et al.*, 2009; Lamarca, 2010; Toldi *et al.*, 2012; Chatterjee *et al.*, 2014; Amaral *et al.*, 2014a; Chatterjee *et al.*, 2015). The main anti-inflammatory cytokines produced by TH2 cells that are involved in normal pregnancy are IL-4 and IL-10 (Nickerson *et al.*, 1994; Strom *et al.*, 1996) and reduction in TH2 cells or IL-4 contributes, at least in part, to the pathophysiology seen during PE. In agreement with this, clinical studies have demonstrated woman with PE have alterations in the NK cell population. There is also an association between low levels of IL-4 and elevated levels of NK cells with multiple spontaneous abortions and PE, (Piccinni and Romagnani, 1996; Hambartsoumian, 1998), and supplementation with IL-4 has improved TH2 cell counts while reducing cytolytic NK cells in pregnant rodent models of PE (Chatterjee *et al.*, 2015; Elfarra *et al.*, 2017).

An exciting area of research involves manipulating such inflammatory mediators responsible for blood pressure fluctuations during pregnancy to better understand the mechanisms involved in PE or miscarriage. We are now just beginning to learn about immune mechanisms and pathways required for normal pregnancies and the alterations seen in those complicated by the spectrum of hypertensive disorders. Although imbalance and improper function of inflammatory mediators is known to exacerbate and incite the hypertensive disorders of pregnancy, the exact role that these cells and cytokines play during this multi-system disease process is not yet fully understood. Furthermore, improvements in treatment strategies that target this pregnancy disorder need to be considered for better understanding, clinical management and improved outcomes.

$CD4^+$ T-cell populations

During pregnancy, the abundance of leukocytes is significantly increased in the uterus. Leukocytes make up 30–40%

of the decidua cells at the maternal–fetal interface and consist mainly of NK cells, $CD14^+$ myelomonocytic cells and T lymphocytes. $CD4^+$ T-cell populations can be composed of helper T-cells including type 1 (TH1), type 2 (TH2) and TH17 cells and immunomodulatory regulatory T-cells (Treg) (Sykes *et al.*, 2012). The imbalance between the $CD4^+$ T-cell subsets, T regulatory (Treg) and T helper 17 (TH17) has been positively associated with the pathophysiology of PE (Santner-Nanan *et al.*, 2009; Toldi *et al.*, 2011; Darmochwal-Kolarz *et al.*, 2012). There is evidence for a shift towards pro-inflammatory $CD4^+$ TH1 cells and away from $CD4^+$ Treg and $CD4^+$ TH2, in PE (Raghupathy, 1997; Saito *et al.*, 1999; Veenstra van Nieuwenhoven *et al.*, 2003; Saito *et al.*, 2010). In the uterus, the cytotrophoblast invasion and proliferation can be facilitated by TH2 and Tregs during normal pregnancies (Sargent *et al.*, 2006). However, in pregnancy disorders, there are more effector TH1 and TH17 cells within the circulation and placentas compromising the normal function of TH2 and Tregs.

The importance of Tregs in maintenance of early pregnancy has previously been established (Toldi *et al.*, 2008; Santner-Nanan *et al.*, 2009; Darmochwal-Kolarz *et al.*, 2012; Toldi *et al.*, 2012). Clinical studies have reported decreased $CD4^+$ regulatory T-cells (Tregs) in the decidua and circulation in preeclamptic pregnancies, compared to women with normal pregnancies. These cells mediate tolerance towards the fetus. Failure of the maternal immune tolerance mechanisms could be associated with placental ischaemia and oxidative stress, both of which are known to be involved in the pathophysiology of PE. Our previous findings have demonstrated that reduced uterine perfusion pressure (RUPP) rats have higher total $CD4^+$ T-cells with a 47% decrease in Tregs compared to NP rats (Wallace *et al.*, 2011). Cornelius *et al.* published recently that adoptive transfer of Tregs from NP rats into RUPP rats decreases BP and vasoactive factors which contribute to the high BP observed in this rat model of PE (Cornelius *et al.*, 2015a). Furthermore, we have demonstrated that the stimulation of Tregs by either administration of a specific stimulus (superagonistic monoclonal antibody for **CD28**) or IL-10 supplementation reduces the signs of PE in response to placental ischaemia (Harmon *et al.*, 2015; Ibrahim *et al.*, 2017). Regulation of the immune response by Tregs is critical to maintenance of maternal health during pregnancy, and the up-regulation of these cells may help to improve the pathophysiology of PE. The benefits of restoration in number of the Treg population still need to be further investigated.

TH17 cells secrete the proinflammatory cytokine IL-17 and have been associated with PE. Previous studies have reported that TH17s are increased in preeclamptic women compared to normal pregnancies (Toldi *et al.*, 2011; Darmochwal-Kolarz *et al.*, 2012). Our laboratory has shown that the abnormally increased TH17 cell population mediates the pathophysiology of PE associated with placental ischaemia, including oxidative stress, intrauterine growth restriction and production of AT_1-AA (Cornelius *et al.*, 2016). In addition to this, we have also demonstrated that infusion of **IL-17** into NP rats lead to an increase in TH17 cells and other signs of PE. Importantly, blockade of IL-17 function with the soluble receptor, **IL-17 RC**, lowered TH17 cell numbers while decreasing hypertension, oxidative stress and AT1-AA production in response to placental ischaemia (Cornelius *et al.*, 2013). Furthermore, administration of losartan attenuated the hypertension after the adoptive transfer of TH17 cells into NP rats, demonstrating the importance of stimulation of the **AT_1 receptor** in TH17 mediated effects of PE. Importantly, the down-regulation of this cell population could improve maternal and fetal outcomes.

B lymphocytes

An important function of $CD4^+$ T-cells is to mediate the B lymphocyte memory immune response and specific antibody production towards a single antigen in a process is known as the T-cell dependent antibody response (Abbus and Lichtman, 2005). Auto-antibodies are produced during PE, suggesting an important role for B lymphocytes in the pathogenesis of this disease. Liao *et al.* demonstrated that the percentage of circulating memory B lymphocytes were significantly greater in preeclamptic women than in the NP cohort (Liao *et al.*, 2009). Conventional memory B cells, known as B2 B lymphocytes, undergo antigen processing by recognizing the MHC class II peptide complex with the activated $CD4^+$ T lymphocyte (Abbus and Lichtman, 2005). For B cell maturation and IgG production, several co-stimulatory signals must occur between the antibody producing B lymphocyte and the $CD4^+$ T helper cell (Abbus and Lichtman, 2005). One of these includes stimulation of the CD20 receptor on the surface of the B cell. This recognition prompts the B cell to enter the circulation and produce antigen specific Ig antibodies. Another necessary co-stimulatory molecule for B cell maturation is CD40 located on the surface of the B cell which binds with the **CD40 ligand** on the surface of the T-cell (Abbus and Lichtman, 2005). B cells then progress through the stages of proliferation, differentiation and internal isotype switching leading to production of specific antigen stimulated antibodies which leads to the formation of short lived plasma cells that secrete antibody and memory B cells residing in the germinal lymph node centres, which will be available for rapid response in future interactions with antigen-specific T-cells.

A number of therapeutic agents that inhibit specific interactions between immune molecules on cells have been developed to treat various autoimmune diseases. In a recent study, we utilized a chemotherapeutic agent that has shown efficacy among autoimmune patients by blocking the **CD20** (**Rutiximab**) co-stimulatory molecule (Cianchini *et al.*, 2007; LaMarca *et al.*, 2011). Rutiximab is used to inhibit B lymphocytes from entering the circulation and secreting antibody, a process known as B cell depletion (Abbus and Lichtman, 2005; Cianchini *et al.*, 2007). We found that with B cell depletion, RUPP rats had lower BP, circulating TNF-α, autoantibodies and tissue **ET-1** as compared to control RUPP rats (LaMarca *et al.*, 2011). We exposed endothelial cells to serum from B cell depleted RUPP rats and found that ET-1 secretion was completely attenuated when compared to control RUPP sera. These data supported the hypothesis that B lymphocytes stimulated through T-cell interaction in response to placental ischaemia in pregnant rats play an important role to increase BP, circulating inflammatory cytokines and ET-1, possibly *via* autoantibody production, during pregnancy.

Although this study demonstrated a role for memory B2 B lymphocytes in the pathogenesis of hypertension in response to placental ischaemia, it did not clarify antigenic stimulation or examine the role for the other B cell subtypes in the progression of this disease. B lymphocytes can be characterized as either B1 or B2 cells, each having distinct markers and roles in facilitating immune reactions. B1 lymphocytes can be further divided into B1a or B1b cells (Abbus and Lichtman, 2005; Liao *et al.*, 2009). These cells express IgM in greater quantities than IgG and are the primary source of natural antibodies produced in the absence of antigenic stimulation. These antibodies are polyreactive and cross-react with multiple antigens such as autoantigens, other immunoglobulins and bacterial polysaccharides (Abbus and Lichtman, 2005; Jensen *et al.*, 2012). B1 B cells have been implicated in the progression of autoimmune diseases and are elevated in lupus erythematosus and rheumatoid arthritis. B1 B cells are present in low numbers in the circulation, lymph nodes and spleen and are predominantly found in the peritoneal and pleural cavities. B1 B lymphocytes are responsible for T-cell independent antibody production.

We recently demonstrated that importance of B1 lymphocyte communication with activated $CD4^+$ T helper cells in NP rats (Cornelius *et al.*, 2015b). In this study, CD40L on RUPP $CD4^+$ T helper cells was blocked with a neutralizing antibody. Adoptive transfer anti-CD40L treated RUPP $CD4^+$ T helper cells into NP rats caused a significant decrease in hypertension, placental ROS and importantly AT_1-AA production compared with NP rats who received untreated RUPP $CD4^+$ T helper cells. Importantly, blockade of CD40L on CD4 T-cells significantly decreased circulating IL-6. This may be due to decreased CD40 mediated activation of B cells, as CD40-activated B cells have been shown to secrete IL-6 (Daudelin *et al.*, 2013). Therefore, the decrease in IL-6 may also be due to decreased B cell activation by the RUPP CD4 T-cells which would account for less AT_1-AA. This study demonstrated that interaction between endogenous cells and RUPP $CD4^+$ T helper cells *via* CD40–CD40L binding is one important mechanism that leads to much of the pathophysiology of PE.

Jensen *et al.* uncovered an important role for B1 lymphocytes in the progression of PE (Jensen *et al.*, 2012). Preeclamptic placentas stained positive for markers of B1 B lymphocytes ($CD19^+CD5^+$). Furthermore, these authors demonstrated that B1 B lymphocytes were stimulated to produce AT_1-AA when co-cultured with sera from preeclamptic women but not from NP women. This study further illustrated the importance of B cells in the preeclamptic placenta and their stimulation by a soluble factor to produce AT_1-AA and contribute to the progression of this disease. Furthermore, high levels of B1 cells is yet another important characteristic that preeclamptic women share with patients presenting with autoimmune diseases.

NK ratios

NK cells are granular lymphocytes of the innate immune system that develop in the bone marrow from common lymphoid progenitor cells. NK cells participate in the control of viral or bacterial infection, regulation of haematopoiesis, production of cytokines and cytotoxicity of neoplastic cells. However, a specialized population of NK cells in the decidua also play important roles in the establishment of and maintenance of human pregnancy. The decidual NK (dNK) cells make up approximately 70% of the uterine leukocytes and are the most abundant maternal leukocyte population during the first trimester in human pregnancy (Moffett-King, 2002; Fukui *et al.*, 2011). The dNK cells have a cytokine-producing rather than cytotoxic phenotype and have several roles in human pregnancy (Dosiou and Giudice, 2005; Fukui *et al.*, 2011). The dNK cells interact closely with trophoblast cells and secrete cytokines that promote trophoblast growth and mediate trophoblast differentiation, invasion and spiral artery remodelling (Dosiou and Giudice, 2005; LaMarca *et al.*, 2013). The dNK cells also have roles in maintenance of maternal–fetal tolerance throughout pregnancy. The dNK cells recognize HLA antigens on fetal trophoblasts which protect them from cytotoxic targeting. Additionally, the dNK cells have a role to help mediate the increased Treg population in the placenta and inhibit proliferation, survival and activation of fetal-antigen specific effector T helper cells (Dosiou and Giudice, 2005; Arck and Hecher, 2013; Vacca *et al.*, 2013).

The type 1 shift in the immune profile of women with PE is observed not only in adaptive immune cells but also in innate immune cells, specifically NK cells. The type 1 (NK1) subset of NK cells is characterized by release of **IFN-γ** and TNF-α and potent cytolytic activity upon activation (Peritt *et al.*, 1998; Vacca *et al.*, 2011). Tregs can inhibit **IL-2** mediated polarization of NK1 cells by decreasing availability of IL-2 (Katsumoto *et al.*, 2004; Kerdiles *et al.*, 2013). The NK2 subset is characterized by their release of the anti-inflammatory cytokines **IL-5** and **IL-13** and a decrease in their cytolytic activity (Peritt *et al.*, 1998; Vacca *et al.*, 2011). NK2 differentiation is mediated through signalling by the anti-inflammatory cytokine IL-4 (Peritt *et al.*, 1998; Vacca *et al.*, 2011). This suggests a role for anti-inflammatory and regulatory $CD4^+$ T-cells are able to regulate innate immune cell polarization and activation (Figure 1).

The aberrant activation of NK cells is observed both in the periphery and in the decidua of women with PE (Sargent *et al.*, 2007). A number of studies have demonstrated that changes in the decidual population of NK cells are reflected in the periphery (Park *et al.*, 2010; Fukui *et al.*, 2011). Borzychowski *et al.* suggested that systemic type 1 and type 2 immunity in normal pregnancy and PE may be mediated by NK cells (Borzychowski *et al.*, 2005). This study demonstrated significant increases in type 1:type 2 ratios in both $CD56^{bright}$ and $CD56^{dim}$ NK cells from peripheral blood mononuclear cells in women with PE, compared with women with normal pregnancies (Borzychowski *et al*, 2005). The results of these studies were further supported by findings that expression of IFN-γ was higher in NK cells from women with PE, than in normal pregnancy (Darmochwal-Kolarz *et al.*, 2002; Germain *et al.*, 2007; Saito *et al.*, 2010).

Natural cytotoxicity receptors (NCRs) are markers unique to NK cells that regulate NK cell cytokine production and cytotoxicity. Expression of the NCR, NKp46, has been

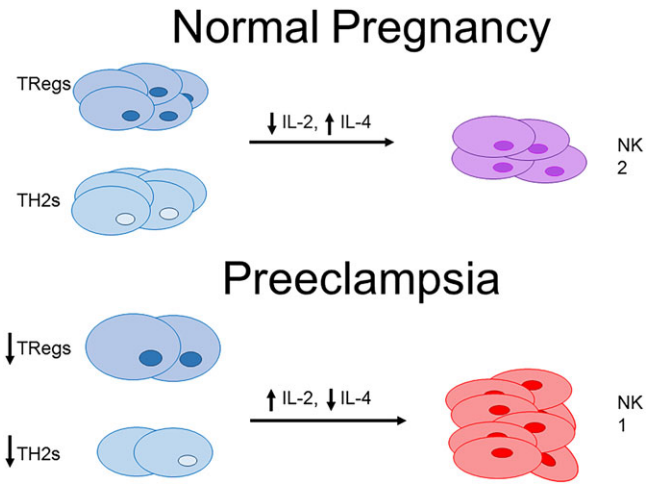

Figure 1

Adaptive CD4$^+$ T-cell populations may be regulators of NK cell proliferation and polarization. The decreased population of Tregs in PE may increase IL-2 bioavailability and mediate polarization of NK1 cells. Decreased TH2 populations in PE may lead to decreased levels of NK2 polarizing cytokines, such as IL-4.

examined in peripheral blood in women with PE. Pregnant women who developed PE demonstrated a significantly decreased percentage of NKp46$^+$ cells compared to women without PE (Fukui *et al.*, 2011). Furthermore, the decrease in NKp46 NK cells correlated with an increase in IFN-γ and TNF-α positive NK cells, suggesting that the lower expression of NKp46 is associated with the type 1 shift in NK cells in PE. Additional *in vitro* studies of the activity of NK cells from patients with PE and normal pregnancies investigated the proliferative state and cytotoxic function of NK cells from maternal and cord blood. These studies demonstrated that the proliferative and killing ability of NK cells in PE patients was significantly higher than in normal third trimester pregnant women (Zhang *et al.*, 2004). The increased number of cytotoxic NK cells in this study further supports the increased ratio of type 1 to type 2 NK cells in PE and may identify this cytotoxic population of type 1 NK cells as a therapeutic target in PE.

Targeting the abnormal population of NK cells activated in PE may be a potential therapeutic option to improve treatment or management of PE. Although it is known that IL-2 and IL-12 signalling promote differentiation of NK cells to the NK1 subset, it has also been demonstrated that IL-17 may enhance cytolytic activity of NK cells, suggesting that TH17 cells may play a role in mediating differentiation into the NK1 population subset (Al Omar *et al.*, 2013). IL-17 induced cytolytic NK cell activity against tumours which suggests a possible therapeutic strategy in cancer treatment (Qian *et al.*, 2017). IL-17 was also shown to enhance NK cytolytic competence in fungal infection (Bar *et al.*, 2014). Thus, blockade or neutralization of these cytokines may inhibit polarization of NK1 cells in PE. Additionally, expansion of the endogenous Treg population in PE may favour a type 2 shift in NK cells through decreasing IL-2-induced NK1 polarization.

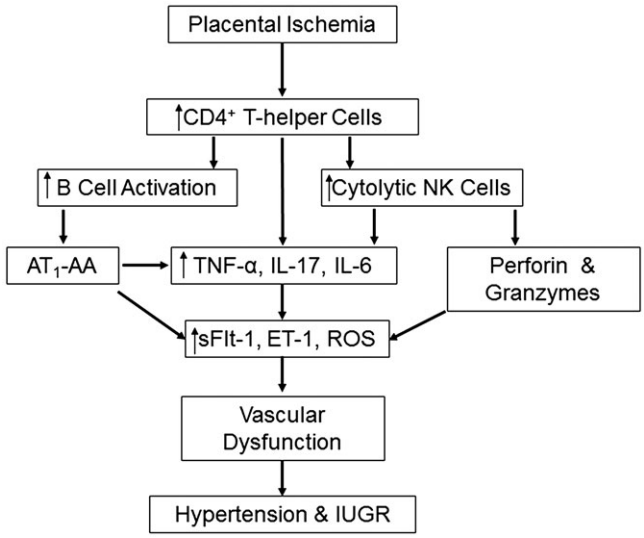

Figure 2

Placental ischaemia leads to an altered population of CD4$^+$ T helper cells that facilitate B cell activation and NK cytolytic polarization leading to increased inflammatory cytokines and effector proteins. This in turn causes maternal system endothelial dysfunction resulting in the development of hypertension and intrauterine growth restriction (IUGR).

Conclusion

The spectrum of hypertensive disorders of pregnancy is associated with inflammation and chronic immune activation. The immune profile of women with PE shifts from a controlled state of mild inflammation with a balance of both pro-inflammatory and anti-inflammatory components, to an altered state characterized by increased inflammatory cytokines and effector immune cells with a concomitant decrease in anti-inflammatory factors and regulatory cells (Figure 2). Preclinical studies suggest that normalization of the immune imbalance in PE may be a potential strategy for the development of therapeutic interventions that could improve maternal and fetal outcomes associated with this maternal syndrome.

Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Harding *et al.*, 2018), and are permanently archived in the Concise Guide to PHARMACOLOGY 2017/18 (Alexander *et al.*, 2017a,b,c).

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Conflict of interest

The authors declare no conflicts of interest.

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