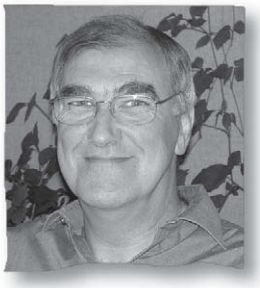
Article

Immunoregulation in normal pregnancy and pre-eclampsia: an overview



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Abstract

Pre-eclampsia is a major disorder of human pregnancy, which may have an immunological basis. It is a disease of two stages. The first stage concerns the relative failure of early trophoblast invasion and remodelling of the spiral arteries, leading to a poor blood supply to the placenta, exposing it to oxidative stress. The inadequate trophoblast invasion may result from decreased expression of human leukocyte antigen-G (HLA-G) leading to an abnormal interaction with decidual natural killer (NK) cells, which are believed to play a major role in these processes through the production of immunoregulatory cytokines and angiogenic factors. Recent evidence suggests that the interaction between trophoblast human leukocyte antigen-C (HLA-C) olecules and decidual NK cell receptors may be the point at which the apparent partner specificity of the disease originates. The second stage is the maternal syndrome, which is characterized by a generalized systemic inflammatory response involving both leukocytes and endothelium. The inflammatory stimulus is believed to come from the placenta. In pre-eclampsia, placental oxidative stress may lead to increased shedding of apoptotic and/or necrotic syncytiotrophoblast debris into the maternal circulation. There is evidence that such trophoblast debris interacts with maternal leukocytes and endothelial cells to stimulate the release of proinflammatory cytokines, which could then trigger the maternal disease.

Keywords: *HLA-C, HLA-G, placental debris, pre-eclampsia, Th1/Th2*

Implantation and pregnancy failure

The success of pregnancy depends on the successful implantation of the embryo. Poor implantation is believed to be the cause of a spectrum of pregnancy problems. At one end, total failure of implantation is manifested as infertility. If implantation occurs but subsequent placentation fails this leads to first trimester miscarriage. At the other end of the spectrum, successful implantation followed by poor placentation allows the pregnancy to continue into the second or third trimesters but the inadequate placenta cannot sustain the fetus normally and its dysfunction disturbs maternal systems, leading to pre-eclampsia. The aim of this review is to highlight some of the key immunological features that enable a normal pregnancy but when dysregulated may lead to pre-eclampsia.

Pre-eclampsia is a two-stage disease

To understand how pre-eclampsia develops, it is best thought of as a two-stage disease (Redman, 1991). The recognizable maternal signs (hypertension, proteinuria and oedema) and the poor growth of some fetuses are in fact components of the second stage of the disease. In most cases its origins (stage 1) lie in the placenta, as demonstrated by the fact that pre-eclampsia only occurs during pregnancy; there is no similar disease in non-pregnant women. However, it does not depend on the presence of a fetus, as it is particularly prevalent in cases of hydatidiform mole where there is a large placental mass but no fetus. The uterus is not necessarily involved as pre-eclampsia can occur in extra-uterine pregnancies. Finally, the only current 'cure' for the disorder is to deliver the baby and the placenta. Post-partum, pre-eclampsia can persist if parts of the placenta

are retained after delivery of the baby (Piering *et al.*, 1993). The placenta must therefore be the cause of the disease.

The placenta and pre-eclampsia

Each of the two stages of pre-eclampsia is related to events occurring at a different area of contact between the mother and placenta (Redman and Sargent, 2005). The primary contact in stage 1 is between the invasive extravillous cytotrophoblast, which migrates from the tips of the anchoring villi and invades into the decidua (interface 1). This interface is therefore one of tissue contact between maternal cells and fetal trophoblast and is important early in pregnancy (first trimester) in stage 1. The second interface is between the syncytiotrophoblast layer, which covers the surface of the chorionic villi and is in direct contact with maternal blood (interface 2). This interface is extended by the shedding of syncytiotrophoblast fragments, microparticles and cell-free DNA and RNA into the maternal circulation throughout pregnancy (Sargent *et al.*, 2003). Interface 2 is dominant in the second half of pregnancy. It is where the second stage of pre-eclampsia originates, causing a systemic inflammatory response in the maternal vascular compartment and the mother's symptoms (Redman *et al.*, 1999).

Trophoblast invasion at interface 1: stage 1 of pre-eclampsia

At interface 1, extravillous cytotrophoblast invades around and into the spiral arteries, which supply all the blood to the intervillous space of the placenta. This is associated with dramatic remodelling of these arteries (Redman and Sargent, 2005). The effect is to enlarge the vessels, allowing them to carry the increased blood flow which is essential to supply the growing fetus in the later stages of pregnancy. This process may be restricted in pre-eclampsia, leading to a poor placental blood supply, which is often insufficient to sustain the developing fetus and may lead to a reduction in the oxygen supply. This may be further exacerbated by a process called acute atherosis, where fat-filled macrophages adhere to the walls of the spiral arteries, causing complete occlusion (Pijnenborg *et al.*, 2006). The consequences are placental infarcts, oxidative stress and reduced placental function.

Is there an immunological cause for poor trophoblast invasion?

A key question in the development of pre-eclampsia is what causes the poor trophoblast invasion. A major area of interest is the possibility that it is caused by an aberrant maternal immune response against the trophoblast. To understand the nature of such an immune response, it is first necessary to know the patterns of expression of class I major histocompatibility complex (MHC) antigens (the principle stimulators of graft rejection) on trophoblast cells. There are six main class I MHC loci: HLA-A, -B and -C (the classical class I antigens) and HLA-E, -F and -G (the non-classical class I antigens) (reviewed in Hviid, 2006; Ishitani *et al.*, 2006). The principal difference between these two groups is that the classical class I antigens are highly polymorphic and predominantly interact with T cells, whereas the non-classical class I antigens are virtually monomorphic and primarily interact with natural killer (NK) cells. There are also important differences in their tissue distribution. Normal adult and fetal cells express HLA-A, -B, -C and -E, and to a limited extent HLA-F, whereas the invasive extravillous cytotrophoblast at interface 1 express only HLA-C, -E, -F and -G; the principal stimulators of graft rejection (HLA-A and -B) are missing (Hviid, 2006; Ishitani *et al.*, 2006). The expression of MHC antigens on the syncytiotrophoblast at interface 2 is even more unusual, with no class I antigens being expressed on the surface membrane, although the soluble form of HLA-G has been reported to be secreted by this tissue (Solier *et al.*, 2002).

Role of extravillous cytotrophoblast MHC in immunoregulation

HLA-G has been shown to interact with T cells and down-regulate the activity of both $CD4^+$ and $CD8^+$ cells, which could protect trophoblast from T-cell-mediated attack (Hviid, 2006). However, the principal interaction between invasive trophoblast and maternal immune cells is thought not to be with T cells, but rather with the specialized population of $CD56^{bright}$ NK cells, which are present in the decidua in early pregnancy (Moffett-King 2002). These interactions are mediated through the binding of HLA-E, -G and -C to their appropriate receptors on the NK cells, as summarized below. Although HLA-F has been reported to be expressed on extravillous cytotrophoblast in the decidua, its receptor and function in pregnancy are as yet unknown (Ishitani *et al.*, 2006).

HLA-E interacts with the CD94/NKG2A receptor on decidual NK cells, and the principal effect of this is believed to be inhibition of NK-cell-mediated killing of the trophoblast (Ishitani *et al.*, 2006).

HLA-G exists in both membrane bound and soluble forms. It interacts with the killer immunoglobulin-like receptor KIR2DL4 on decidual NK cells and stimulates the production of proinflammatory and immunoregulatory cytokines, together with factors involved in the control of angiogenesis, which are believed to be important in vessel remodelling (Tabiasco *et al.*, 2006).

Until recently, the role of the polymorphic HLA-C expressed by invasive or extravillous trophoblast had been difficult to fit into a conceptual framework owing to its potential interactions with T cells. However, it has now been recognized that it interacts with KIR2D receptors on decidual NK cells and in that way has the potential to control their repertoire of cytokine production (Hiby *et al.*, 2004). KIR receptors can be activating or inhibitory and there are two main KIR haplotypes that can be expressed: A, which has no activating receptors and B, which has one to five activating receptors. Similarly, HLA-C has two main haplotypes according to the residue at position 80 in the amino-acid sequence. C2 binds to and interacts with KIR more strongly than C1. Therefore, different combinations of trophoblast HLA-C and maternal decidual NK cell KIR will either activate NK cells (HLA-C1 trophoblast, KIRB decidual NK cells) and promote trophoblast invasion, or inhibit them (HLA-C2 trophoblast and KIRA decidual NK cells) and diminish trophoblast invasion. Interestingly, the latter combination is more prevalent in women who develop pre-eclampsia (Hiby *et al.*, 2004). The involvement of the polymorphic HLA-C antigen in these interactions may

account for the apparent paternal specificity of pre-eclampsia (Dekker and Robillard, 2005), although the mechanisms are not yet understood.

Aberrant expression of HLA-G is also believed to be associated with abnormal pregnancy. There have been several reports that IVF embryos that secrete soluble HLA-G are more likely to implant than those that do not (Fuzzi *et al.*, 2002; Sher *et al.*, 2005). Furthermore, concentrations of soluble HLA-G in the circulation of women with miscarriage or pre-eclampsia are lower than in normal pregnant women of the same gestational age (Rebmann *et al.*, 1999; Yie *et al.*, 2004) and the expression of cell surface HLA-G is said to be reduced on the invasive extravillous cytotrophoblast in miscarriage and pre-eclampsia (Emmer *et al.*, 2002; Goldman-Wohl *et al.*, 2000). It is not yet known whether there are also differences in HLA-E expression in these groups.

Fetal and maternal syndromes of pre-eclampsia (stage 2)

From the above, it is easy to understand how poor blood supply to the placenta will affect the fetus. Poor placental growth and damage to placental tissue may severely compromise placental function and may lead to retardation of the growth of the fetus. What is more difficult to understand is how an inadequate placenta can lead to the maternal syndrome, which comprises a diverse array of features including hypertension, proteinuria, oedema, liver and kidney damage, activation of the clotting system and in the worst cases cerebral haemorrhage and fits. These pathologies can all be explained by generalized activation or dysfunction of the endothelium of the mother's blood vessels (Redman and Sargent, 2005). Thus, endothelial dysfunction will lead to the release of vasoactive substances, such as endothelin 1 (Slowinski *et al.*, 2002), which raise the blood pressure; damage to the endothelium will alter its permeability, allowing fluid to leak into the tissues causing oedema (Haller *et al.*, 1998), or if in the kidney, proteinuria (Lafayette *et al.*, 1998), or in the brain (Demirtas *et al.*, 2005) may lead to fits.

However, it is now apparent that this endothelial dysfunction is part of a more generalized systemic inflammatory response involving the activation of leukocytes in the mother's blood (Redman and Sargent, 2004). This is demonstrated by an increase in the numbers of circulating granulocytes and monocytes in pre-eclampsia, activation of the clotting system, leukocyte activation and increased production of pro-inflammatory cytokines, including interleukins IL-6 and IL-8 (reviewed in Redman and Sargent, 2004). Interestingly, this inflammatory response is also present in normal pregnant women, but to a lesser extent.

It has been found that leukocytes from normal pregnant women are primed to produce higher concentrations of the proinflammatory cytokines IL-12, tumour necrosis factor α (TNFα) and IL-18 than non-pregnant women, but concentrations of interferon γ (IFNγ) are suppressed [S Germain, D Phil thesis, Oxford]. In contrast, in pre-eclampsia, although the levels of production of IL-12 and TNFα are similar to those seen in normal pregnancy, IFNγ production is significantly raised. It is therefore likely that IFNγ production may be central to the exaggerated inflammatory response and endothelial cell dysfunction of the maternal disease of pre-eclampsia.

Immunoregulation in normal pregnancy and pre-eclampsia

For many years, the working model for immunoregulation in pregnancy has been based on that of a shift of the maternal immune response away from Th1 (T-helper 1 – cell-mediated graft rejection responses) to Th2 (T-helper 2 – antibody-mediated responses), thereby protecting the conceptus from maternal cell-mediated immune attack (Wegmann *et al.*, 1993). The basis for this model is that in a healthy non-pregnant individual the response elicited by an antigen presented to a Th0 helper cell will depend on the cytokine environment in which the Th0 cell finds itself. A Th1 environment, with cytokines such as IL-12 and IL-18, will lead to the development of Th1 helper cells which, by producing IL-2 and IFNγ, promote cell-mediated immunity involving cytotoxic T cells, NK cells and macrophages (**Figure 1a**). Alternatively, if the Th0 cell is in a Th2 environment, with cytokines such as IL-4 and IL-10, this will lead to the development of Th2 helper cells, which in turn secrete Th2 cytokines such as IL-4, promoting antibody-mediated immunity. A key aspect of this system is that Th1 cytokines such as IFNγ can negatively feedback onto the Th2 arm and suppress Th2 responses. Similarly, Th2 cytokines can suppress Th1 cytokine production. Thus, in non-pregnant individuals there is a balance between the two arms of the immune response and they are able to elicit both cell-mediated and humoral immune responses.

However, in pregnancy this situation is significantly altered by the presence of the placenta, which acts as a Th2 cytokine-producing organ, producing both IL-4 and progesterone, which stimulates a Th2 bias (Piccinni *et al.*, 2000). This promotes antibody-mediated immunity and inhibits the development Th1 helper cells (and in particular IFNγ production), thereby suppressing Th1 cell-mediated immunity (**Figure 1b**). Although this model has been developed in the mouse, there is circumstantial evidence that this is also the case in humans. A disease such as rheumatoid arthritis, which is caused by cytotoxic T cells, improves during pregnancy, whereas intracellular infections such as herpes and malaria, which are normally suppressed by cell-mediated immune responses, get worse.

In pre-eclampsia, the pregnancy shift to Th2 either does not occur or is reversed early in the disorder. Thus, Th1 responses are not suppressed and IFNγ production is normal (**Figure 1c**). A key question is therefore what is the 'antigen' that drives the Th1 response and IFNγ production in pre-eclampsia?

Role of interface 2 in stage 2 of pre-eclampsia

As the original Th1/Th2 hypothesis was developed from studies in the mouse where maternal T cell responses to paternal antigens appear to play a role in the success of pregnancy, it has often been assumed that this is also the case in human pregnancy. However, the inflammatory response of normal pregnancy and pre-eclampsia takes place in the maternal circulation and therefore the relevant maternal-placental interface is interface 2, where the syncytiotrophoblast is devoid of any MHC antigens. This has led to speculation as to whether NK cells in the peripheral blood, which are very potent producers of cytokines (and in particular IFNγ), rather than T cells, play a primary role, as has been shown

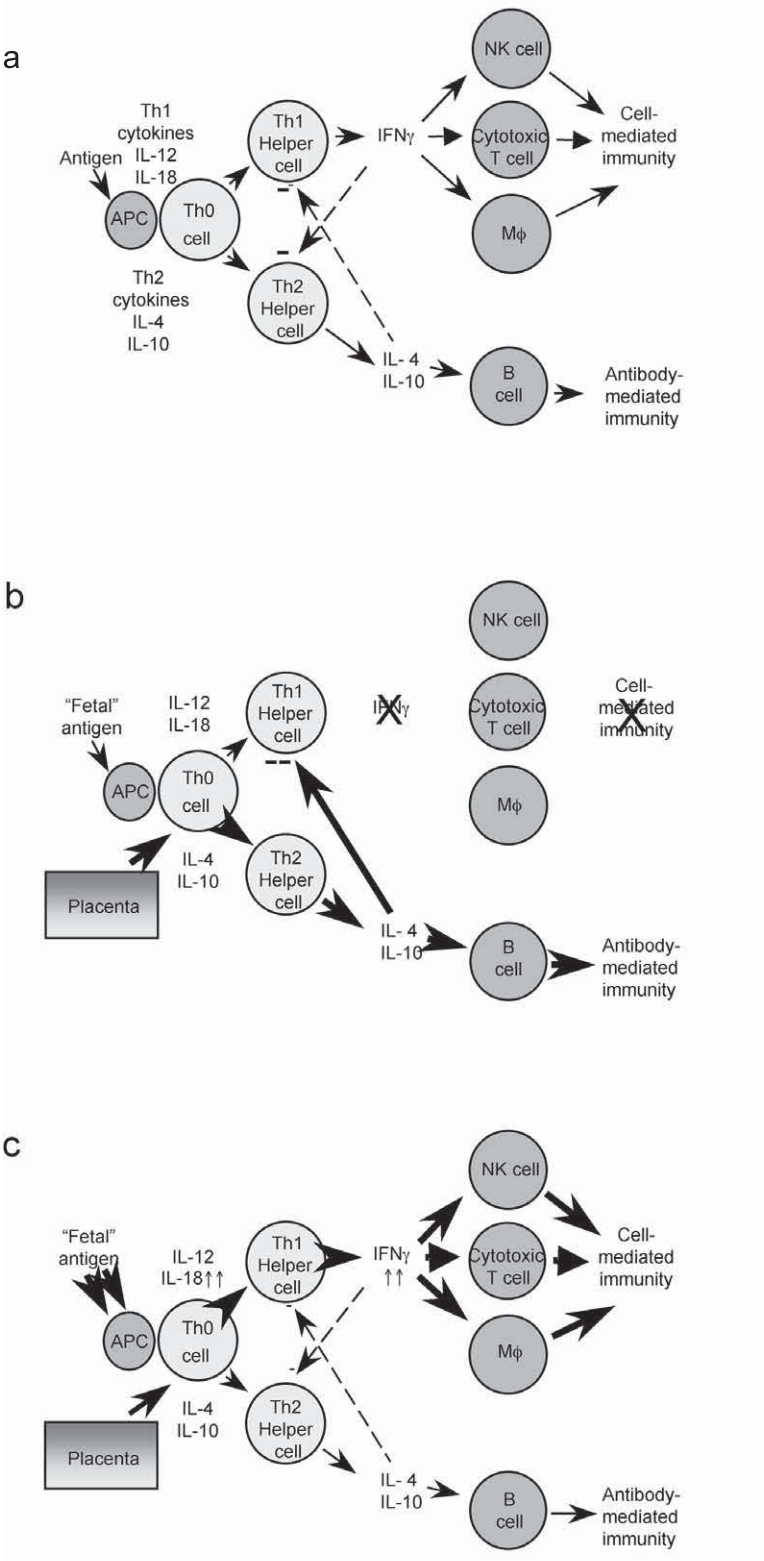

Figure 1. Th1/Th2 hypothesis of immunoregulation in normal pregnancy and pre-eclampsia. (**a**) Non-pregnant; (**b**) normal pregnancy; (**c**) pre-eclampsia. APC = antigen-presenting cell (macrophage/dendritic cell); IFNγ = interferon γ; IL = interleukin; mϕ = macrophage; NK = natural killer; Th = T helper.

for uterine NK cells in the decidua (discussed above).

When it was formulated, the Th1/Th2 concept concerned T helper cell function and was used as such to explain immune homeostasis in pregnancy. The concept has now been extended by the finding that cytotoxic T (Tc) and NK cells can also show comparable polarities in their cytokine secretion profiles (Carter *et al.*, 1995; Perrit *et al.*, 1998). This has introduced the larger concept of type 1/type 2 balance, which is more applicable to the systemic inflammatory response in normal pregnancy. To investigate the role of NK cells, cytokine production was not measured in stimulated peripheral blood lymphocytes, but two stable and universal surface markers were used for type 1 (IL-18R) and type 2 (ST2L) subsets, which can be analysed by flow cytometry on unstimulated cells (Chan *et al.*, 2001) with concurrent discrimination between lymphocyte subsets. The study showed that the type 2 shift in pregnancy was predominantly in the NK ($CD56^{bright}$ and $CD56^{dim}$) and NKT ($CD56^{+}CD3^{+}$) cell populations rather than in the Th or Tc populations (Borzychowski *et al.*, 2005). The shift to type 1 in pre-eclampsia was also evident in the NK and NKT cell populations, suggesting that NK rather than the T cells could be the pivotal populations in pregnancy. This would not preclude the involvement of T cells, but would suggest that they act more as downstream responders to signals generated by the NK/NKT populations.

The relegation of T cells to a secondary role in pregnancy immunoregulation might appear to be inconsistent with reports in the literature that regulatory T cells (Trowsdale and Betz, 2006) prevent T cell-mediated abortion in the mouse and are increased in human pregnancy (Saito *et al.*, 2005). However, it must be remembered that unlike the human syncytiotrophoblast, mouse trophoblast cells express polymorphic paternally derived MHC class I molecules (Zuckerman and Head, 1986) and thus are susceptible to T cell-mediated immune attack if it is not controlled. This important point is often missed by authors who extrapolate findings from the mouse to human pregnancy. Regulatory T cells can also suppress both NK cells (Ghiringhelli *et al.*, 2005) and NKT cells (Godfrey and Kronenberg, 2004), both in terms of proliferation and cytokine production. They might suppress type 1 responses in normal pregnancy by this route rather than through their effects on classical T cells. Failure of this regulation could lead to the exaggerated inflammatory response seen in pre-eclampsia, although a recent report has found no differences in circulating regulatory T cell numbers in normal pregnancies compared with pre-eclamptic pregnancies (Paeschke *et al.*, 2005).

How might the syncytiotrophoblast stimulate an inflammatory response? As discussed above, interface 2 is extended from the surface of the placenta throughout the mother's body by the shedding of syncytiotrophoblast cellular fragments and microparticulate debris into the maternal circulation. This is believed to be part of a normal renewal and repair process mediated by apoptosis in normal pregnancy. However, in pre-eclampsia there is increased apoptosis due to the placental hypoxia and there may also be shedding of necrotic debris from infarcted areas of the placenta (Redman and Sargent, 2003). This leads to a significant increase in the amounts of debris shed in pre-eclampsia compared with normal pregnancy. This debris would be cleared by the monocytes and dendritic cells in the maternal circulation and in that way may trigger the inflammatory response (see **Figure 2**). In support of this, preliminary data have been obtained showing that preparations of syncytiotrophoblast microparticles stimulate the production of TNFα, IL-12, IL-18 and IFNγ by peripheral blood mononuclear cells from non-pregnant individuals. In the revised 'type 1/type 2' model, it was speculated whether these cytokines may then drive maternal NK and NKT cells to a type 1 bias, leading to the higher levels of IFNγ production seen in pre-eclampsia (**Figure 2**). It has also been demonstrated that in-vitro preparations of trophoblast microparticles are highly disruptive to cultured endothelial cells (Smarason *et al.*, 1993; Gupta *et al.*, 2005), which *in vivo* would further contribute to the clinical features of pre-eclampsia.

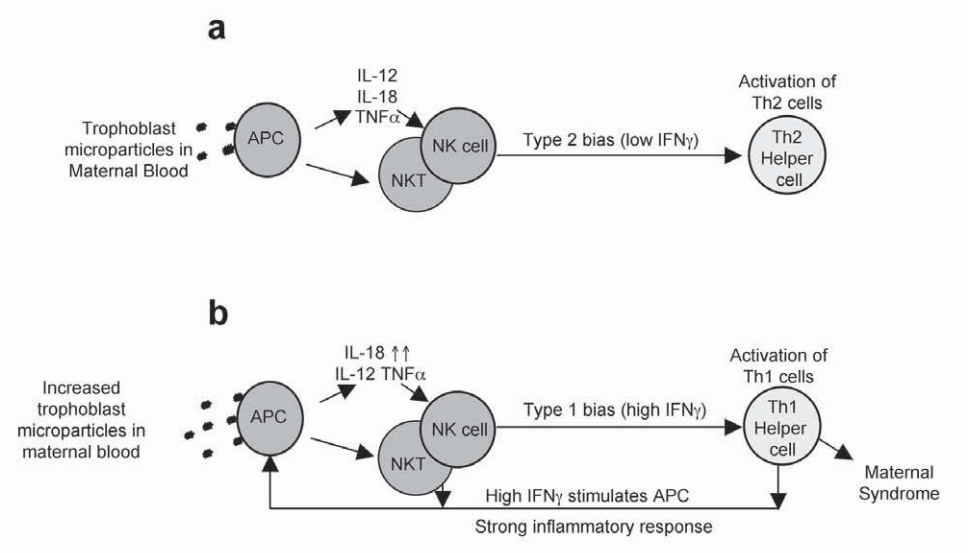

Figure 2. Type 1/type 2 model of normal pregnancy and pre-eclampsia. (**a**) Normal pregnancy; (**b**) pre-eclampsia. APC = antigen-presenting cell (macrophage/dendritic cell); IFNγ = interferon γ; IL = interleukin; NK = natural killer; Th = T helper; TNFα = tumour necrosis factor α.

Conclusion

In conclusion, it is believed that immune responses may play a key role in both stages of pre-eclampsia: in early pregnancy by restricting trophoblast invasion through the interaction of trophoblast MHC and decidual NK cells, and in later pregnancy through the interaction of syncytiotrophoblast debris and circulating NK cells to stimulate the intense systemic inflammatory response that characterizes the disorder. However, the details of the mechanisms involved remain to be elucidated.

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