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REVIEW

Role of placentally produced inflammatory and regulatory cytokines in pregnancy and the etiology of preeclampsia

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Abstract Human pregnancy is a metabolic and immune challenge for the mother who has to accommodate in her womb a semi-allogeneic fetus whose energy needs increase tremendously with gestation. Recent compelling research has suggested that proper inflammatory changes and oxidative balance are a requisite for successful pregnancy. The placenta is an integral component of this inflammatory response as it actively produces a variety of cytokines and immunomodulatory hormones. In preeclampsia, a life-threatening disorder of pregnancy that is characterized by widespread damage and dysfunction of the maternal endothelium, placental oxidative stress and aberrant cytokine expression induces an exaggerated maternal systemic inflammatory response to pregnancy.

Keywords Pregnancy · Preeclampsia · Placenta · Cytokines · Inflammatory response

Introduction

Human pregnancy imposes a massive stress to the maternal body, which has to accommodate the increasing energy needs of the developing fetus at the expense of its own needs. Therefore, several physiologic and metabolic changes take place in the maternal body to adapt to such a challenge. The most striking physiologic alteration during pregnancy, apart from the evident weight gain as a consequence of fat and protein deposition in maternal stores, is the increase in blood volume, which is needed for extra blood flow to the uterus and increased perfusion of other organs, especially the kidneys. The pregnant uterus undergoes important tissue and vascular remodeling, the most remarkable of which is the transformation of the uterine spiral arteries into low-resistance flow vessels that enable large volumes of blood to gain access to the placental intervillous space [1]. Additional metabolic changes, such as increased red blood cell counts, insulin resistance and elevated cardiac output further guaranty that the placental villous tree bathes in a nutrient- and oxygen-rich milieu.

The success of pregnancy requires an appropriate immunological interplay between the mother and the developing fetus, as the latter, which expresses paternal antigens, is considered to be a semi-allograft to the maternal immune system [2]. Thus, mechanisms have developed to allow the fetal entity to escape from maternal immune attack, and above all, avoid rejection. To begin with, the fetus is physically secluded from the maternal immune system by the protective shell of embryonic trophectoderm-derived trophoblast cells, which make up the placenta and the chorionic membrane. Most interestingly, the placenta has been identified as a site of immune privilege. This tissue is the source of production of many immunomodulatory hormones and cytokines, and one prevalent hypothesis is that several of these factors released at the feto–maternal interface or into the maternal blood stream contribute to the regulation of the local and systemic immune changes required for a successful pregnancy. By contrast, aberrant placental production of these factors has been shown to be associated with pregnancy-related disorders or even failed pregnancies. The action of several cytokines in the success of

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pregnancy and in the development of preeclampsia will be reviewed here.

The immunology of pregnancy

The placenta, which is in direct contact with maternal cells in the uterine wall and with maternal blood, is an important immunological barrier between maternal and fetal antigens. This tissue lacks expression of the conventional polymorphic major histocompatibility molecules (MHC) class I, human leukocyte antigen (HLA)-A and HLA-B, and class II [3], and thus, is protected from cytotoxic T lymphocyte (CTL)-mediated destruction. To avoid killing by natural killer (NK) cells, which are programmed to recognize HLA-null cells, trophoblast cells express instead a combination of the nonclassical MHC molecules HLA-G [4], HLA-E, and HLA-F [5]. Whereas the role of HLA-F in pregnancy still awaits elucidation, accumulating research has provided convincing evidence that HLA-G and HLA-E possess immunosuppressive properties, especially towards NK cells and subsets of T lymphocytes, and the idea that placental HLAs facilitate pregnancy, in part, by inhibiting maternal immune cytotoxic responses towards placental cells is now well established [6, 7]. However, a different regulatory mechanism must apply to decidual NK cells, which constitute 50 to 70% of all maternal immune cells present in the pregnant uterus, as these cells do not appear to possess lytic activity [8]. Instead, they are thought to positively regulate pregnancy through secretion of cytokines and angiogenic factors, which have crucial actions on the vascular and decidual transformations occurring in the uterine wall during the early weeks of pregnancy [9–11]. Nevertheless, their regulation might also be mediated by HLA-G and by HLA-C, also present in high amounts on extravillous trophoblasts invading the pregnant uterus [12, 13].

In addition to strategies conferring a relative immune "invisibility" to the placenta, adjustments in the maternal immune system have been suggested to help in sustaining a successful pregnancy. The concept of a maternal CD4-positive T helper cell (Th) 2-biased immunity in pregnant women has been appreciated for over a decade [14]. Th2 immunity is characterized by the dominance of humoral immune responses over cell-mediated, more destructive responses, more likely to be detrimental to the fetal allograft. CD4-positive Th2 lymphocytes develop from naïve T helper cells in the presence of interleukin (IL)-4 and IL-10, whereas Th1 cells arise when IL-2 and interferon (IFN)-γ are present. In turn, Th1 and Th2 lymphocytes express a panel of membrane-bound or soluble immunomodulatory mediators, which influence the activity of other cells of the adaptive immune system, therefore controlling the immune response. A type 2 bias seems to take place both in the intrauterine milieu and in the systemic maternal circulation during pregnancy. It has been reproducibly demonstrated that the placental bed encloses a high incidence of the Th2 factors IL-4 and IL-10 [15–19]. Several isoforms of the immunosuppressive transforming growth factor (TGF)β have also been localized in the placenta, adding to the immune privilege of this tissue [20–22]. Trophoblast cells themselves contribute to the generation of this cytokine milieu as they spontaneously secrete these immunoregulatory molecules, locally, but also into the intervillous space where these may likely participate in the constitution of the peripheral type 2 response. By contrast, type 1 cytokines appear to be marginally expressed or completely absent from the feto–maternal interface [23, 24]. Moreover, the profile of cytokine synthesized by maternal peripheral blood lymphocytes during pregnancy further sustains the development of type 2 immune responses [25]. Conversely, failure to generate a Th2 cytokine milieu, or alternatively, a Th1 cytokine environment has been associated with poor pregnancy outcome [26–28]. However, this long-standing paradigm has been recently disputed [29], as the networks of cytokines targets and actions have become increasingly intricate.

Normal pregnancy and inflammation

A series of intriguing findings have lead to the suggestion that pregnancy is, in fact, a condition of controlled mild maternal systemic inflammation, during which cells of the innate immune system display activated phenotypes [30–32] and circulating levels of particular pro-inflammatory cytokines, such as tumor necrosis factor (TNF)α, IL-6, and IL-1 are raised compared to nonpregnant women [33, 34]. By some aspects, the inflammatory changes in peripheral blood leukocytes were found to be similar to those occurring in patients with sepsis [30]. In addition, monocytes from normal pregnant women were shown to be primed to produce the potent Th1 cytokine IL-12 [35], fueling the debate on the strict dependence on a type 1 vs type 2 adaptive immunity in pregnancy. What is more confounding is the fact that trophoblast cells as well appear to be the source of production of these pro-inflammatory cytokines [36–41]. In vitro, in a dually perfused placental cotyledon, most of placental TNFα was released to the maternal side [42], confirming the importance of placentally produced inflammatory mediators in the induction of the maternal systemic changes. Yet, generalized maternal inflammation is not associated with illness in pregnancy, but has been suggested to be part of the mother's adaptation to pregnancy and might be crucial for successful pregnancy

by not only potentially compensating for a suppressed maternal adaptive immune system and therefore help protect against infection, but also by promoting the physiologic and metabolic changes taking place in the mother's body [43].

Preeclampsia

Preeclampsia is a serious complication of the second half of human pregnancy, which can have harmful effects on the immediate and long-term health of the mother and the baby [44, 45]. This disease is characterized by multiple maternal disturbances, among which the more prominent symptoms are de novo hypertension, proteinuria, and edema. Additional metabolic dysfunctions may be present, such as activation of the clotting system, impaired liver function, renal failure or pulmonary edema, in particular, in cases of severe, early onset disease [46]. In the absence of intervention, preeclampsia can progress in generalized convulsions or eclampsia. The symptoms resolve only once the placenta is removed, and thus, preeclampsia remains one of the most common reasons for induced preterm delivery.

While the etiology of the disorder is still elusive, it is quite clear that it requires a placenta to develop. Risk factors are known and include primiparity, multiple pregnancies, a previous history of preeclampsia, and chronic medical conditions such as obesity, hypertension, vascular disease, or diabetes [47]. However, there is no definitive predictive factor and no preventive treatment available so far. There may undoubtedly be a genetic component at the basis of some cases of preeclampsia, at least in those with a familial history [48, 49]. However, such a genetic cause has not been convincingly demonstrated until now, most likely because polymorphisms in not only one but in several genes are likely to predispose to the development of this complex multifactorial disease. On the other hand, recent work clearly reveals that immune maladaptation and overt activation of the maternal innate immune system are involved in preeclampsia [50, 51]. Remarkably, although the maternal symptoms of preeclampsia appear very heterogeneous at first sight, they can all be ascribed to a generalized endothelium dysfunction [52], which is undeniably part of this exaggerated systemic inflammatory response to pregnancy [53].

Two-stage model of the disease

The symptomatic phase of the disease is, in reality, the second step of a two-stage pathological process, which has its origins in the placenta and occurs during the first weeks of pregnancy [54, 55]. There is evidence of inadequate immunological interactions at the feto–maternal interface already very early in pregnancy. It has been described that HLA-G is under-expressed in preeclamptic placentas [56–58], whereas certain combinations of placental HLA-C and their receptors on maternal NK cells appear to be selectively linked to the risk of developing the disease [13, 59]. Moreover, the number and distribution of macrophages in placental beds are significantly altered in preeclampsia in comparison to normal pregnancy [60–62]. Furthermore, it was also shown that activated macrophages have the potential to induce apoptosis of extravillous trophoblasts in vitro [63]. Increased trophoblast cell death is believed to be central to the impaired placentation that is observed in most cases of preeclampsia. These cells detach from the tip of the primitive trophoblastic outgrowths of the embryo, the anchoring villi, soon after embryo implantation, and actively invade the uterine wall around and into the spiral arteries, to initiate vessel remodeling and establish the uteroplacental circulation. In normal pregnancy, extravillous trophoblasts migrate deep into the decidual part of the arteries and ultimately adopt an endothelial cell-like phenotype and replace their musculo-endothelial lining. The arteries are thus transformed into low-resistance, high-flow channels that provide the appropriate blood flow to the fetus. Preeclampsia is associated with widespread apoptosis of cytotrophoblasts that invade the uterus [64]. Correspondingly, extravillous trophoblasts invasion is abnormally shallow, and the remodeling and enlargement of the spiral arteries is restricted to their placental–proximal part [65, 66].

It has been hypothesized that as a consequence of failed remodeling, blood supply to the placenta is greatly reduced, and this may trigger placental hypoxia [67, 68]. An alternative interpretation of the histopathologic findings has proposed that after incomplete modification of the spiral arteries by the extravillous cytotrophoblasts, these retain a certain capacity to contract in their myometrial part. Phases of contraction followed by relaxation would then lead to cycles of hypoxia/reoxygenation within the placenta [69]. Whatever mechanism at play, the end result would be placental oxidative stress and dysfunction.

Oxidative stress occurs when the cellular levels of reactive oxygen species (ROS) exceed the cell antioxidant capacities. It has been reproducibly observed that ROS are increased, and the levels of several detoxifying enzymes are reduced in preeclamptic placentas, leading to damage of cellular lipids and various other cellular components [70–74]. Moreover, in vitro triggered oxidative stress of a trophoblast cell line reproduced the placental abnormalities of preeclampsia [75]. Deficient oxygenation and increased oxidative stress most probably occur as early as week 10–12 of gestation when maternal blood first gains access to

the placenta; however, the antioxidant capacity of placental cells might counteract or contain the insult for some time, until the levels of ROS, by far, surpass the placental redox capacity. Subsequently, placental damage and dysfunction becomes disproportionate. Hence, preeclamptic placentas are often aberrantly structured, with histological evidence of vasculitis, thrombosis, and areas of ischemic or necrotic tissue. These placentas also exhibit increased trophoblast apoptosis [76, 77], a feature that can be reproduced in vitro in models of placental hypoxia or hypoxia/reoxygenation [78–80]. It has been proposed that unusual loads of placental debris and toxic factors, among which pro-inflammatory cytokines, are released in the intervillous space, and in turn, interact with maternal endothelium and cells of the innate immunity, causing the vast array of maternal symptoms that distinguish the disease [81]. We and others have shown that the amount of placental debris, such as cell-free apoptotic DNA [82, 83] and syncytial microparticles, is indeed elevated in peripheral blood of women with preeclampsia [84, 85].

Cytokines in preeclampsia

It is generally agreed that preeclampsia is associated with both local and systemic changes in type 1/type 2 cytokine balance compared to normal pregnancy. Decidual lymphocytes and peripheral blood mononuclear cells from patients with preeclampsia are generally primed to synthesize high levels of the Th1 cytokines, IL-2, IL-12, and IFN-γ [86–89]. On the other hand, they exhibit low spontaneous or phytohemaglutinin-induced expression of the Th2 cytokines IL-10 and IL-5 [90–92]. Whereas these findings initially lead to the conclusion that a maternal T lymphocyte-mediated cytotoxic reaction against the fetal allograft was possibly associated with, and maybe the cause of preeclampsia, it is now believed that such a cytokine environment rather reflects the state of exaggerated inflammation that characterizes the disease. Monocytes and granulocytes present an activated pattern of leukocyte adhesion molecules on their surface and show an increased incidence of basal or induced oxidative stress response compared to their counterparts from normal pregnancy [30, 93]. Spontaneous monocytic cytokine expression is higher in preeclampsia in comparison with normal pregnancy [94]. This is mirrored in the maternal plasma cytokine environment. The circulating levels of TNFα and IL-6, which are already more elevated in healthy pregnant women compared to nonpregnant controls, are further raised in patients with preeclampsia [95–98]. There are also numerous reports of increased serum or plasma levels of several other pro-inflammatory cytokines and of their modulators, such as, IL-2, IL-8, IL-12, IL-15, IL-18, IL-1 receptor antagonist, soluble IL-4 receptor, and soluble TNF receptor (Table 1) [96, 99–104]. The increased levels of soluble cytokine receptors found in patients with preeclampsia may represent a protective response to increased cytokine activity and be a marker for overt inflammation. However, these findings remain very controversial as others did not detect alterations in the levels of pro-inflammatory molecules between healthy pregnant controls and preeclamptic patients [104–106]. Of course, plasma cytokine milieu does not reflect the strict contribution of the placenta, as cytokine production by the dysfunctional maternal endothelium and peripheral blood mononuclear cells is obvious. However, it is undoubted that placental contribution is likely to be significant, as cytokine imbalance and elevated expression of pro-inflammatory molecules is also evident in preeclamptic placentas. Increased production of TNFα, IL-1, and IFN-γ has been documented in these placentas [107–110].

Oxidative stress and placental production of pro- and anti-inflammatory cytokines

A recent set of data has demonstrated that placental expression of many cytokines and soluble mediators of inflammation is tightly regulated by the oxygen tension and cellular oxidative stress that are imposed on the tissue. They provide, therefore, a direct link between the aberrant placental tissue oxygenation and altered cytokine patterns observed in preeclamptic placentas. It was shown that explants of placental villous tissue, derived from normal term placentas, significantly enhance their production of TNFα, IL-1α, and IL-1β when they are incubated in hypoxia, in comparison with the levels produced upon incubation in normoxia [111, 112]. The expression levels of these cytokines are similarly raised under alternative culture conditions which reduced oxygen availability, such as in

Table 1 Placentally produced inflammatory and immunomodulatory cytokines in preeclampsia

Cytokines	In placenta[a]	In peripheral blood[a]
TNFα	No change/increased	Increased
IL-1	No change/increased	No change
IL-6	No change/reduced	Increased
IL-8	Increased	Increased
IFN-γ	Increased	No change/increased
IL-12	Reduced	Increased
IL-15	Reduced	No change/increased
IL-10	Reduced	No change/increased
IL-4	No change	No change/reduced

[a] Changes relative to normal pregnancy. Contradictory data are mentioned.

the presence of an iron chelator or cobalt chloride. It is interesting to note that late first trimester villous tissue also responds to hypoxia by increasing pro-inflammatory cytokine secretion, whereas early first trimester villous tissue is relatively insensitive to the changes in oxygen tension [111]. Furthermore, villous explants derived from preeclamptic placentas were found to be equally sensitive to the effect of hypoxia on TNFα and IL-1 expression [113].

Hypoxia/reoxygenation also increases TNFα synthesis by placental villous tissue in vitro [114]. Notably, in this particular experimental setting, hypoxia/reoxygenation was shown to be a more potent inducer of cytokine secretion than hypoxia alone. Finally, chemicals which trigger placental oxidative stress also stimulates elevated TNFα and IL-1 production by villous explants [112]. In this context, it is interesting to note that in the presence of the antioxidant vitamin C, the secretion of TNFα by term placental villous explants is significantly reduced by 20% (Fig. 1). In contrast, IL-1β secretion did not show such a regulation. This would suggest that therapeutic interventions with antioxidant agents could possibly be developed, even though clinical trials with vitamin supplementation have so far failed to prevent disease occurrence in women at increased risk [115, 116].

Whether IL-6 expression is also controlled by oxygen levels is still debatable. No hypoxia-driven changes in IL-6 synthesis by placental explants were documented. In contrast, isolated cytotrophoblast cells derived from preeclamptic placentas were shown to express higher levels of this molecule than their normal counterparts and to respond to hypoxia by further increasing IL-6 secretion [117]. These latter data seem to contradict the finding that preeclampsia is associated with decreased placental IL-6 production [113, 118].

It is interesting to note that placental expression of immunosuppressor cytokines also seems to be modulated by oxygen tension. Cytotrophoblasts isolated from preeclamptic placentas show a hypoxia-induced reduction in IL-10 synthesis [117]. This feature is in agreement with the description of deficient placental IL-10 production in preeclampsia [119, 120]. Trophoblast expression of TGFβ3 is also regulated by oxygen tensions, in particular, during the switch from early to late first trimester. This gestational age-dependent dichotomy in cytokine production might be explained by the fact that early placental development takes place in the total absence of oxygen, as at that time, spiral arteries remodeling is not fully complete, and the intervillous space is largely devoid of blood flow. But by the end of the first trimester, maternal blood reaches the placenta, and TGFβ3 production is down-regulated [121]. In contrast, TGFβ3 remains overexpressed in preeclamptic placentas [122], a finding that may reflect the state of tissue oxidative stress, but could also participate in the development of later placental dysfunctions. Recently, it was shown that IFN-γ synthesis by trophoblast cells similarly failed to switch from high to low expression as placental environment switches from early hypoxic to late normoxic condition [110].

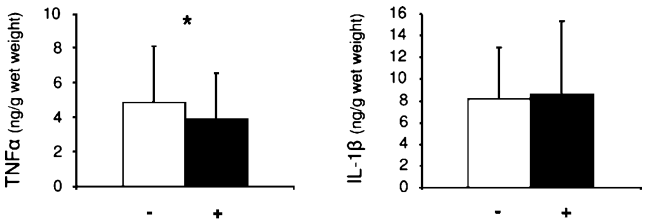

Fig. 1 Placental villous explants were cultured for 24 h in the absence (−) or in the presence (+) of vitamin C and levels of TNFα (*left panel*) and IL-1β (*right panel*) secreted in the culture supernatant were measured by enzyme linked immunosorbent assay and related to explant wet weight. Paired Student *t* test was used. *$p<0.05$, $N=10$

Cytokines and placentation

During early pregnancy, the interstitial and endovascular trophoblast cells, which invade the decidua and the lumen of the uterine spiral arteries, respectively, differentiate from a fraction of highly proliferative extravillous trophoblast stem cells located in the anchoring villi. These differentiated cells express a new repertoire of adhesion molecules and secrete numerous proteinases, which enables their migration through the uterine stoma and along the endothelial lining of the vessels. In preeclampsia, invading trophoblast cells exhibit an altered protease expression profile and fail to acquire a vascular adhesion phenotype [123, 124]. Remarkably, the proliferation, invasion, and apoptosis of extravillous trophoblasts are orchestrated by several growth factors and almost all cytokines present in the intrauterine wall.

The switch in phenotype from a proliferative to an invasive state appears to be principally controlled by epidermal growth factor and hepatocyte growth factor [125, 126]. This process is also very sensitive to oxygen tension [127], possibly because of the overproduction of cytokines and other mediators of angiogenesis by the extravillous trophoblasts themselves. For instance, IL-1α, IL-1β, and IL-6 have been described as positive regulators of trophoblast differentiation along the invasive pathway as these cytokines can stimulate matrix metalloproteinase (MMP) 9 and MMP2 expression and activity [128, 129]. Specifically, IL-1β expression was shown to parallel the invasive potential of cytotrophoblasts in vitro [130]. On the contrary, IL-10 and TGFβ inhibit trophoblast production of proteases and trophoblast invasion [131, 132]. Failure to down-regulate TGFβ3 expression in proliferative cytotrophoblasts has been linked to shallow placentation and

predisposes the pregnancy to preeclampsia [122]. TNFα has also been implicated in the control of trophoblast cell fate. Notably, TNFα, in combination with IFN-γ, stimulates apoptosis of cultured cytotrophoblasts and syncytiotrophoblasts [133, 134]. This suggests a mechanism for deficient placentation in preeclampsia, where local concentrations of both cytokines are high. In contrast, conflicting results exist relative to the role of TNFα in modulating extravillous trophoblast migration potential [135, 136]. Nevertheless, the sum of these in vitro data suggests that the unbalanced placental expression of several cytokines early in pregnancies destined to develop preeclampsia likely plays a role in the etiology of the disease.

TNFα also negatively affects the integrity of the syncytiotrophoblast layer by stimulating increased apoptosis in vitro [137]. Under normoxia, the underlying cytotrophoblasts were shown to reconstitute the syncytiotrophoblast. In contrast, when the placental environment was hypoxic, the syncytiotrophoblast failed to regenerate. TNFα has also been reported to impair the syncytialization process [138]. Thus, in preeclampsia, increased production of TNFα by trophoblast cells in response to deficient uteroplacental blood flow could, in an autocrine manner, lead to continuous syncytiotrophoblast damage and dysfunction. In addition, placental inflammation might be triggered locally, via the release of TNFα after adhesion of activated maternal monocytes to the syncytiotrophoblast [139].

The placental expression of several gestational hormones and mediators of metabolic pathways is also determined by the local cytokine milieu [140]. This area of research has been extensively studied in pregnancies affected with obesity or diabetes mellitus, but less in pregnancies complicated with preeclampsia. It is, nevertheless, likely that the dysregulated expression of these molecules is also occurring in preeclampsia as a result of the aberrant placental cytokine production pattern hallmarking this disease. However, this aspect will not be discussed here.

Cytokines and feto-placental tolerance

IL-10 and IL-4 are pleiotropic immunosuppressors, which display inhibitory effects on cytotoxic and inflammatory reactions. Their expression at the feto–maternal interface is suggested to help in counteracting the harmful effects of pro-inflammatory mediators on placental cells [141]. Remarkably, IL-10 also seems to be an important regulator of trophoblast survival, as it has been shown to selectively induces HLA-G expression in human cytotrophoblasts [142]. In line with these results, low IL-10 levels and diminished HLA-G expression have been observed in preeclampsia. Hence, deficient placental IL-10 expression might not only confer increased susceptibility to pro-inflammatory signals but also amplify inflammation-driven cell damage and NK cell-mediated trophoblast cell death. By opposition, increased trophoblast production of IFN-γ may account for the altered decidual lymphocyte subset distribution and increased number of CD8-positive T cells in the placental bed [143, 144]. IL-6 bears both pro- and anti-inflammatory actions, depending on the cell type and cellular microenvironment it acts on. In the placenta, IL-6 appears to be a positive regulator of pregnancy, as trophoblast-derived IL-6 acts in an autocrine manner on these cells to stimulate their secretion of the immunomodulatory hormone, human chorionic gonadotropin (hCG) [145]. However, serum levels of hCG are raised in preeclamptic patients despite decreased placental IL-6 production, and the role of IL-6 in fetal tolerance awaits elucidation.

Another possible player in promoting fetal tolerance is the subset of $CD4^+CD25^+$ regulatory T lymphocytes. These cells have been found to infiltrate the pregnant uterine wall and are, in fact, the second largest population of maternal immune cells present at the feto–maternal interface after uterine NK cells [146]. They function by dampening T cell mediated immune responses via the production of immunosuppressive cytokines [147], and they possibly play a role in the local maintenance of immune privilege [148]. Although preeclampsia is not associated with changes in the levels of regulatory T cells at the periphery [149], the cells may not perform adequately in this condition as TNFα, which is expressed in excess both at the feto–maternal interface and systemically, has been shown to inhibit their suppressive function in vitro [150]. Whether their numbers or activity is altered within the placentas of preeclamptic patients remain to be established.

Cytokines and the maternal symptoms

The endothelium plays a major role in several processes like the regulation of the coagulation cascade, the activation of platelets and leukocyte function, and is therefore an integral part of an inflammatory response. TNFα and IL-1 are the main pro-inflammatory cytokines that stimulate both structural and functional alterations in endothelial cells [151]. It has been suggested that placental IL-1 and TNFα could be potential mediators of maternal endothelial dysfunction in preeclampsia. The reasons for this are multiple. First, the circulating concentration of both cytokines is raised in pregnant women. In vitro, placentally produced IL-1 alters human umbilical vein endothelial cell proliferation and induces the secretion of soluble ICAM and IL-6 [152]. The latter are indeed found in increased levels in the peripheral blood of women with preeclampsia

[153–155]. On the other hand, the elevated secretion of TNFα by placental villous tissue in response to hypoxia/reoxygenation causes a reduction of endothelial cell viability and up-regulates the expression of the adhesion molecule E-selectin by the endothelial cells [114]. Maternal serum from preeclamptic patients also stimulates the endothelial production of the vasoactive substances, endothelin-1 and prostacyclin, which might maintain or amplify maternal hypertension [156, 157]. According to recent research, hypertension might be initially triggered by the dysregulated placental production of the angiogenic factors vascular endothelial growth factor (VEGF), soluble fms-like tyrosine kinase (Flt)-1, and placental growth factor (PlGF) [158, 159]. Serum from women with preeclampsia also disrupts the membrane localization of cadherin-5, which may decrease the number of adhesion complexes at the cytoplasmic membrane and lead to vascular permeability [160]. It remains to be established whether these particular endothelial responses to serum are also mediated by cytokines.

Despite these numerous findings, some have questioned the idea that the maternal blood stream carries a placental "toxic" factor to the periphery which contributes to systemic maternal endothelial dysfunction, as they failed to find any effect of plasma factors on endothelial gene expression in vitro [161]. It has been suggested that the activation of maternal leukocytes during their uteroplacental passage may instead play an important part in the dissemination of an inflammatory response to the periphery [162]. Leukocyte activation could be triggered by their interaction with locally activated endothelium or placenta. In favor of this hypothesis, it has been shown that endothelial cells incubated with placental syncytiotrophoblast debris release factors, which can activate peripheral blood leukocytes in vitro [163]. It is interesting to note that placental syncytiotrophoblast debris and placentally derived IL-8 are also potent activators of neutrophils, in that they stimulate the formation of neutrophil extracellular traps (NET), made from DNA and granule proteins, by these cells [164]. Large numbers of NETs are indeed present in the intervillous space of preeclamptic placentas, demonstrating the importance of local neutrophil activation in this disease. Thus, two modes of propagation of the inflammatory reaction from the placental site into the maternal periphery, one encompassing soluble factors, among which cytokines, and the other being cell-mediated, are possibly at work in preeclampsia.

Conclusions

This review has attempted to describe how cytokine networks are affected by pregnancy, and how in return, these networks can affect the success of pregnancy. Cytokines are involved throughout pregnancy, from the implantation of the conceptus to parturition, including placentation, and the maintenance of fetal tolerance. A complete presentation of this large array of cytokine requirements was beyond the scope of the present work. We focused here on the role of placentally produced cytokines on the maternal and fetal events, which are substantially affected in preeclampsia, that is, placental function and maternal inflammatory response to pregnancy. It is clear that placental cytokines integrate into the general maternal cytokine networks to modulate these events, and it is most likely that positive feedback regulatory loops between placental and maternal cells amplify the load of cytokines present in the maternal body, and subsequently, the maternal syndromes. In conclusion, dysregulated cytokine expression by placental cells is certainly one facet of the elusive placental "toxic" factor, or factors, causing the maternal symptoms in preeclampsia.

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