

Placental cytokines and preeclampsia

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1. ABSTRACT

Preeclampsia is a serious and life-threatening pregnancy complication. Reduced uteroplacental perfusion and oxygen tension, impaired trophoblast differentiation and invasion, and altered placental production of immunomodulators and growth factors are all considered to be important aspects in the aetiology of the condition. The placenta expresses a variety of pro and anti-inflammatory cytokines, adipokines and cytokine-like angiogenic growth factors, production of which is altered in preeclampsia, driven (at least in part) by hypoxia. Altered levels of cytokines have been measured in the circulation of women with preeclampsia, although for reasons that are not always apparent much of the data are disturbingly inconsistent. While the placenta undoubtedly makes an important contribution to plasma cytokine levels, production by

maternal peripheral blood mononuclear cells (PBMCs) and other tissues is also likely to be significant, although to what extent remains undetermined. Increased placental expression of soluble receptors occurs with preeclampsia, resulting in elevated circulating concentrations which confer impaired angiogenesis, deficient placental vascularisation, increased placental apoptosis and endothelial dysfunction. The extent to which these changes reflect a response to the disorder, as opposed to being a causative factor in the development of maternal disease, is a matter of some debate. Nevertheless, convincing evidence is now accruing that autocrine/paracrine interactions between placental cytokines/growth factors and the maternal endothelium play a central role in the pathogenesis of preeclampsia.

2. INTRODUCTION

The term 'cytokine' can be loosely used to define a class of small to medium sized (8-20 kDa range) extracellular signalling proteins typically involved in the regulation of recruitment, activation, proliferation and cell-to-cell communication of the immune system (1). Many cytokines, however, also have more widespread actions throughout the body, are often produced by resident non-immune tissues, and interact with homeostatic systems such as the endocrine and nervous systems. Cytokine signalling plays important roles in both healthy and disease states; moreover, cytokine "profiles" are characteristic of a variety of immune activation states, and have well-established roles in the pathophysiology of numerous diseases and disorders. In addition, a number of other protein factors are known which, although not specifically involved in immune activation or resolution, exhibit cytokine-like characteristics such as similarities in structure, receptor activation or signalling pathways. Examples of these discussed in this review include adipocyte-derived cytokines (adipokines), angiogenic growth factors (angiokines) and various members of the transforming growth factor (TGF)-beta superfamily.

Immune mediators, including cytokines, are intimately involved in many aspects of pregnancy – from implantation and placentation, to cervical ripening and uterine activation (2,3). Indeed, pregnancy-specific immunomodulation is a prerequisite for successful initiation, maintenance and completion of pregnancy (4-6). An inappropriate or over exuberant immune reaction, on the other hand, is associated with the major pregnancy pathologies including recurrent miscarriage, preeclampsia, gestational diabetes and preterm labour (3,7-9). The placenta expresses a wide variety of molecules typically associated with immunomodulation and inflammatory activation, including many cytokines, which act on both immune and non-immune cells via specific receptors to carry out a variety of functions (2,3). Cytokine-related growth/angiogenic factors and their receptors are also important regulatory factors of significance in both placental and endothelial pathophysiology (10-12).

Preeclampsia is a relatively common syndrome in pregnancy manifesting as maternal hypertension, proteinuria, endothelial dysfunction, various coagulopathies and an increased systemic inflammatory response (13,14). Although the causes of preeclampsia are complex and only partially understood, there is consensus that factors released by the placenta, possibly as a consequence of faulty placentation, may trigger the onset of maternal disease by causing endothelial dysfunction resulting in hypertension and proteinuria (15,16). In this review we will summarise what is known of placental cytokine expression in the context of the causes of preeclampsia and its manifestations, and discuss potential mechanistic links between placental (and systemic) cytokines and the disorder.

3. PLACENTAL CYTOKINE EXPRESSION IN NORMAL PREGNANCY

3.1. Cellular sources and gestational age dependence

A wide variety of cytokines are produced by placental tissues (including the extraplacental membranes,

the amnion, chorion and decidua) throughout normal gestation; these are listed in Table 1. Placental cytokine expression varies with gestational age, reflecting the specific roles played by cytokines within these tissues during fetoplacental development. Cytokines are produced by the resident cells of normal healthy placental tissues, as well as by infiltrating leukocytes. Cytokine receptors are expressed also in placental tissues, indicating that they are both sources and targets of these important biological mediators.

In the first trimester of pregnancy, tumour necrosis factor (TNF)-alpha, interleukin (IL)-1alpha, IL-1beta, IL-6, and macrophage inhibitory factor (MIF) expression have been documented in placenta/trophoblast and decidua (Table 1). Placental trophoblasts are major producers of the inflammatory cytokines, although inflammatory cytokines are also secreted by fetal macrophages (Hofbauer cells) and stromal cells in the placenta (17-19). In first-trimester decidua, mRNA and protein for IL-1beta, IL-1alpha, IL-6, and TNF-alpha have been localized to cells of immune origin (6,20-22), but are also produced by other decidual cell types (17,21,23). Immunodetectable MIF has also been identified in first-trimester decidua (24).

At term, mRNAs for the proinflammatory cytokines TNF-alpha, IL-1alpha, IL-1beta, and IL-6 have been identified in placenta/ trophoblast and decidua and these cytokines are produced and secreted by both tissue types (Table 1). In the fetal membranes it has been reported that the chorion contains mRNA for TNF-alpha, IL-1beta, and IL-6 but expresses protein for only IL-1beta and IL-6 (25,26), while amnion expresses all three proteins (25,26). IL-1beta is produced by both trophoblasts and placental macrophages (27), and trophoblasts also release IL-1alpha (27). IL-1alpha and IL-1beta production by trophoblast has been detected during the first trimester and at term, declining over the course of gestation (28). IL-6 staining intensity and production rates in the placenta are increased at term compared to early pregnancy. IL-6 is the only villous placental cytokine whose production has been shown to be upregulated with the onset of labour (29).

Placental tissues also express and secrete anti-inflammatory cytokines. Messenger RNA and protein for both IL-4 and IL-10 have been located in placenta/trophoblast and decidua throughout pregnancy. Reports of IL-10 production in the fetal membranes have been inconsistent. Immunohistochemical results indicate that abundance of IL-4 and IL-10 in the placenta decreases with increasing gestational age, while decidual production of these cytokines increases (30). In contrast, others (31) have found that secretion of IL-10 by trophoblasts in culture was stable over gestation. IL-10 (32), IL-4 (32,33) and IL-1 receptor antagonist (IL-1ra) (34) have been detected in amniotic fluid collected at term. Increases in amniotic fluid concentrations of both IL-10 (35) and IL-1ra (36,37) have been observed between the second trimester and term. Amniotic fluid IL-1ra may be derived from the amnion and/or chorion, which are reported to produce this cytokine at term (38). IL-1ra is also produced by first-

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Table 1. Cytokines produced in the human placenta during normal pregnancy.

Proinflammatory cytokines		
IL-1 α/β	Trophoblast and Hofbauer cells	Throughout gestation
IL-6	Trophoblast and Hofbauer cells	Throughout gestation
IL-12		3 rd trimester
IL-16	Not determined	
IL-18	Not determined	1 st trimester trophoblast and term
TNF-alpha/ β	Trophoblast and Hofbauer cells	Throughout gestation
MIF	Trophoblast	1 st trimester
PBEF		Throughout gestation
Anti-inflammatory cytokines		
IL-4	Placenta including trophoblast,	Throughout gestation
IL-10	Trophoblast and Hofbauer cells	Throughout gestation
IL-13		Throughout gestation (1 st trimester mainly)
IL-1RA	Trophoblast, stroma and Hofbauer cells	Throughout gestation
Other cytokines		
IL-11	Chorionic villi	1 st trimester,
Oncostatin M	Not determined	
TRAIL	Trophoblast and stromal cells	Throughout gestation
TWEAK		Throughout gestation
G-CSF		Throughout gestation, mostly term
GM-CSF		Term
Chemokines		
IL-8	Trophoblast	Throughout gestation
ENA-78	Not determined	
RANTES	Not determined	
MIP-1 α/β	Not determined	
MIP-3 α	Not determined	
MCP-1/2/3/4	Trophoblast	Throughout gestation
SDF-1	Trophoblast	1 st trimester only tested
MIPF-1	Not determined	
PREF-1	Not determined	
Fractalkine	Not determined	
Adipocytokines		
Leptin	Not determined	Term
Resistin	Not determined	Term
Adiponectin	Syncytiotrophoblast	Term
PBEF/Visfatin	Not determined	Term

See text for details and citations

trimester trophoblasts(17,39) and first trimester and term decidua (17,38). IL-13 mRNA has been identified in placental trophoblasts from all stages of gestation, but IL-13 immunoreactivity has only been identified in first trimester placenta (40).

IL-8 is the most actively studied placental chemokine. A member of the CXC chemokine family, IL-8 is produced constitutively by all the tissues of gestation in the later stages of pregnancy. Production of IL-8 by the placenta has been reported to increase towards term, although expression of mRNA for this chemokine does not appear to change (41). Amniotic fluid contains detectable levels of IL-8 (42-44) and another CXC chemokine, GRO-alpha (45), throughout gestation and concentrations of both these chemokines increase with advancing gestational age (44,45). Similarly, the CXC chemokine ENA-78, which, like IL-8, is a neutrophil attractant, has also been detected in amniotic fluid and is produced by gestational membranes in vitro (46). Amnion tissue levels of ENA-78 were found to be increased following term labor, but not amniotic fluid concentrations, although amniotic fluid ENA-78 concentrations were positively correlated with gestational age at sampling. In contrast, amniotic fluid concentrations of the chemokine IL-16 decline from mid-gestation to term (47).

The CC beta chemokine family contains a number of well-characterized chemokines, including the monocyte chemoattractant proteins (MCPs), RANTES (Regulated on Activation and Normal T-cells Expressed and Secreted), and the macrophage inflammatory proteins (MIPs). These chemokines primarily activate monocytes, lymphocytes, basophils, and eosinophils. MCP-1 mRNA is present in mid-trimester and term decidua (48) and the placenta throughout gestation with increased expression in the third trimester, coinciding with an increase in production of MCP-1 protein (49). Secretion of MCP-1 from third-trimester decidua, chorion, and amnion has also been reported, and this cytokine is also present in amniotic fluid (50). Of the other CC chemokines, mRNA for MCP-2 has been detected in placenta (51) and RANTES is secreted from the chorion, decidua, and placenta at term (50). RANTES is also detectable in amniotic fluid in the second and third trimesters and concentrations of this chemokine decrease with advancing gestational age (52). MIP-1alpha has also been detected in amniotic fluid at mid-gestation and term (53), although it is present in only a proportion of women in the absence of labour (54). Constitutive secretion of MIP-1alpha from gestational tissues has not been reported, although cultured human chorionic (55) and decidual (56) cells from term pregnancies produce this

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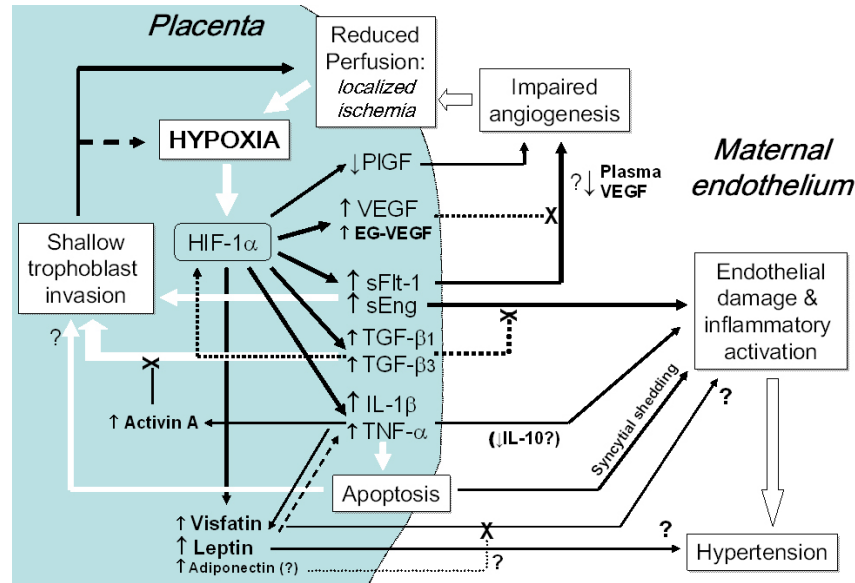


Figure 1. Placental-endothelial cytokine interactions in preeclampsia. Diagrammatic representation of the interrelationships between placental cytokines, their soluble receptors, and factors implicated in the pathophysiology of preeclampsia (boxed text). Dotted lines represent feedback pathways, whereas a cross signifies inhibition or abrogation of an effect. A question mark indicates a potential/postulated interaction lacking conclusive supporting data.

chemokine when stimulated with inflammatory cytokines or bacterial products.

3.2. Roles of placental cytokines: maternal and placental aspects

Within the placenta, cytokines are involved in modulating five fundamental processes (57):

1. Maternal-placental immune dialogue
2. Trophoblast invasion and differentiation
3. Placental growth, proliferation & apoptosis
4. Placental metabolic and endocrine homeostasis
5. Placental angiogenesis

Establishment of placental immune privilege around the time of implantation involves coordinated actions of cytokines such as IL-1, IL-11, leukemia inhibitory factor (LIF), colony stimulating factor (CSF)-1 and interferon (IFN)-gamma at the feto-maternal interface (58-60). The pro-inflammatory cytokines IL-1, LIF and activin promote trophoblast differentiation towards an invasive phenotype, whereas TGF-beta exerts generally inhibitory functions in the placenta, most notably on trophoblast proliferation, invasion and differentiation (58-61). Another immunosuppressive cytokine, IL-10, also inhibits invasion through inhibition of placental MMP release (62). Angiogenic cytokines vascular endothelial growth factor (VEGF) and placental growth factor (PIGF) are expressed in the placenta and modulate extravillous trophoblast proliferation but not invasion or migration (63,64). TNF-alpha, IFN-gamma and placental-TGF-beta (also known as MIC-1/PL74) are also inducers of trophoblast apoptosis (65), whereas VEGF and PIGF have anti-apoptotic properties (61,66,67). Cytokines also have effects on placental hormone production: TNF-alpha, IL-

1beta, IL-6 and TGF-beta have all been documented as having effects on production of placental hormones (hCG and progesterone), suggesting roles in maintaining normal endocrine function (57). Finally, placental angiogenesis has been shown to be regulated by factors such as VEGF/PIGF (67-69) and leptin (70,71)

In addition to their intra-placental actions, cytokines produced by the placenta enter the maternal circulation and interact with maternal endothelial and haematopoietic cells, although it must not be forgotten that cells within the vasculature are also sources of cytokines (72). TNF-alpha, which is produced by fetoplacental macrophages and trophoblasts (most notably invasive extravillous trophoblast (73)), exerts potent effects on endothelial and platelet function, promoting enhanced coagulation, microvascular leakage, vasoconstriction, endothelial activation, tissue factor and inflammatory cytokine production (74,75). It is likely, therefore, that placental cytokines play a major part in manifesting the exaggerated maternal intravascular inflammatory response in the second half of pregnancy that is a defining characteristic of preeclampsia, in addition to reflecting abnormalities in placentation or the placental microenvironment (76). However, placental angiogenic growth factors also have a profound influence on the pathogenesis of preeclampsia via their effects on the maternal vascular endothelium (13) (Figure 1).

4. CHANGES IN PLACENTAL CYTOKINE EXPRESSION WITH PREECLAMPSIA

Numerous studies have documented abnormal cytokine production in the preeclamptic placenta, although there are discrepancies between studies which may be due

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to inconsistencies in assay methodology, patient classification, disease severity/stage, and experimental conditions. Expression array studies conducted by Pang and colleagues (77) indicated widespread upregulation of expression of cytokines and their receptors in the placentas of preeclamptic pregnancies, findings that are supported by more focused studies.

4.1. Pro-inflammatory cytokines and chemokines

Placental production rates of several cytokines are altered by preeclampsia. Elevated TNF- α expression and secretion by the preeclamptic placenta has been documented by many investigators (78-80) and is consistent with reports of elevated levels of TNF- α in plasma from preeclamptic women (81-84). Pang & Xing (77) reported in a microarray study that expression of 10 members of the TNF ligand/receptor superfamily were upregulated in the placenta with preeclampsia, including TNF- α . It should be noted, however, that several studies have failed to find elevated circulating TNF- α levels in preeclampsia (85,86)(Keelan & North, unpublished). Similarly, elevated placental IL-6 expression/production and maternal plasma concentrations have been observed in some studies (81,83,85,87-90), but not others (91,92). There are also reports of higher levels of secretion or expression of IL-1 β , (76,77), IL-1RA,(77), IL-2 (77,82), IL-18 (90,93), MIF (94), colony stimulating factor (CSF)-1 (77) and macrophage colony stimulating factor (M-CSF) (95,96) in preeclamptic placentas. Increases in immunodetectable IL-2 in the decidua (97) have also been reported, as has an increase in placental chemokine (IL-8, MCP-1, fractalkine, eotaxin, MIPs) expression in preeclampsia (77,83,98). The IL-8 findings are in agreement with documented evidence of elevated maternal serum levels of IL-8 (87) and enhanced activation of neutrophils in both the maternal and fetal circulations (99). In contrast, some investigators have failed to observe an increase in serum IL-8 concentrations (88), while other authors have found *decreased* placental production of IL-8 (100) in preeclampsia. The placenta is not the only source of circulating cytokines, of course (72), and there is evidence that preeclampsia is associated with higher rates of production of TNF- α (101,102) and IFN- γ (101-103) by maternal PBMCs. There have also been reports of reduced IL-12 secretion from PBMCs from women with preeclampsia (104,105) although others have not been able to confirm these findings (87,106,107). The reasons for the many discrepancies in cytokine measurements in preeclampsia are far from clear, although overall the picture would appear to be one of increased placental and systemic cytokine levels, consistent with increased systemic inflammatory activation, release of vasoconstrictor substances, endothelial dysfunction and hypertension that is a characteristic of preeclampsia (62) (Figure 1). TNF- α and IL-1 β have multiple actions on endothelial cells, including promoting coagulation and inflammatory responses (89,108-110), that are particularly relevant in the context of the preeclampsia syndrome. Within placental tissues elevated TNF- α concentrations may also increase rates of trophoblast apoptosis, leading to accelerated syncytial shedding (a potential trigger of endothelial damage) and impaired placental function (111).

TNF- α production by endovascular trophoblast during invasion of the spiral arteries may be both a response to (79) and a regulator of (73) arterial remodeling (Figure 1).

Preeclampsia is also associated with changes in concentrations of amniotic fluid cytokines. Elevations in concentrations of IL-6 and IL-8 in midtrimester amniotic fluid have been associated with the subsequent onset of preeclampsia (112). Stallmach et al reported that in patients with preeclampsia plus IUGR, concentrations of TNF- α in the amniotic fluid during labour were elevated compared to normal pregnancies, while amniotic fluid concentrations of G-CSF, GM-CSF, and IL-1 β were reduced (113). Another study by Opsjon et al reported no difference in bioactive TNF- α or IL-6 in amniotic fluid from preeclamptic or normal pregnancies at the time of delivery, but a decrease in bioactive IL-1 β (92). These authors also reported that the onset of labor results in elevations in amniotic fluid levels of TNF- α , IL-1 β , and IL-6 in preeclamptic pregnancy similar to those observed in normal pregnancy(92) contrasting with the findings of Stallmach (113). The apparent contradictions between studies using immunological detection of cytokines and bioactivity studies may reflect changes in cytokine inhibitory binding proteins during preeclamptic pregnancy. IUGR dissociated from preeclampsia also appears to affect cytokine production; decidual tissue derived from pregnancies complicated by idiopathic IUGR contains less mRNA for IFN- γ than tissue from normal pregnancies, while expression of IFN- γ mRNA by trophoblast is increased in cases of IUGR (114).

4.2. Anti-inflammatory cytokines

While preeclampsia appears to be associated with a general increase in placental cytokine production, *reduced* expression of IL-15 (115) and IL-10 (116), together with lower serum IL-10 concentrations (117) have been described. Additionally, links between a distinct IL-10 genotype and risk of preeclampsia have also been identified (118) (see section 6 below), and an intriguing relationship between HLA-G genotype and PBMC IL-10 secretion has recently been described (102,103,106,119,120). Unfortunately, evidence of *elevated* placental IL-10 expression (90,121,122) and higher IL-10 concentrations in the circulations of women with preeclampsia (89,90) also exists. Of course, plasma cytokine measurements reflect contributions from maternal sources (e.g. endothelial cells, PBMCs) as well as the placental component, and alterations in maternal cytokine production with preeclampsia would be expected in light of its inflammatory pathophysiology. The relative contribution of fetoplacental and maternal sources to circulating cytokine levels in pregnancy remains an important but unanswered question. Hence, it remains unclear whether IL-10 is, or is not, an important immunoregulator in the pathophysiology of preeclampsia. It is interesting to note, however, that negative correlations between blood pressure and circulating IL-10 levels have been observed (123), a relationship that has been documented experimentally in non-human primates (124). These observations might predict therefore, that preeclampsia would be associated with reduced systemic IL-10 bioactivity, a possibility that is certainly supported by some, if not all, of the literature.

4.3. Angiogenic cytokines

A number of growth factors/cytokines with angiogenic properties have been actively studied in the context of preeclampsia (Figure 1). The VEGF family, in particular, has been of great interest, due to its known association with hypertension and nephropathy, and its role as a biomarker of endothelial dysfunction, inflammation, platelet activation and tissue hypoxia (125). VEGF is produced by endothelial cells in response to hypoxia, mechanical stretch, and vasoconstrictors such as angiotensin-II and endothelins (125). The placenta also expresses VEGF (68,126-130) and in addition expresses and secretes placental growth factor (PlGF) (68,130,131) which shares marked homology with VEGF and acts via its receptors (10). Activity of VEGF and PlGF are modulated in part by binding to soluble receptors and other binding proteins; splice variants and heterodimer formation also modulates their biological activity (132). A soluble form of VEGF receptor 1, soluble fms-like tyrosine kinase-1 (sFlt-1/sVEGFR1), is produced by the placenta (66,129,133,134) and is readily detectable in maternal plasma (129,135). Interestingly, placental sFlt-1 production is stimulated by VEGF (136). Animal studies (135) and human pharmacological findings (137,138) collectively suggest that antagonism of VEGF activity by sFlt-1 results in hypertension and proteinuria.

Evidence from immunohistochemical (130,139) and mRNA expression studies (127) indicates that placental VEGF expression is lower with preeclampsia, although higher (140) or unaltered (141) expression has also been reported. Bates et al (142) recently presented evidence of dysregulation of VEGF mRNA splicing with preeclampsia, resulting in changes in ratios of active and inactive isoforms. On the other hand Flt-1 and sVEGFR1 expression and production in the placenta is higher with preeclampsia (66,69,135,140,143-145). PBMCs also contribute to circulating sFlt-1 levels (144). Somewhat surprisingly, PBMCs from women with preeclampsia produce greater amounts of sFlt-1 basally and in response to hypoxia than cells from normal women (144). Hypoxia is a potent driver of placental VEGF expression (10,145,146), whereas PlGF expression, in contrast, is down-regulated by hypoxia and elevated with hyperoxia (145,147,148). In some severe preeclamptic pregnancies, reduced fetal-placental blood flow with dysmorphic villous capillaries is observed. VEGF and PlGF also act within the placenta to drive trophoblast proliferation (63,64) and protect trophoblast cells from apoptosis (66).

There is substantial evidence of alterations in circulating VEGF, PlGF and sFlt-1 levels with preeclampsia, although the effects of binding protein interference and variable immunoassay specificity (149,150) have contributed some contradictory data to the field. Earlier studies reported higher VEGF levels in maternal circulation with preeclampsia (151,152). However, there is now some consensus that in women with established disease, levels of VEGF and PlGF are significantly reduced (135,139,153-155), while sFlt-1 levels are lower compared to controls (135,155-159), preceding the onset of clinical disease by several (up to 10)

weeks (157,160). Enhanced urinary VEGF clearance rates in preeclampsia probably contribute to this phenomenon, in addition to altered VEGF expression and production (161). Assays that measure free VEGF and PlGF report the most dramatic decreases in maternal plasma VEGF/PlGF concentrations with preeclampsia (162). Lower plasma VEGF, PlGF concentrations (153,154) and higher sFlt-1:PlGF ratios (135,157) are also present with severe or earlier onset disease. Soluble Flt-1 in preeclamptic serum has been shown experimentally to inhibit VEGF-mediated angiogenesis (69); therefore, higher rates of sFlt-1 production and a decline in VEGF activity could be an explanation for the angiogenic abnormalities seen in severe preeclamptic pregnancies, possibly reflecting a response to hyperoxic conditions later in pregnancy (163). The fact that these changes can occur prior to development of preeclampsia, and that overexpression of sFlt-1 in a pregnant rat model causes preeclampsia-like manifestations (135), and that sFlt-1 abrogates the angiogenic effects of VEGF in the placenta (164), suggests that the angiogenic imbalance characterized by lower VEGF/PlGF activity and higher sFlt-1 levels may have a causative role in preeclampsia through impaired placental vascularisation.

4.4. TGF-beta superfamily

The TGF-beta superfamily includes inhibins, activins, bone morphogenic peptides (BMPs), growth and differentiation factors (GDFs), Mullerian inhibitory factor (MIF) and macrophage inhibitory cytokine (MIC-1, also known as placental TGF-beta, PL74 or GDF-15). Most, if not all, of these molecules are expressed in the placenta as well as a wide variety of other tissues (165-167). They exert a bewildering array of biological effects via a family of related receptors which bind multiple ligands with varying affinity (168-170).

Some studies have reported greater placental expression and production of TGF-beta1 and -beta3 isoforms in preeclampsia (77,122,171) or elevated circulating levels in maternal serum (122) although these findings have been disputed (172). Maternal plasma levels of free or total TGF-beta isoforms have been measured in preeclampsia, but there is little evidence of an increase with disease (173). To date, although a number of actions have been described for these factors in the placenta, the majority seem to be relatively minor and redundant. The exception appears to be the role of TGF-beta as an inhibitor of trophoblast differentiation and EVT migration, which appears to be both important and indispensable. In the vasculature, TGF-beta is recognized as an important mediator in endothelial cell growth, permeability, vascular inflammation and angiogenesis. TGF-beta upregulates the expression of eNOS which is responsible for production of nitric oxide by the endothelium, a potent vasodilatory factor. This effect is abrogated by the presence of endoglin (174,175), a TGF-beta ancillary receptor which is present on the vascular endothelium (176,177) and is expressed in the placenta. Endoglin has antiangiogenic effects (173), whereas TGF-beta appears to be able to act as both a vasodilator and a vasoconstrictor depending on conditions (175,177,178). A recent publication by Venkatesha et al (173) reported that levels of expression of endoglin were

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markedly higher in preeclamptic placentas, and that levels of a truncated soluble form of endoglin (sEng) were also greater. Measurement of sEng in the circulation of women with preeclampsia revealed significantly higher concentrations in preeclampsia and a positive correlation with severity of disease and also with sFlt-1 concentrations (173). Following delivery, sEng levels declined by 70% suggesting that the placenta contributes the majority of the pregnancy-associated increase. They also showed in a rat model that adenoviral expression of sEng and/or sFlt-1 in mid pregnancy induced the symptoms of preeclampsia, with the combination of the two inducing the most severe phenotype (173). NO-mediated vasodilatory effects of TGF-beta1 and beta3 were blocked by sEng, as was TGF-beta-induced eNOS activation (173). These findings link altered placental endoglin, VEGF and sFlt-1 production with the pathophysiology of preeclampsia, offering novel and exciting avenues for development of new detection and treatment modalities in the future (Figure 1).

In contrast to TGF-beta, many studies have consistently reported that activin and inhibin levels in the sera of women with preeclampsia are markedly elevated. Petraglia et al were the first to describe the now well-established association between elevated maternal plasma activin A levels and preeclampsia (179). Interestingly, they also provided some evidence that activin was not responsible for causing hypertension in pregnancy, at least in rats. Shortly after, Muttukrishna et al, using a more robust assay, published more convincing and dramatic results, finding quite significant (10-fold) increases in maternal serum inhibin A and activin A in women with preeclampsia versus controls, suggesting that measurement of these proteins might have diagnostic applications (180). These findings have been confirmed by other studies (181). Many other researchers (182-186) have explored the predictive/diagnostic possibilities of activin and inhibin measurements, and have shown that activin levels are elevated in the second trimester before maternal symptoms of the disease are evident although a clinically useful predictive test has failed to materialize. The increase in activin and inhibin levels in preeclampsia is correlated with disease severity (186-188) and levels are significantly higher than in pregnancies with idiopathic SGA (186,189). Expression of activin in placentas from preeclamptic pregnancies is higher than in normal pregnancies (190-196), and correlated with serum levels (191), suggesting that the placenta is indeed the source of the elevated concentrations found in the maternal circulation. However, it has been suggested that endothelial or haematopoietic production might also be a contributor (186), a hypothesis subsequently confirmed by Tannetta and colleagues, who demonstrated elevated activin production by PBMCs from pregnant women and a heightened responsiveness to TNF-alpha-induced expression in PBMCs from preeclamptic women. Endothelial cells are also able to produce activin both basally and in response to TNF-alpha (197).

Activin A and inhibin A are both expressed and secreted by placental trophoblasts; placental production is stimulated by pro-inflammatory cytokines (198) and prostaglandins (199). Hypoxia was also predicted to be

associated with elevated trophoblast activin and inhibin production, but two groups independently have demonstrated *in vitro* that this was not the case – indeed, placental activin production is reduced under hypoxic conditions (200,201). However, fetal circulating activin levels have been shown to be increased in hypoxia in pregnant sheep, suggesting that non-placental sources of activin might respond to hypoxia in a different fashion to the placenta (202). Alternatively, elevated IL-1beta and TNF-alpha expression in preeclamptic placentas may contribute to the elevated activin A secretion and plasma levels (203). Levels of the activin binding protein, follistatin, which is also a placental product, are only modestly elevated with preeclampsia (204), suggesting that free biologically active activin concentrations are higher and able to exert increased effects on target tissues. Activin A appears to antagonize several effects of TGF-beta in the placenta, including formation of a syncytium and differentiation along an invasive phenotype (205). Activin exerts anti-inflammatory effects on the placenta, inhibiting TNF-alpha production at concentrations likely to be found in preeclamptic pregnancies, suggesting it may protect the placenta and other tissues from the toxic effects of this cytokine (198). Both pro- and anti-inflammatory effects have been demonstrated on the endothelium (206). Findings of a strong correlation between plasma activin concentrations and maternal erythroblast cell numbers suggest that in preeclampsia activin may act to increase erythropoiesis, perhaps as a protective response to ameliorate the effects of relative hypoxia (207), although as mentioned above placental hypoxia itself does not seem to be a driver of activin production (200,201).

The other major TGF-beta family member derived from the placenta is MIC-1/PL74 (208,209). Like activin A, MIC-1 is expressed predominantly in syncytiotrophoblasts and levels in maternal plasma are readily detectable and increase throughout gestation (210,211). It is over-expressed in the placenta in preeclampsia, and has been proposed to promote trophoblast apoptosis at the expense of differentiation (65). However, unlike activin and inhibin, there are no differences in circulating MIC-1 levels with preeclampsia (211) and its relevance to preeclampsia remains uncertain at present.

4.5. Adipocytokines

A number of studies have been carried out on leptin expression and production in the placenta with preeclampsia and its pathophysiological relevance. Leptin mRNA expression in placentas from preeclamptic pregnancies is markedly higher than normotensive controls (212,213). The cellular source is probably the syncytiotrophoblast and villous vascular endothelial cells (214,215), although interestingly villous mesenchymal cells were identified immunohistochemically as the source of increased leptin production in preeclamptic placentas in one study (212). Production of leptin protein *in vitro* is also elevated in tissues from pregnancies with preeclampsia (216). Placental leptin is exported to both the maternal and fetal compartments (217), so in theory the greater production by the placenta in preeclampsia could contribute

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to elevated circulating levels in both mother and baby. These findings are corroborated by reports of elevated maternal plasma leptin concentrations with preeclampsia (83,86,218-220), although this relationship has been reported to be markedly influenced by maternal body mass index (221) and has not been found in all studies (222,223). Some researchers have found that the increase in leptin is evident only in the third trimester (224), while others found that they precede onset of clinical disease and are evident in mid pregnancy (225). Cytokines such as IL-1beta and TNF-alpha stimulate placental leptin expression (226), and a correlation between maternal serum leptin and TNF-alpha has been described (227). The effects of elevated leptin in preeclampsia have been speculated to include enhanced fetal growth and protection against inflammatory cytokine-induced apoptosis, (228), reflecting a compensatory or protective role. However, positive effects on T_H1 stimulation and sympathetic activity have also been suggested, consistent with the possibility that leptin may play a direct role on the pathophysiology of preeclampsia (228) (Figure 1).

Like leptin, maternal circulating adiponectin levels are altered in preeclampsia, at least in the third trimester. However, there are conflicting reports of the nature of the alteration, with some finding evidence of higher levels (219,229,230) and others reporting lower levels (231). These apparent conflicts may relate to differential responses according to BMI, with women with normal BMIs demonstrating greater adiponectin levels in association with preeclampsia, while obese women with severe preeclampsia exhibit lower plasma adiponectin levels (232). The presence of different forms of adiponectin in the circulation and their differential reactivity in various immunoassays might also contribute to the discrepancies observed. Adiponectin is expressed in the placenta (233,234) and is a product of the placental syncytium. Its expression has been reported to be regulated by cytokines such as TNF-alpha and IL-6 (233), although others have not been able to repeat these findings (234). Corbetta and co-workers described adiponectin expression in fetal tissues (235), although surprisingly were unable to confirm its expression in the placenta. Adiponectin is usually attributed anti-inflammatory actions (236,237), and hence may counter the proinflammatory effects of other adipokines (238), although Lappas et al have recently reported that it stimulates placental cytokine expression (239).

A molecule only recently identified as an adipokine is visfatin (240), also known as pre-B-cell colony-enhancing factor (PBEF). Visfatin, an insulin mimetic shown to be responsive to plasma glucose (241) and free fatty acid (242) concentrations, is also expressed in the placenta and gestational membranes as well as immune cells (243-245). Visfatin expression is responsive to regulation by inflammatory signals (244,246,247). Visfatin expression in placentas from women with preeclampsia is markedly elevated compared to normal pregnancy (77). However, we are not yet aware of any studies describing visfatin levels in the circulation of women during pregnancy with or without preeclampsia, and the pathophysiological significance of these findings is unknown at the present time. Its association with

inflammatory NF-kappaB signalling may implicate placental visfatin (together with other adipokines) in aspects of systemic inflammatory activation that are characteristic of preeclampsia (238,248).

4.6. Cytokines and placental prostanoids

Disruption in synthesis of some prostaglandins, notably prostacyclin and thromboxane, may play a role in vascular disorders of preeclampsia (reviewed by Walsh and colleagues (249)). During normal pregnancy the placenta produces roughly equivalent amounts of thromboxane and prostacyclin, potent vasoconstrictors and vasodilators, respectively. However, in preeclamptic pregnancies the production of thromboxane greatly exceeds that of prostacyclin (249,250). This disruption of placental prostaglandin synthesis is not observed in IUGR without hypertension (251). A decrease in placental IL-8 production, associated with the decrease in prostacyclin, has been reported for villous tissues from preeclamptic pregnancies. Treatment of these tissues with IL-8 improves placental prostacyclin production (252), suggesting a role for this cytokine in maintaining prostaglandin balance during pregnancy. Pro-inflammatory cytokines such as TNF-alpha and IL-1beta are stimulators of placental PG production via enhanced expression of the COX-2 enzyme (253,254). Activin is also able to stimulate placental COX-2 expression and PG production at physiological concentrations (Keelan & Mitchell, unpublished). Hence, disturbances in placental prostanoid levels might be secondary to changes in local cytokine production and action.

5. PLACENTAL HYPOXIA AND CYTOKINE PRODUCTION

Uteroplacental hypoxia is proposed to play a central role in the pathophysiology of preeclampsia (255). In early pregnancy abnormal prolongation of hypoxia is thought to occur as a result of shallow trophoblast invasion (256,257) and improper remodeling of uterine spiral arteries (163,258); subsequently, reduced uterine blood flow and abnormal release of vasodilators/vasoconstrictors secondary to established maternal endothelial damage may also be a causative or compounding factor (109,258). Focal ischemia within the placenta may also result in the generation of diffusible factors from the hypoxic areas (62). These factors may initiate the maternal syndrome of preeclampsia resulting from generalized endothelial damage and dysfunction (16,258). Placental cytokines and angiogenic growth factors are thought to be intimately involved in the manifestation of the detrimental effects of placental hypoxia, both in terms of the response to abnormal oxygen tension and as mediators of the subsequent placental and vascular maladaptation (259,260) (Figure 1).

5.1. Placental hypoxia and hypoxia inducible factor

Hypoxia inducible factor (HIF) is a heterodimeric transcription factor that is regulated by hypoxia and mediates the effects of hypoxia on gene expression. HIF-1 is expressed in the placenta in a gestational-age dependent fashion (261), with levels being higher in the first trimester declining as oxygen levels increase later in pregnancy

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(255,261). The work of Dahl and colleagues suggests that HIF activation is closely involved in regulating placental morphogenesis, angiogenesis, and trophoblast differentiation (262,263), while Caniggia and Winter proposed that preeclampsia can result from a failure of the placenta to respond appropriately to changing oxygen tension during placental development by reducing HIF expression (264). Under hypoxic conditions, HIF-1 is stabilised and transactivates oxygen-regulated genes such as VEGF and iNOS. Expression of HIF-1 α and HIF-2 α protein in the placenta is increased with hypoxia (265,266). Mice lacking the HIF-1beta subunit, with subsequent loss of responsiveness to hypoxia, exhibit severe abnormalities in trophoblast populations in their placentas, combined with aberrant placental vascularisation (267). A recent report by Schaffer and colleagues demonstrated, however, that in murine pregnancy mechanisms exist to protect the placenta from acute hypoxia and subsequent HIF-1 activation (268). The importance of duration of hypoxia needs to be taken into account when interpreting these findings, however, and the relevance of this finding to human pregnancy remains uncertain. Nevertheless, studies of placental structure in human high altitude pregnancies suggest that the placenta is able to adapt to protect itself from the effects of hypoxia (269). The extent to which such protective mechanisms might be significant in the establishment of the preeclamptic placenta is uncertain.

5.2. Placental cytokine expression in response to hypoxia

Hypoxia regulates the expression of a number of genes that have important implications to our understanding of the pathogenesis of preeclampsia. VEGF, an archetypal hypoxia-driven gene, is expressed in the placenta under the influence of HIF activation (146,270,271), as is Flt-1 (69,272,273) and leptin (213,274,275). A newly-identified form of VEGF, called endocrine gland-derived VEGF (EG-VEGF) is also hypoxia-responsive and a product of trophoblast cells (276). These data regarding hypoxia-induced increased VEGF expression are somewhat in conflict with findings of lower placental VEGF expression and maternal plasma concentrations with preeclampsia (135,139,153-155), although as mentioned above, reports to the contrary have been published. Increased circulating sFlt-1 concentrations with preeclampsia has been consistently described, however, consistent with the description of increased release of sFlt-1 by the placenta during hypoxia (145). Interestingly, maternal PBMCs also express Flt-1, and sFlt-1 production is increased by hypoxia and is higher in cells from women with preeclampsia (144). In contrast, hypoxia down-regulates placental PIGF expression (67,145,147,148,271). Collectively, these changes are postulated to result in reduced angiogenic activity and hence impaired placental perfusion (69,275).

Expression of TGF-beta3 in the placenta is increased by hypoxia/HIF-1 (255,277-280), and alterations in expression of this cytokine have been put forward as a causal factor in the failure of trophoblastic invasion and maturation associated with preeclampsia. A marked decrease in transcription of TGF-beta3 after 9 weeks of

gestation in normal pregnancy has been documented, correlating with an increase in trophoblast differentiation and invasion (255,277) and increased perfusion. However, TGF-beta3 is over-expressed in placentae from preeclamptic pregnancies (279); inhibition of TGF-beta3 expression or activity restores the invasive capability of explants of preeclamptic placentas to normal levels (255,277). Importantly, elevated levels of HIF-1 have been documented in placentas from preeclamptic pregnancies (279), while placental HIF-1 expression is in turn up-regulated by TGF-beta (281). Hypoxia also induces the expression of several proinflammatory cytokines in the placenta including IL-1alpha, IL-1beta, and TNF-alpha, presumably acting through the HIF-1alpha transcription factor (69,76,78,255,277,278,282). The TNF-alpha and IL-1beta promoters both contain hypoxia-response enhancer elements (76). Placental IL-6 expression, however, does not appear to be hypoxia-regulated (78,283). Perfused placental cotyledons (284) and villous placental explants express or secrete greater amounts of IL-1beta, IL-6, IL-10 and TNF-alpha under hypoxic conditions (78,79,90,283). IL-1beta also increases expression of HIF-1alpha and VEGF in the placenta (285).

With respect to anti-inflammatory cytokines, IL-10 production in preeclampsia-derived trophoblasts has been reported to be reduced with hypoxia, although in contrast trophoblast IL-6/-8 production was greater in cells from both normal and preeclamptic placentas. Whether this observation is related to elevated HIF-1 expression with preeclampsia remains to be determined. Since IL-10 is a potent suppressor of pro-inflammatory cytokine production (TNF-alpha in particular), this finding may indicate that the preeclamptic placenta responds abnormally to hypoxia with inadequate IL-10 production, resulting in increased production of inflammatory cytokines, thereby contributing to the maternal intravascular disease. Reduced IL-10 bioactivity within the placenta might also influence invasion/differentiation through diminished suppression of placental protease release, although higher expression of placental IL-10 receptors documented with preeclampsia might compensate for the low levels of ligand. The recent finding that IL-10 may have compensatory vasodilatory effects in maternal vasculature early in pregnancy adds further interest to this observation (124).

Hypoxia has been explored as the cause of elevated expression and production of activin A and inhibin A (200,201). However, contrary to expectation, two groups found that hypoxia actually lowers activin production within the placenta, disproving what was otherwise an attractive hypothesis (200,201).

6. CYTOKINE POLYMORPHISMS AND PREECLAMPSIA

Preeclampsia appears to have a heritable component, and as such has been the subject of many genetic studies. Among these, several have been published in which associations between preeclampsia and polymorphisms in cytokine genes have been explored. It is important to note here that these are studies of maternal genotype, not fetal/placental.

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In a study of siblings from 150 Dutch families, nine polymorphisms in the TNF/LTA promoter region were studied but none showed any significant linkage with preeclampsia (286). Interestingly, in this study the presence of the TNF-I haplotype was significantly associated with preeclampsia or HELLP syndrome, but was not found in similarly affected sisters. Livingstone et al (287) also failed to find evidence of altered genotypic frequencies of TNF-alpha mutant alleles in women with severe preeclampsia. Similar negative findings have been reported by others (288,289). In contrast, several other studies have found interesting associations between TNF promoter polymorphisms and preeclampsia. In a recent study involving 133 Finnish women with preeclampsia (290) investigators found two polymorphisms in the TNF-alpha promoter (-308A and -850T) to be associated with susceptibility to preeclampsia (the variant A allele being overrepresented in the preeclampsia group). In contrast, Heiskanen et al (291) found significant genotype distribution of the C-805T polymorphism in women with preeclampsia (reduced incidence of the variant T allele) suggesting a protective effect of the variant allele. In a much larger German study of 1480 women, a significant association was found between the TNF-alpha -308A allele and higher urinary protein secretion, but not hypertension, although when combined with an IL-6 promoter polymorphism carriers of both alleles did have significantly elevated blood pressure (292). Circulating TNF-alpha concentrations were not measured in these studies, unfortunately, so the functional impact of the polymorphism on expression and secretion of TNF-alpha is unknown.

Associations between preeclampsia and other cytokine genes have also been investigated. Hefler et al (293) studied three polymorphisms in the IL-1beta and IL-1RA genes and their association with preeclampsia in a Hispanic population, but found no evidence of a causative association. However, a suggestion of a linkage between the polymorphisms and severity of preeclampsia was noted. Several other investigators have also reported negative findings for IL-1beta polymorphisms (289,292,294). A mutation in the inhibin-alpha gene was investigated in 50 women with preeclampsia, but this was not significantly associated with the condition (295).

A number of studies of IL-10 polymorphisms have been carried out, with mixed results. A threefold reduced risk for preeclampsia was observed by de Groot et al (118) in women with the IL-10 -2849AA genotype (but not with three other IL-10 promoter polymorphisms), which the authors interpreted as evidence for a genetic protection against preeclampsia involving IL-10. Recently, in a small study of placental IL-10 promoter polymorphisms, pregnancies with the -1082AA mutation were found to have lower IL-10 expression in the placenta and lower maternal plasma IL-10 concentrations (123).

Maternal VEGF polymorphisms and preeclampsia have also been studied. Papazoglou et al (296) found no significant associations between any of three VEGF polymorphisms (-2578C/A, -634G/C, 936C/T) and preeclampsia. However, the greater frequency of the 936C/T polymorphism in association with severe

preeclampsia suggests that this allele may affect disease severity. In the most recent study of this topic to be published Banyasz et al (297) explored the association between two VEGF polymorphisms and risk of preeclampsia in 84 women with severe preeclampsia and 96 normotensive controls. Carriers of the +405G allele had reduced susceptibility to preeclampsia. Again, VEGF protein / bioactivity levels were not measured, and the mechanistic significance of this association awaits explanation. No data on placental VEGF polymorphisms and preeclampsia have been described.

In summary, studies of cytokine polymorphisms and preeclampsia have been inconclusive due to small sample size, differences in study populations, and lack of phenotypic data on cytokine production, plasma concentrations or bioactivity.

7. SUMMARY & PERSPECTIVE

Studies performed over the past two decades have helped to shed considerable light on the role of placental cytokines and cytokine-like factors in the pathophysiology of preeclampsia. Despite the surprisingly large amount of contradictory data that has been published, the collective weight of evidence now strongly supports the view that interactions between elevated placental cytokine expression and lower angiogenic activity (due mainly to elevated circulating soluble receptor levels) constitute an important link between the aetiology of the disorder and the pathogenesis of maternal disease (Figure 1). There remains, however, several outstanding questions requiring clarification.

Firstly, the “chicken and egg” question relating to abnormal uteroplacental angiogenesis, shallow trophoblast invasion, hypoxia and altered cytokine/angiogenic factor secretion and activity. Since the latter can contribute to the former, and vice versa, which comes first? The likelihood is that there is dynamic regulation throughout pregnancy, responding to episodes of hypoxia and reperfusion, with different functional manifestations depending on genotype, environmental circumstances and gestational age. However, our understanding of the ontogeny of this complex process is far from complete. It is also not clear how interactions between the maternal immune system and the conceptus in very early stages of pregnancy contribute to the initiation of these anatomical and cellular abnormalities. Secondly, the relative contributions of fetal (e.g. placental) and maternal (e.g. endothelial, haematopoietic) tissues to the concentrations of circulating factors thought to contribute to the development of hypertension and proteinuria are unknown. Some genetic and immunological evidence suggests that the maternal component is significant, but the relative contributions (which are likely to change as the placental contribution increases with gestational age) have not been estimated. Thirdly, the nature of the cytokine (e.g. $T_H1:T_H2$) imbalance that may or may not occur in preeclampsia, and its origin and significance, remains disappointingly obscure due mainly to a lack of consistent information. Whether this relates to weaknesses in assay methodology or

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experimental design, differences in patient classification or demographics, or is simply a reflection of the inherent heterogeneity that exists in preeclampsia is not clear. Fourthly, the pathophysiological significance of the finding of higher adipokine secretion by the placenta in preeclampsia awaits elucidation. While some suggestions of effects on vascular tone and inflammation have been put forward, there is little strong evidence linking elevated circulating adipokines concentrations with any of the maternal symptoms of preeclampsia. Finally, despite much work and optimism, the diagnostic potential of measuring systemic cytokine concentrations to accurately predict the onset of maternal disease has yet to be realized.

Clearly, there is much that remains to be done to improve our understanding of the relationship between placental cytokines and the causes and manifestation of preeclampsia. Nevertheless, an impressive body of information has been accumulated and significant advances have been made. There is new optimism that this work will soon be translated into improved prediction and treatment strategies that can be made available to women to reduce the morbidity and mortality associated with this serious and relatively common pregnancy disorder.

8. ACKNOWLEDGEMENTS

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