Published in final edited form as:

Microvasc Res. 2008 January ; 75(1): 1–8.

MOLECULAR MECHANISMS OF PREECLAMPSIA

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Abstract

Preeclampsia is a major cause of maternal, fetal, and neonatal mortality worldwide. The mechanisms that initiate preeclampsia in humans have been elusive, but some parts of the puzzle have begun to come together. A key discovery in the field was the realization that its major phenotypes, such as hypertension and proteinuria, are due to excess circulating soluble fms-like tyrosine kinase-1 (sFlt-1, also referred to as sVEGFR-1). sFlt-1 is an endogenous anti-angiogenic protein that is made by the placenta and acts by neutralizing the pro-angiogenic proteins vascular endothelial growth factor (VEGF) and placental growth factor (PlGF). More recently, soluble endoglin, another circulating anti-angiogenic protein was found to synergize with sFlt1 and contribute to the pathogenesis of preeclampsia. Abnormalities in these circulating angiogenic proteins are not only present during clinical preeclampsia, but also antedate clinical symptoms by several weeks. This review will summarize our current understanding of the molecular mechanism of preeclampsia, with an emphasis on the recently characterized circulating anti-angiogenic proteins.

Introduction

Preeclampsia is a disease of pregnancy characterized by hypertension and proteinuria developing after 20 weeks of gestation. It has been estimated that 5 to 7% of pregnancies worldwide are complicated by this disorder resulting in a very large disease burden (Sibai et al., 2003; Walker, 2000; Zhang et al., 2003). Potential fetal complications include low birth weight, prematurity and death. Maternal complications include renal failure, HELLP syndrome (hemolysis, elevated liver enzymes, and thrombocytopenia), liver failure, cerebral edema with seizures and rarely death.

Until recently most work on the disease has focused on abnormal placentation, genetic and epidemiologic factors, as well as treatments aimed at slowing the progression of the disease. Nephrologists have been interested in the condition because of the prominence of proteinuria in the clinical presentation and the unique pathologic changes in the kidney. In the last few years, however, new discoveries suggest that preeclampsia is in fact related to an imbalance of circulating angiogenic factors resulting in endothelial dysfunction. The implication of this theory is that preeclampsia is primarily a disease of the vascular endothelium. Notably, risk

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Disclosures

S.A.K is listed as a co-inventor on multiple patents filed by the Beth Israel Deaconess Medical Center for the use of angiogenic proteins for the diagnosis and therapy of preeclampsia. S.A.K. is a consultant to Johnson & Johnson, Beckman Coulter and Abbott Diagnostics.

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factors for preeclampsia include maternal obesity, insulin resistance, hyperlipidemia, hypertension, kidney disease and thrombophilias which may be markers for underlying vascular disease (Said and Dekker, 2003; Thadhani et al., 2004; Thadhani et al., 1999; Wolf et al., 2001; Wolf et al., 2002). Preeclampsia thus warrants the close attention of vascular biologists as further investigation of this disease will no doubt shed light on endothelial function in general.

Traditionally, preeclampsia has been viewed as a self limited condition that resolves after delivery of the placenta with little long term sequelae for the mother, although fetal morbidity may be great. However, recent data has shown that maternal endothelial dysfunction may persist years after the episode, and women who have suffered from preeclampsia may be at higher risk for cardiovascular events in the future. For example, Doppler studies of brachial artery reactivity in women who have had preeclampsia shows abnormal endothelial dependent flow-mediated arterial dilation three years after pregnancy (Chambers et al., 2001).

In this review we highlight some of the recent advances in our understanding of the impaired placentation, describe the imbalance of angiogenic and anti-angiogenic factors which confer the disease phenotype, and conclude with potential future applications for diagnosis and treatment. While anti-angiogenic therapy is now seeing success in cancer therapy, preeclampsia provides an interesting example where pro-angiogenic therapies aimed at repairing disturbed endothelial function may be useful.

Background

The constellation of clinical findings of preeclampsia has only been observed in pregnant women leading to the conclusion that a placenta is necessary. Preeclampsia has been observed in patients with molar pregnancy where a fetus is absent demonstrating that the placenta is also sufficient to cause the condition. Interestingly, the fetus does not develop clinical findings similar to the maternal syndrome and fetal morbidity and mortality is believed to result exclusively from placental insufficiency. In almost all cases, the disease regresses shortly after delivery of the placenta, but may persist if placental tissue is retained. These observations have led investigators to speculate that there may be a circulating factor (or factors) produced by the placenta that contribute to the maternal disease. Work to date has shown that the placenta of women with preeclampsia is abnormally developed and probably relatively hypoxic. Maternal endothelial dysfunction, possibly related to circulating factors elaborated from the abnormal placenta, is a key feature (Roberts et al., 1989).

Disordered vascular endothelial function seems to be important. Women with preeclampsia demonstrate increased sympathetic tone (Schobel et al., 1996), increased pressor response to norepinephrine (Chesley et al., 1965) and are more sensitive to angiotensin II (Gant et al., 1973). There are also alterations in endothelial derived vasoactive mediators such as decreased amounts of the vasodilators prostaglandin I₂ (PGI₂) (Baker et al., 1996) and nitric oxide (Williams et al., 1997) as well as increased amounts of the vasoconstrictors thromboxane A₂ (Mills et al., 1999) and endothelin (Clark et al., 1992). Historically the search for a secreted placental factor has been hampered by lack of a suitable animal model and a plausible mechanism to explain all of the disease manifestations. On the other hand, human placental tissue is readily available and much work has been done to characterize the changes in placentation unique to preeclampsia. Recently, mRNA microarray of placental tissue from patients with preeclampsia has identified increased amounts of at least two circulating proteins that may play an important part in the pathogenesis of the disease. These proteins, soluble fms-like kinase 1 (sFlt-1) and soluble endoglin (sEng) contribute to endothelial dysfunction, reproduce the clinical syndrome in a rat model and may predict the onset of the disease

(Maynard et al., 2003; Venkatesha et al., 2006). Most importantly they provide potential targets for therapy.

Disordered Placentation

The placenta is essential for exchange of nutrients, oxygen and waste between the mother and the developing fetus. Coordinated vascularization of the placenta is essential for the proper placental development and involves the processes of vasculogenesis (new blood vessel formation) and angiogenesis (growth of blood vessels) (Cross et al., 1994). Normal placentation is thought to involve a two stage process including the formation of a branching network of vessels within the chorionic villi of fetal origin followed later by modification of the existing vascular network and transformation from a high resistance relatively hypoxic vascular bed into a low resistance circuit with increased oxygen tension (Cross et al., 1994; Kaufmann et al., 1985; Leiser et al., 1985).

Two to three weeks after conception the placenta is composed of primary villi which are columnar structures consisting of cytotrophoblast cells surrounded by a layer of syncytiotrophoblast. Mesenchymal cells later invade the villi forming secondary villi and give rise to placental blood vessels. Mesenchymal derived macrophages (Hofbauer cells) express VEGF and other angiogenic factors and are thought to initiate vasculogenesis in the placenta (Ahmed et al., 2000; Ahmed et al., 1995; Demir et al., 1989). Later in placental development, additional capillaries form by branching angiogenesis from pre-existing capillaries.

A key event in normal placentation is invasion of the maternal spiral arteries in the decidua and myometrium by fetal cytotrophoblasts. Extensive work by Susan Fisher's group has shown that this process is defective in preeclamptic placentas (Damsky and Fisher, 1998; Zhou et al., 2003a; 1997a; 1997b; 2003b). Normally trophoblast cells transform from an epithelial phenotype to an endothelial phenotype as they invade the maternal deciduas and myometrium in a process termed pseudovasculogenesis. They express markers such as vascular endothelial-cadherin (VE-cadherin), and $\alpha_v\beta_3$ integrin (Zhou et al., 1997a). These migrating trophoblasts transform the maternal spiral arterioles that supply maternal blood to the placenta from small caliber resistance vessels to large caliber capacitance vessels allowing adequate maternal blood flow to the placenta. In preeclampsia this process is disordered and the fetal trophoblasts fail to properly invade the maternal myometrium and spiral arterioles (Brosens et al., 1972). Normally, early placental development occurs in a hypoxic environment and the placenta becomes increasingly oxygenated with time (Genbacev et al., 1997). It has been theorized that this failure of conversion of spiral arterioles results in persistent placental hypoxia, placental insufficiency and ultimately maternal endothelial dysfunction and the clinical syndrome of preeclampsia.

Identification of Circulating Factors

Endothelial dysfunction is thought to contribute to the clinical syndrome of preeclampsia (Roberts and Cooper, 2001). Hallmarks of the disease include arterial hyperreactivity to exogenous and endogenous stimuli, proteinuria related to increased glomerular permeability, cerebral edema and increased CNS permeability, as well as vascular thrombosis resulting in the (HELLP) syndrome all of which may result from disordered endothelial function (Roberts, 1998; Roberts and Cooper, 2001). Studies have shown increased endothelial cell permeability, lipid peroxidation (Hubel et al., 1996), platelet activation (Kolben et al., 1995; Kolben et al., 1996) and oxidative stress (Davigde, 1998). Several investigators have hypothesized that a circulating factor or factors, probably elaborated by the placenta, cause the maternal disease (Ferris, 1991; Roberts et al., 1989). Serum from patients with preeclampsia show increased levels of circulating factors associated with endothelial injury including fibronectin, factor VIII antigen, and thrombomodulin (Friedman et al., 1995; Hsu et al., 1993; Taylor et al., 1991).

Also, patients with preeclampsia show abnormal arterial vessel endothelial function even before the onset of disease (Cockell and Poston, 1997; McCarthy et al., 1993; Savvidou et al., 2003). Additional data supporting endothelial dysfunction includes decreased generation of endothelins, diminished production of endothelium-derived vasodilators such as prostacyclins and increased vascular sensitivity to angiotensin II and norepinephrine mediated vascular constriction (Clark et al., 1992; Gant et al., 1973; Gant et al., 1987; Mills et al., 1999).

There has been an active search for circulating factors that cause or contribute to endothelial dysfunction. Variation in the serum levels of several substances that may alter endothelial function have been demonstrated including TNF- α , interleukin (IL)-6, IL-1 α , IL-1 β , Fas ligand, oxidized lipid products, endothelin B, and asymmetric dimethylarginine (Benyo et al., 2001; Conrad et al., 1998; Page et al., 2000; Savvidou et al., 2003) although it is not clear if these variations are causal or simply an epiphenomenon. Bradykinin (B2) receptors are up-regulated in preeclampsia and may heterodimerize with angiotensin II type 1 receptors and increase responsiveness to angiotensin II in vitro (Abdalla et al., 2001). Interestingly, antibodies to angiotensin receptor-1 have been identified in humans with preeclampsia as well as in a transgenic rat model of the disease and may augment the normal response to angiotensin II (Dechend et al., 2005; Dechend et al., 2000; Roberts and Cooper, 2001; Wallukat et al., 1999). However, they have not been shown to reproduce the entire phenotype of preeclampsia or antedate the onset of disease.

Soluble Fms-like Tyrosine Kinase-1 (sFlt-1)

Recent work by our group and others has demonstrated increased placental production and maternal serum levels of sFlt-1 in patients with preeclampsia (Ahmad and Ahmed, 2004; Chaiworapongsa et al., 2004; Koga et al., 2003; Maynard et al., 2003; Shibata et al., 2005). sFlt-1 is an alternatively spliced and truncated version of vascular endothelial growth factor receptor 1 (VEGF-R1). It contains the extracellular ligand-binding domain but lacks the transmembrane and cytoplasmic portions of VEGF-R1 (He et al., 1999; Kendall and Thomas, 1993). sFlt-1 is able to bind both VEGF and PlGF. Free in serum, it may diminish binding of these growth factors to their cognate receptors VEGF-R1 and VEGF-R2 also known as fms-like tyrosine kinase-1 (Flt-1) and kinase domain region (Flk/KDR) respectively (Kendall et al., 1996). The placenta is known to produce a number of other angiogenic factors including VEGF, PlGF, the angiopoietins (Ang-1 and Ang-2) as well as their receptor Tie-2 (Dunk et al., 2000; Geva et al., 2002; Goldman-Wohl et al., 2000).

In patients with preeclampsia, increased sFlt-1 is associated with decreased free VEGF and PlGF in the serum. Using an adenoviral vector, sFlt-1 has been overexpressed in pregnant rats (Maynard et al., 2003). The animals developed proteinuria, hypertension and glomerular endotheliosis which are hallmarks of preeclampsia. Notably the phenotype was also present in non-pregnant animals expressing sFlt-1. When soluble VEGF receptor-2 (sFlk-1), which antagonizes VEGF but not PlGF, was overexpressed in pregnant rats they did not develop changes consistent with preeclampsia arguing that antagonism of both VEGF and PlGF is necessary to reproduce the disease (Maynard et al., 2003). Antibodies against VEGF or sFlt-1 protein has also been shown to induce glomerular endothelial damage with proteinuria in non-pregnant mice (Kitamoto et al., 2001; Sugimoto et al., 2003).

There is strong evidence to suggest that the capillary endothelium of the kidney, for example, is extremely sensitive to VEGF which is produced locally by the visceral epithelium (podocytes) and may explain why renal dysfunction is an important and early marker of the disease. VEGF is necessary to maintain the normal fenestration of glomerular endothelial cells (Ballermann, 2005; Maharaj et al., 2006). In non-pregnant mice a 50% reduction of VEGF leads to glomerular endotheliosis and proteinuria similar to what is seen in preeclampsia

(Eremina et al., 2003). In addition, it has been reported that patients receiving VEGF antagonists for cancer treatment may develop hypertension, proteinuria and endothelial activation (Kabbinavar et al., 2003; Kuenen et al., 2002; Yang et al., 2003). In preeclampsia it is likely that VEGF signaling is decreased in the kidney due to excess sFlt-1 leading to the glomerular changes of endotheliosis and proteinuria.

Regulation of sFlt-1 and Placental Hypoxia

Much work has been done regarding placental ischemia/hypoxia and its possible role in preeclampsia. Clinical data shows that women who develop preeclampsia have decreased uteroplacental blood flow (Lunell et al., 1984). Hypoxic conditions are known to stimulate expression of a number of pro-angiogenic proteins in endothelial and tumor cells including endothelin (Kourembanas et al., 1991) VEGF (Shweiki et al., 1992) and Flt-1 (Gerber et al., 1997). The transcription factor hypoxia-inducible factor 1 (HIF1 alpha) regulates VEGF and Flt-1 gene transcription (Forsythe et al., 1996; Gerber et al., 1997) and importantly HIF-1 alpha and HIF-2 alpha protein levels are significantly elevated in the preeclamptic placenta (Caniggia et al., 2000; Rajakumar et al., 2003; Rajakumar et al., 2001). Lowered oxygen tension in primary cytotrophoblast culture and villous explants causes increased sFlt-1 expression suggesting that sFlt expression may be stimulated by hypoxia (Ahmad and Ahmed, 2004; Nagamatsu et al., 2004). As predicted VEGF expression was also increased but free VEGF and PlGF in the supernatant were low suggesting that the sFlt-1 induction exceeded VEGF production resulting in a net anti-angiogenic state. Furthermore, there is increased expression of sFlt-1 noted both in vitro and in vivo models of placental hypoxia (Nevo et al., 2006). More recently, it has been reported that uteroplacental ischemia induced in primates results in preeclampsia-like phenotype that was accompanied by elevated circulating sFlt-1 (Makris et al., 2007). Collectively, these data suggest that placental ischemia/hypoxia may alone be sufficient to induce preeclampsia through sFlt-1 up-regulation. Whether placental ischemia is necessary for the induction of human preeclampsia is still unknown.

It has also been reported that heme oxygenase -1 via carbon monoxide may be a negative regulator of sFlt-1 production in the placenta (Cudmore et al., 2007). These findings may have explain the clinical observation that the incidence of preeclampsia is lower in smokers who are exposed to high levels of carbon monoxide (England et al., 2003).

Does sFlt-1 predict the onset of preeclampsia?

The hypothesis that preeclampsia may be caused by an imbalance of circulating angiogenic factors suggests that these changes may precede the onset of clinical disease and may be useful in designing screening and/or diagnostic tests to identify patients at risk for preeclampsia. Such a test would be invaluable to clinicians who may offer close follow-up and therapeutic interventions early in the course of disease. Several retrospective studies using preeclamptic serum have shown that sFlt-1 concentrations in serum are high as much as five to six weeks before any clinical findings are noted (Chaiworapongsa et al., 2005; Hertig et al., 2004; Levine et al., 2004; McKeeman et al., 2004). In addition, free VEGF and PlGF are low (Hertig et al., 2004; Levine et al., 2004) and may predict the onset of disease. Urinary markers are convenient in that they do not require venopuncture and one study has shown decreased urinary PlGF prior to the development of clinical preeclampsia (Levine et al., 2005). A recent systematic review of the literature to assess if elevated sFlt-1 or decreased PlGF in the serum could accurately predict the onset of preeclampsia concluded that third trimester increases in sFlt-1 and decreases in PlGF are associated with preeclampsia but there is currently insufficient data to recommend these as screening tests (Widmer et al., 2007). The authors recommended well constructed and rigorous prospective trials to determine the clinical usefulness of these tests.

Additional Circulating Factors

Although overexpression of sFlt-1 reproduces the clinical changes of preeclampsia in rats, and elevated levels of sFlt-1 associated with decreased free VEGF and PlGF are present prior to the onset of preeclampsia, sFlt-1 excess is probably not sufficient to explain all the manifestations of the disease. For example, rats expressing very high levels of sFlt-1 do not develop coagulation abnormalities, liver dysfunction or seizures which may be seen in the human disease.

Recently, attention has focused on endoglin (Eng), a co-receptor for transforming growth factor β 1 and β 3, and a protein expressed in large quantities by the placenta in preeclampsia. Endoglin is highly expressed in vascular endothelial cells (Cheifetz et al., 1992) and syncytiotrophoblasts (Gougos et al., 1992). It regulates vascular tone through interactions with endothelial nitric oxide synthase (Toporsian et al., 2005). The extra-cellular domain of endoglin may be shed and is found in the serum where it is referred to as soluble endoglin (sEng). sEng inhibits endothelial capillary tube formation and promotes vascular permeability (Venkatesha et al., 2006). When overexpressed by adenoviral vector in rats, sEng causes proteinuria and hypertension that are more mild than seen with sFlt-1 overexpression alone. However, when sEng is co-expressed with sFlt-1, the rats develop severe proteinuria, hypertension, intrauterine growth restriction as well as low platelets and elevated LDH similar to human HELLP syndrome (Venkatesha et al., 2006). Like sFlt-1, sEng is increased in maternal serum two to three months prior to the onset of disease (Levine et al., 2006). sEng and sFlt-1 both cause endothelial dysfunction by different mechanisms but may cooperate to produce the clinical syndrome of preeclampsia.

Persistent Maternal Endothelial Dysfunction

Women who have had preeclampsia are at higher risk for developing chronic hypertension, coronary artery disease, and stroke. It remains unknown if this represents the presence of risk factors that predispose to both preeclampsia and vascular disease including obesity, hypertension, and insulin resistance or if a history of preeclampsia confers a new risk factor for later vascular disease. For example, the CHAMPS study found an increased risk of hospital admissions or arterial revascularization in women who had a history of preeclampsia compared with controls (Ray et al., 2005). Another retrospective study showed an 8.1 fold increased risk of cardiovascular death in women who had preeclampsia and delivered prior to 37 weeks gestation (Irgens et al., 2001).

It is plausible that preeclampsia may reflect an underlying predisposition to developing vascular disease later in life. Some have suggested that it may serve as an endothelial “stress test” unmasking those with a predisposition to endothelial and vascular dysfunction. One study that attempted to control for underlying genetic and environmental factors found that women with preeclampsia were more likely to develop hypertension than non-preeclamptic siblings (Irgens et al., 2001). A recent study showed that women with preeclampsia were more likely to have impaired brachial artery endothelium-mediated vasodilation up to two years after delivery. They also had lower serum nitrates and higher cholesterol compared with controls (Germain et al., 2007).

A provocative theory posits that women with a history of preeclampsia have a residual anti-angiogenic balance and may be somewhat protected from growth of solid tumors which rely on VEGF and other angiogenic factors for neovascularization, tumor growth and metastasis. In fact some studies (Cohn et al., 2001; Vatten et al., 2002), although not all (Paltiel et al., 2004) have shown a decreased incidence of breast cancer in women with a history of preeclampsia. There is also evidence to suggest a lower incidence of other solid tumors (Aagaard-Tillery et al., 2006).

Implications for Therapy

The implications of these advances on our clinical management of preeclampsia may be profound. Pharmacological intervention aimed at restoring the angiogenic balance may prevent or modify the course of preeclampsia. The availability of reliable animal models that closely mimics human preeclampsia should allow rapid testing of novel therapeutic compounds. In this regard, VEGF-121 (an isoform of VEGF) has been recently shown to ameliorate preeclamptic signs and symptoms in a rat model of preeclampsia (Steve Pollitt and Ananth Karumanchi, unpublished observations). Safely prolonging pregnancy by only a few weeks could substantially reduce maternal and neonatal morbidity and mortality resulting from preeclampsia.

Conclusions

Preeclampsia is a condition characterized by systemic vascular endothelial dysfunction. It is associated with elevated levels of markers of endothelial damage in the serum as well as impaired vascular homeostasis. sFlt-1, a soluble version of the VEGF receptor 1, is present in high quantities in the serum of women with preeclampsia and is associated with low levels of free VEGF and PlGF. Overexpression of sFlt-1 in rats reproduces a phenotype that is very similar to human preeclampsia. Increased levels of sFlt-1 have been documented in women several weeks before the onset of clinical disease in conjunction with decreased levels of free PlGF and predict the onset of clinical symptoms. It is not yet clear if abnormal sFlt-1 production is a cause or consequence of abnormal placentation and specifically how placental hypoxia caused by disordered vasculogenesis contributes to the disease. An additional anti-angiogenic protein, sEng, is also produced in high quantities by the placenta and seems to cooperate with sFlt-1 in a rat model to produce a severe form of the condition similar to HELLP syndrome. Moreover, sEng levels rise in maternal serum several months before the onset of preeclampsia and may be particularly useful to predict those patients who will develop a more severe form of the disease. Future studies focusing on the regulation of angiogenic gene products and their role in placental angiogenesis and systemic vascular health will lead to a better understanding of the pathogenesis of preeclampsia as well as better therapeutic options.

Acknowledgements

S.A.K. is funded by R01 grants from the National Institute of Diabetes, Digestive and Kidney Diseases (DK 065997) and the National Heart, Lung, and Blood Institute (HL079594).

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