Molecular Mechanisms of Preeclampsia

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Preeclampsia is one of the leading causes of maternal morbidity/mortality. The pathogenesis of preeclampsia is still under investigation. The aim of this paper is to present the molecular mechanisms implicating in the pathway leading to preeclampsia.

1. Introduction

Preeclampsia is one of the leading causes of maternal morbidity/mortality and preterm delivery worldwide [1]. It is a syndrome defined by the onset of hypertension (≥140/≥90 mmHg) and proteinuria (≥0.3 gr/24 h) after 20 weeks of gestation in a previously normotensive woman that also may be associated with myriad, other signs and symptoms, and often with subnormal fetal growth [2, 3]. Most commonly, preeclampsia occurs in healthy nulliparous women. However, multiparous pregnant women with a new partner have an increased risk of preeclampsia similar to that of nulliparous women [4]. Women with a history of preeclampsia in a prior pregnancy are at increased risk of developing preeclampsia in future pregnancies [5]. A history of preeclampsia in the father’s mother also confers an increased risk [6]. Several medical conditions, such as chronic hypertension, diabetes mellitus, renal disease, and hypercoagulable states are associated with increased preeclampsia risk [7, 8]. Additionally, obstetrical conditions with increased placental mass increase the risk of preeclampsia. These include hydatidiform mole [9] and multifetal gestation [10].

Delivery of the placenta remains the only known treatment for this clinical disease, suggesting that the placenta is the principal contributor to the pathogenesis of preeclampsia. It is well known that the first step for the development of preeclampsia is the inadequate placental cytotrophoblast invasion, impaired trophoblast invasion, and inadequate maternal spiral artery remodeling which results in placental ischemia and hypoxia. However, placental ischemia does not always generate the clinical symptoms of preeclampsia. Many molecular mechanisms are contributed to the pathogenesis of preeclampsia. Altered angiogenic balance, systemic inflammation, dystregulation of renin-angiotensin system, and placental hypoxia and ischemia are mechanisms which contribute to the pathogenesis of pre-eclampsia, although it is unknown whether the mechanisms act independently or have synergistic effects.

2. Altered Angiogenic Balance

2.1. Angiogenic Factors.

A variety of angiogenic factors are produced from the human placenta. The most important between them are the vascular endothelial growth factor (VEGF) and the placental growth factor (PIGF) [11]. VEGF is an endothelial-specific mitogen that plays a key role in promoting angiogenesis. VEGF stabilizes endothelium in mature blood vessels [12]. VEGF’s activities are mediated primarily by its interaction with two high-affinity receptors tyrosine kinases—kinase-insert domain region (KDR or VEGF R-2) and fms-like tyrosine kinase-1 or flt-1. Both receptors are expressed on vascular endothelial cell surface [13]. PIGF is also an angiogenic growth factor that is thought to amplify VEGF signalling by displacing VEGF from the flt-1 receptor and allowing it to bind to the more active kinase-insert domain (KDT) receptor [14, 15].

Recent research has shown that soluble flt-1 is released by the placenta into the maternal circulation and, that is, contributes to the hypertension, proteinuria, and endothelial cell dysfunction associated with preeclampsia [16]. sflt-1 antagonizes both VEGF and PIGF by binding them in
the circulation and preventing interaction with their endo-
genous receptors [17, 18]. New variants of sflt-1 have been
discovered such as sflt1–14, which is also a potent VEGF
inhibitor [19, 20]. The level of SFLT-1 in the plasma of
women with preeclampsia is elevated and that of VEGF is
diminished in comparison with that of women with com-
licated pregnancies [21]. Furthermore, administration of
sflt-1 to rats resulted in elevated blood pressure and pro-
teinuria, indicating that excessive placenta-derived sflt-1 max-
contributed to preeclampsia [21].

Factors responsible for excessive production of self-1 in
preeclampsia have not been identified. However, recently it
has been found that angiotensin II type 1 (AT) receptor auto-
antibodies which occur in women with preeclampsia con-
tribute to increased production of sflt-1. Thus, IgG from
women with preeclampsia stimulates the synthesis and secre-
tion of sflt-1, via AT1 receptor activation in human placental
villous explants and human trophoblast cells. Another
factor which contributes to increased production of sflt-1 is
the hypoxic placenta [22]. Under other pathophysiological
conditions such as cancer and hypoxia which generally stim-
ulates angiogenic signalling, it remains poorly understood
why hypoxic placenta produces the molecules that suppress
angiogenesis in preeclampsia [23].

Soluble endoglin is another antiangiogenic protein,
which acts to get it with sflt-1 to induce a severe preeclam-
pia-like syndrome in pregnant rats. Circulating soluble endo-
glin levels increased markedly beginning from 2 to 3 months
before the onset of preeclampsia. An increased level of solu-
ble endoglin was usually accompanied by an increased ratio
of sflt-1 [24].

Experiments data have shown that VEGF stimulates the
production of both nitric oxide (NO) and PGI2 [25]. On the
other hand, a high concentration of asymmetric dimethy-
larginine (ADMA), an endogenous inhibitor of endothelial
nitric oxide synthase, has been found in preeclamptic women
[26].

Women with bilateral notches who later developed pree-
clampsia had a striking elevation in the concentration of the
NO synthase inhibitor [27].

ADMA is normally metabolized to citruline through
the action of dimethylarginine-dimethylaminohydrolase I, II
(DDAH I, II). Oxidative stress seen in preeclampsia dimin-
ishes the action of the alone enzymes leading to high concen-
tration of ADMA [27].

3. The Role of Relaxin in Preeclampsia

Relaxin is produced by the corpus luteus of the ovary and
rises early in pregnancy, and chorionic gonadotropin pro-
duced by the placenta is a major stimulus for relaxin secre-
tion during pregnancy.

Relaxin has renal vasodilatory effect [28], and it also dim-
imishes the relaxin vasoconstrictor response to angioten-
sin II. Moreover, reduced myogenic reactivity of small renal
arteries is observed after relaxin administration [29, 30].
Recently, it has been proposed that relaxin via relaxin recep-
tor upregulates vascular gelatinase activity during pregnancy,
contributing to renal vasodilation through activation of en-
dothelial endothelin B (ETB) receptor which activates nitric
oxide synthase III and the production of NO [31]. Thus,
increased vascular gelatinase activity by relaxin is thought to
be a proximal step in the vasodilatory pathway of pregnancy
[32].

Circulating levels of immunoreactive relaxin have been
reported to be similar in women with preeclampsia and nor-
mal pregnancy [33]. However, whether circulating relaxin
bioactivity may be deficient during the disease is uncertain
[34]. Furthermore, mutations or polymorphisms of the ETB
receptor or of endothelial NO synthase that reduce activity
may predispose a woman to preeclampsia by impairing tro-
phoblast invasion on the one hand or by compromising ma-
ternal endothelial behaviour on the other [35, 36].

4. Inflammatory Cytokines in
the Pathophysiology of Preeclampsia

Reduced uterine perfusion during pregnancy is an important
initialising event in preeclampsia. Inflammatory cytokines are
thought to link placental ischemia with cardiovascular and
renal dysfunction [37]. In normal pregnancy TNF-α is low in
the first trimester and subsequently increases with advancing
gestation age [38]. Some studies report higher TNF-α levels
in women with established preeclampsia [39, 40]. Increased
levels of TNF-α antigen and mRNA have been described in
placental tissue from preeclamptic women [41].

Because TNF-α may impair insulin signalling, inhibit
lipoprotein lipase, induce PAI-1, and directly contribute to
endothelial dysfunction, this cytokine may be involved in the
pathogenesis of preeclampsia [42].

There are also findings showing that chronic infusion
of IL-6 into normal pregnant rats stimulates the renin-
angiotensin system (RAS) [37].

Natural killer (NK) cells, dendritic cells, and macroph-
ages are mediators of innate immunity. Macrophages and
dendritic cells are the major antigen-presenting cells in the
uterus, and they facilitate adaptation of the immune response
to prevent rejection of the embryo [43].

Several studies have found a statistically significant in-
crease in macrophages and dendritic cells in preeclamptic
placentas compared to placentas from normotensive preg-
nancies [43, 44]. An increase in the concentration of cytoki-
nes, molecules capable of recruiting macrophages, and den-
tritic cells has also been found in preeclamptic placentas [44].

The increased presence of cytokines, macrophages, and
dendritic cells in preeclamptic placentas supports the hypo-
thesis that an inflammatory milieu presents in women with
preeclampsia [44].

5. Activation of Renin-Angiotensin
System (RAS)

Renin-angiotensin system is one that controls blood pressure
[45], The expression of rennin mRNA was detected in human
decidua, macrophages, chorioamniotic membrane, and vas-
cular smooth muscle cells [46].
Angiotensin II receptor type I (\(\text{AT}_1\)) was shown to be localized both in villous and extravillus trophoblasts, and this \(\text{AT}_1\) responds to exogenously administrated angiotensin II [47].

The circulating level of angiotensin II increases as the pregnancy advances [48]. In preeclampsia, the circulating level of angiotensin is rather decreased [49], despite the fact that the vascular sensitivity to angiotensin is elevated in hypertensive pregnant women.

The \(\text{AT}_1\) receptor gene expression was higher in placenta than in decidua for both normal and preeclamptic women. However, the decidua of preeclamptic women has a significantly higher \(\text{AT}_1\) receptor gene expression than normal pregnant women [50]. It has been found that the gene encoding the \(\text{AT}_1\) receptor was upregulated in the decidua of preeclamptic women but not in normal control [51]. Circulating agonistic autoantibodies directed at the angiotensin II type 1 receptor (\(\text{AT}_1\)-\(\text{AA}_x\)) have been discovered in women with preeclampsia [52].

Thus the increased decidual \(\text{AT}_1\) expression in preeclampsia may be the initial step for a profound RAS activation. Furthermore, the presence of \(\text{AT}_1\)-\(\text{AA}_x\) is able to activate cells via the \(\text{AT}_1\) receptor and initiate signaling events that could contribute to development of preeclampsia. Thus, release of soluble f\(\text{lt}-1\) can be triggered by angiotensin II stimulation, raising an imbalance between angiogenic vascular endothelial growth factors and antiangiogenic soluble factors [21]. Zhou et al. [21] have shown that the inhibition of \(\text{AT}_1\); administration of losartan or FK506 resulted in reduced SVEGFR-1. Thus, maternal SVEGFR-1 can be elevated not only by poor placentation but also by \(\text{AT}_1\) activation in which angiotensin II and \(\text{AT}_1\)-\(\text{AA}_x\) are potentially implicated.

### 6. Placental Hypoxia and Ischemia

Impaired trophoblast invasion and inadequate maternal spiral artery remodelling result in placental ischemia and hypoxia. It is unknown, however, whether abnormal placentation leads to systemic vascular dysfunction and the appearance of preeclampsia.

Defective trophoblast invasion and inadequate maternal spiral remodelling frequently result in intrauterine growth restriction or other complications of pregnancy (preterm labor e.g.) without preeclampsia even to normal full-term pregnancy [53]. Women living in high altitudes have an increased risk of developing preeclampsia [54], while cigarette smoking is associated with a reduced risk for preeclampsia [55]. Experiments in animals suggest that placental hypoxia contributes to preeclampsia by upregulating soluble antiangiogenic factors, inflammatory cytokines, downregulating angiogenic, and vasodilator factors [56].

Furthermore, in pregnant mice, an absence of 2-methoxyestradiol (2-ME), a natural metabolite of estradiol, results in a deficient of catechol-o-methyltransferase (COMT). These animals showed a preeclampsia-like phenotype [57]. The addition of 2-ME was shown to improve preeclampsia and suppress placental hypoxia and sflt-1 expression [57]. It is, however, unclear whether or not decreased COMT is the cause of the consequence of impaired placentation.

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