sFLT1 in preeclampsia: trophoblast defense against a decidual VEGFA barrage?

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Preeclampsia, a life-threatening complication of human pregnancy, has a spectrum of clinical signs and is likely caused by an array of pathological mechanisms. However, elevated levels of soluble fms-like tyrosine kinase-1 (sFLT1) in the placenta and in the maternal circulation has emerged as a common finding in women with preeclampsia and likely is a causative factor in this disorder. In this issue of the JCI, Fan and colleagues provide experimental evidence from both humans and mice that suggests placental trophoblast cells overexpress sFLT1 in self defense against excessive VEGFA produced by maternal decidual cells. The authors’ work thus implicates the decidual cells of the mother as the culprit responsible for increased placental expression of sFLT1, a VEGFA antagonist that enters the maternal circulation and consequently induces the clinical signs of preeclampsia.

The elusive cause of preeclampsia

Preeclampsia is a life-threatening complication of human pregnancy and a leading cause of maternal and perinatal morbidity and mortality worldwide (1). The disorder typically arises in the third trimester and is characterized by maternal hypertension and/or signs of organ dysfunction, including proteinuria, thrombocytopenia, impaired liver function, pulmonary edema, and/or cerebral or visual symptoms (1). Although a definitive cause for preeclampsia remains elusive, theories abound (2). It is now considered likely that failure to identify consistent biomarkers (3) or genetic linkages (4) is because preeclampsia is not a single disease (5). Instead, similar clinical signs are elicited by multiple pathological mechanisms. This conclusion is supported by the diversity of clinical signs and placental pathologies among individuals diagnosed with preeclampsia (6), by the diversity in abnormally expressed genes in placentas from patients with preeclampsia (7), and by the wide range of interventions that evoke preclamptic signs in animal models (8).

Nevertheless, in many preeclamptic pregnancies, maternal circulating levels of soluble fms-like tyrosine kinase-1 (sFLT1) are elevated in late gestation, often before the onset of clinical signs, which suggests that sFLT1 promotes pre-eclampsia (9). Moreover, in animal models, experimental elevation of sFLT1 can evoke preeclampsia-like signs in late gestation (8). Thus, the discovery that sFLT1 promotes preeclampsia was greeted with considerable excitement (10). Placental overexpression of sFLT1, specifically in the fetal-derived trophoblast cells, was implicated as the underlying cause of preeclampsia (11). The next burning question became, what causes fetal-derived trophoblast cells to overexpress placental sFLT1? In this issue, Fan and colleagues turn the tables and provide a body of work that suggests fetal-derived trophoblast cells overexpress sFLT1 in self defense against excessive VEGFA produced by maternal decidual cells (12). Thus, the authors’ study blames the victim, implicating the decidual cells of the mother as the culprit responsible for disease.

Decidual VEGFA overexpression as a cause of preeclampsia

Fan et al. examined VEGFA and sFLT1 expression in decidual cells near the placental interface (i.e., the basal plate) in a cohort of women with preeclampsia. The authors found that VEGFA mRNA expression was augmented specifically in maternal decidual cells, whereas sFLT1 mRNA was highly overexpressed in fetal extravillous trophoblast cells that had invaded the decidua — a normal event in placentaion (12). These in situ hybridization findings were supported by quantitative RT-PCR, which revealed markedly elevated expression of VEGFA and sFLT1 mRNA in basal plate tissue samples. Fan and colleagues next used adenovirus-based gene delivery and developed a murine model with augmented decidual VEGFA expression. Enhanced decidual VEGFA caused pregnant mice to develop preeclampsia-associated signs in late gestation, including increased placental sFLT1 protein and mRNA, increased sFLT1 in maternal serum, and maternal hypertension and proteinuria (12). Intriguingly, this etiology appears to define a specific subtype of preeclampsia, given that basal plate biopsies in other cohorts of preeclamptic women have shown no change in VEGFA mRNA (13) or a marked decrease in VEGFA protein and mRNA (14).

In addition to evoking preeclamptic signs in mice, Fan and colleagues found that decidual VEGFA overexpression halved the number of viable fetuses by late gestation, with fetal survivors being markedly growth restricted (12). Fetal losses appeared to occur in midgestation due to hemorrhaging at the maternal-fetal interface, and placental
histology revealed dilation and engorge-
ment of vessels carrying maternal blood
back into the maternal circulation. The
authors’ work highlights the relevance
of their model to preeclampsia; however,
they importantly point out that decidual
VEGFA overexpression may also under-
lie other pathological outcomes — includ-
ing intrauterine growth restriction, early
pregnancy loss, and placental abruption
— in human pregnancy, where only one
conceptus is the norm (12).

To determine whether the ill effects
of decidual VEGFA overexpression were
caused by the induction of high levels
of sFLT1, Fan and colleagues evaluated
the effects of lentivirus-mediated knock-
down of sFLT1 expression in trophoblast
cells. sFLT1 deficiency in trophoblast cells
resulted in similar hemorrhaging and
venous enlargement, which suggests that
increasing the ligand (VEGFA) and reduc-
ing the antagonist (sFLT1) promotes simi-
lar vascular effects on the venous outflow
vessels of the placenta (12). Moreover,
the combination of both decidual VEGFA
overexpression and sFLT1 knockdown in
placental trophoblast caused greater
placental pathology and fetal death com-
pared with single manipulation. These
results suggest that placental sFLT1 over-
expression sequesters VEGFA, reducing
placental damage caused by VEGFA over-
expression in the adjacent decidua.

Overexpression of sFLT1 only par-
tially rescued phenotypes associated with
overexpression of decidual VEGFA, with
considerable placental pathology even in
venous channels embedded within the
sFLT1-overexpressing junctional zone (15,
16). In mice, the junctional zone is consid-
ered analogous to the trophoblast cell col-
umns of the basal plate in the human pla-
centa (17,18). Both the human trophoblast
columns and the murine junctional zone
are at the decidual interface, are devoid
of endothelial cells, express high levels
of sFLT1, and give rise to invasive cyto-
trophoblast cells (15,17–19). Curiously,
in contrast to preeclamptic pregnancies,
in which maternal plasma sFLT1 may be
elevated several-fold (20), the increase
in maternal plasma sFLT1 caused by
decidual VEGFA overexpression in mice
was modest (~25%). Furthermore, the
increase in sFLT1 occurred after the onset
of maternal hypertension and proteinuria.

These observations raise the question
of whether maternal preeclamptic signs
were actually caused by elevated plasma
levels of sFLT1 in this model, or rather by
some other mechanism.

**Does decidual VEGFA overexpression alter placental endocrine function?**

The decidua and junctional zones are
important endocrine organs during rodent
pregnancy (21–23). The junctional zone
produces multiple prolactins (23), includ-
ing PII (Prl3b1), for example, which in
turn influences ovarian endocrine func-
tion (24). Thus, in addition to altering pla-
cental sFLT1 expression, decidual VEGFA
overexpression could alter expression of a
myriad of important pregnancy hormones,
directly or indirectly. We recently found
that reducing VEGFA expression in the
junctional zone in all mouse conceptuses in
a pregnancy causes maternal hypotension
with no change in placental or maternal
plasma sFLT1 expression, and there was a
surprising increase in maternal plasma
VEGFA (25). Given that blood perfusing
the junctional zone returns in the maternal
venous circulation (16), we speculated that
VEGFA deficiency altered endocrine func-
tion of the junctional zone, thereby alter-
ing endocrine control of the maternal car-
diovascular system (25). Similarly, in the
model developed by Fan and colleagues
(12), it is interesting to question whether
decidual VEGFA overexpression altered
maternal arterial pressure not by placental
sFLT1 release, but by altered decidual and/
or junctional zone endocrine function.

**Does impaired spiral artery remodeling influence preeclampsia?**

Although preeclamptic signs were evoked
in their mouse model, Fan and colleagues
were surprised to find that spiral artery
remodeling and trophoblast invasion into
the decidua were not impaired (12). This
result implies that these abnormalities,
which are typically observed in human
preeclamptic pregnancies (26), may be
independent of increases in placental
sFLT1 production and independent of
maternal signs of preeclampsia, includ-
ing maternal hypertension and pro-
teinuria. This observation is consistent
with prior work that found blunted spi-
ral artery remodeling in diverse human
pregnancy pathologies without signs of
preeclampsia (26), and other studies that
found that failed spiral artery remodel-
ing in mutant mice did not cause pre-
eclamptic signs (27). Thus, the current
study adds to accumulating evidence that
impaired spiral artery remodeling and
reduced trophoblast invasion into the
decidua may play associative rather than
causative roles in preeclampsia.

**Future directions**

In the cohort of human preeclamptic
cases studied by Fan and colleagues,
decidual VEGFA expression in the basal
plate was elevated overall; however, the
authors did not report how often a marked
increase was observed (12). For example,
how many women with preeclampsia had
levels >2 SD above the mean for women
without preeclampsia? Given that prior
reports have not observed an elevation in
basal plate VEGFA (15,14) and that pla-
cental gene expression pathology in pre-
eclampsia has known heterogeneity (7), it
is highly likely that an increase in deci-
udal VEGFA explains only a portion of pre-
eclamptic cases. In future studies, it will
be valuable to examine a larger cohort
of women with preeclampsia in order to
determine how common this etiology is
and to determine whether there is a cor-
relation between decidual VEGFA and
sFLT1 expression, as would be predicted
on the basis of the study by Fan et al.
(12). It would also be valuable to examine
other pathologies associated with human
pregnancy in order to assess the specific-
ity of the association between decidual
VEGFA and preeclampsia. Moreover,
what is the cause for elevated VEGFA in
decidual cells in these patients with pre-
eclampsia? Does it predate pregnancy, or
is it caused by pathological signals from
the implanting conceptus? If the latter is
the case, the underlying causative defect
in preeclampsia would be put back in the
fetal court.

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