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Placental ischemia and soluble fms-like tyrosine kinase 1: Cause or consequence of preeclampsia?

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Elevated circulating soluble fms-like tyrosine kinase 1 (sFLT-1) is associated with the development of the clinical signs and symptoms of preeclampsia. Placental ischemia has been suggested as one of the etiological factors that mediate increased sFLT-1 production in patients with preeclampsia, but definitive evidence for this hypothesis was lacking. Makris *et al.* demonstrate that inducing placental ischemia in primates is sufficient to induce sFLT-1 upregulation and the clinical signs and symptoms of preeclampsia.

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Although the etiology of preeclampsia is still unclear, its manifestations, including endothelial dysfunction, hypertension, and proteinuria, are thought to mediated by high circulating concentrations of antiangiogenic proteins such as soluble fms-like tyrosine kinase 1 (sFLT-1, or sVEGFR1).[1,2] sFLT-1 induces endothelial dysfunction by inhibiting vascular endothelial growth factor (VEGF) signaling, particularly in endothelial cells that are fenestrated and that have constitutive expression of VEGF, such as those that reside in the glomerulus of the kidney (Figure 1). The evidence that sFLT-1 plays a causal role in mediating the clinical symptoms of preeclampsia is gradually accumulating. It includes the following:

(1) Patients with clinical disease have high circulating concentrations of sFLT-1.[3–5] Levels of sFLT-1 are highest among those patients with the most severe forms of the disease, such as in preterm preeclampsia or in those whose infants are small for gestational age (SGA).[5–7]

(2) The levels of sFLT-1 start rising at least 5–6 weeks before the onset of symptoms and reach a peak with the onset of the disease.[7–10]

(3) Increased circulating levels of sFLT-1 are associated with a fall in free VEGF and free placental growth factor (a related proangiogenic molecule) in patients with preeclampsia.[4,11,12]

(4) A fall in sFLT-1 levels following delivery of the placenta correlates with improvement in clinical symptoms.[4] Moreover, the spontaneous resolution of preeclampsia symptoms in pregnant patients with parvovirus-induced hydrops after correction of fetal anemia and hydrops is associated temporally with a fall in circulating sFLT-1 concentrations.[13]

(5) The endothelial dysfunction induced by preeclamptic serum can be reversed by removal of sFLT-1[14] or by addition of excess VEGF in endothelial-cell culture studies.[4]

(6) Elevating sFLT-1 levels in pregnant rats induces hypertension, proteinuria, and glomerular endotheliosis, the hallmarks of preeclampsia.[4]

(7) Anti-VEGF antibodies given to experimental animals lead to glomerular endothelial damage with proteinuria,[15,16] as does genetic deletion of podocyte production of VEGF.[17]

(8) Several risk factors for preeclampsia can be explained by increases in sFLT-1 levels. These include multigestational pregnancies, high-altitude pregnancies, trisomy 13, and nulliparity (Y Bdolah *et al.*, *J Soc Gynecol Investig* 2006; **13**: A670, abstr.).[18–20] Furthermore, a decrease in circulating sFLT-1 levels among smokers may explain the decreased incidence of preeclampsia in this subgroup.[6,21]

(9) The use of VEGF inhibitors in some cancer patients may not only induce hypertension and proteinuria but occasionally produce reversible posterior leukoencephalopathy — a syndrome characteristic of patients with eclampsia.[22–24]

(10) Increased incidence of cardiovascular diseases[25] and relative paucity of solid cancers[26] in patients with a history of preeclampsia may suggest that there may be a persistent antiangiogenic state in these patients.

The etiology of increased sFLT-1 in preeclampsia is still not known. Although the placenta appears to be the major source of circulating sFLT-1,[4,27] other sources, such as activated mononuclear cells, may also contribute to the rise in circulating levels.[28] Whereas the role of sFLT-1 in inducing the maternal syndrome is fairly well understood, its actions in the placenta are still not known. sFLT-1 inhibits trophoblast migration and differentiation *in vitro* and therefore has been hypothesized to be responsible at least in part for the placental abnormalities noted in preeclampsia.[14,29] It is interesting that the maternal circulating levels of sFLT-1 rise toward the end of pregnancy, though not to the extent seen in preeclampsia.[6,7,29,30] It is tempting to hypothesize that this 'normal' production of an antiangiogenic protein is nature's way of slowing and reversing the exuberant placental angiogenesis that marks

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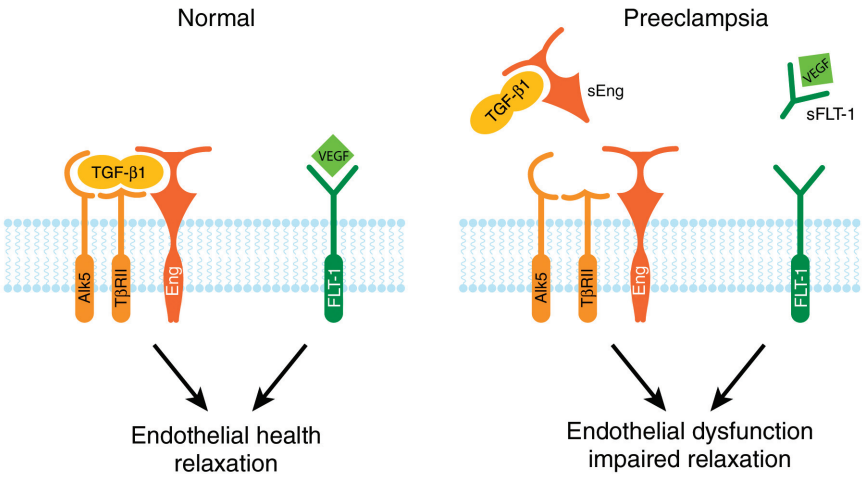

Figure 1 | Soluble fms-like tyrosine kinase 1 and soluble endoglin cause endothelial dysfunction by antagonizing vascular endothelial growth factor and transforming growth factor-β1 signaling. There is mounting evidence that vascular endothelial growth factor (VEGF) and transforming growth factor-β1 (TGF-β1) are required to maintain endothelial health in several tissues, including the kidney and perhaps the placenta. During normal pregnancy, vascular homeostasis is maintained by physiological levels of VEGF and TGF-β1 signaling in the vasculature. In preeclampsia, excess placental secretion of soluble fms-like tyrosine kinase 1 (sFLT-1) and soluble endoglin (sEng) (two endogenous circulating antiangiogenic proteins) inhibits VEGF and TGF-β1 signaling, respectively, in the vasculature. This results in endothelial-cell dysfunction, including decreased prostacyclin, nitric oxide production, and release of procoagulant proteins. Eng, endoglin; sEng, soluble endoglin; FLT-1, fms-like tyrosine kinase 1.

mammalian pregnancy. However, *in vivo* evidence for this hypothesis is lacking. Given that sFLT-1 becomes elevated near the time of clinical disease (usually in the latter half of pregnancy), other factors that impair placentation early in pregnancy may induce placental ischemia/hypoxia that in turn leads to sFLT-1 upregulation. Indeed, sFLT-1 is upregulated in response to hypoxia *in vitro*.[31]

The article by Makris *et al.*[32] (this issue) describes an artificial model of preeclampsia produced in nonhuman primates by decreasing the blood flow to the uteroplacental compartment. These animals develop hypertension and proteinuria that is very similar to the picture of placental ischemia produced in rodents.[33] However, in contrast to rodents, in which evidence of glomerular endotheliosis has not been consistently noted, these primates develop a renal lesion resembling the endotheliosis of human preeclampsia. Fetal growth restriction, a hallmark of preterm preeclampsia but not term preeclampsia, was not noted in this primate model. Very interestingly, the authors report tenfold-increased circulating concentrations of sFLT-1 associated with the appearance of hypertension and proteinuria. These data provide further evidence in favor of sFLT-1 as the mediator of the clinical symptoms of preeclampsia. Furthermore, Makris *et al.*[32] provide direct evidence that preeclampsia can be produced by placental ischemia. Although placental ischemia may not be responsible for all cases of human preeclampsia, the article by Makris *et al.*[32] gives strong evidence that placental ischemia alone is sufficient to induce preeclampsia and that the signs and symptoms of preeclampsia thus induced are mediated by sFLT-1.

This primate model of preeclampsia provides a wonderful opportunity for investigators to test novel therapeutic strategies against sFLT-1, such as VEGF, placental growth factor, or neutralizing antibodies designed to bind sFLT-1. It would be interesting to see whether this model of preeclampsia is also characterized by high circulating concentrations of soluble endoglin, a novel antiangiogenic substance that has been recently shown to synergize with sFLT-1 in the pathogenesis of preeclampsia (Figure 1).[34]

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Evidence mounts for a role of the kidney in lipoprotein(a) catabolism

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Numerous studies have suggested a role of the kidney in lipoprotein(a) (Lp(a)) catabolism, but direct evidence is still lacking. Frischmann *et al.* demonstrate that the marked elevation of Lp(a) observed in hemodialysis patients results from a decrease in Lp(a) clearance rather than an increase in Lp(a) production, consistent with the notion that the kidney degrades Lp(a). More studies are needed to prove the biological relevance.

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Lipoprotein(a) (Lp(a)) consists of a low-density lipoprotein (LDL)-like particle containing one molecule of apolipoprotein B-100 (apoB-100) covalently linked by a sulfhydryl bond to one molecule of apolipoprotein(a) (apo(a)). The carbohydrate-rich glycoprotein apo(a) is highly polymorphic and is formed by variable copies of the kringle 4 domain, one copy of a kringle 5 domain, and an inactive protease domain.

Lp(a) is almost exclusively derived from the liver. Frischmann and co-workers[1] (this issue) compared the *in vivo* turnover rates of both the apoB-100 component and the apo(a) component of Lp(a) by stable-isotope technology in healthy controls and in hemodialysis patients. This work demonstrated that the apoB-containing lipoproteins from which Lp(a) is assembled are almost exclusively a newly synthesized pool derived from the liver in both controls and hemodialysis patients whereas only a very small percentage of Lp(a) is assembled from circulating LDL. Plasma levels of Lp(a) are highly variable; most of the variation is attributed to differences in the Lp(a) production rate controlled by the apo(a) gene locus. Considerable progress has been made in regard to our understanding of Lp(a) assembly and production, but little is known about the sites and mechanisms responsible for Lp(a) clearance (Figure 1).

There is now a considerable amount of evidence supporting the concept that the kidney plays a significant role in Lp(a) clearance. First, Lp(a) plasma concentrations are elevated in patients with impaired renal function,[2] and the degree of Lp(a) elevation inversely correlates with the glomerular filtration rate.[3] Interestingly, the majority of studies have suggested that the high-molecular weight forms of Lp(a) are selectively elevated in patients with impaired renal function. Second, after kidney transplantation in patients with impaired renal function, Lp(a) concentrations generally decrease.[4] Third, Kronenberg and co-workers[5] reported that Lp(a) levels in the renal vein are lower than those in the ascending aorta, suggesting that Lp(a) is removed in the renal circulation. Fourth, Reblin and co-workers[6] showed, in a heterologous rat model, that when Lp(a) is injected in rats, Lp(a) accumulates in the kidney tubules and apo(a) fragments are excreted in the urine. Fifth, patients with impaired renal function have decreased urinary apo(a) excretion.[2] Frischmann and co-workers[1] have extended these observations that support a role of the kidney in the clearance of Lp(a) by demonstrating that hemodialysis patients with impaired renal function have a decrease in Lp(a)

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