ANGIOGENESIS IN PLACENTA FROM NORMAL AND PATHOLOGICAL PREGNANCIES

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The objective of hemochorial placentation for the developing human fetus is penetration of fetal blood vessels into proximity to maternal vessels to create a conduit for nutrient and gas exchange. This phenomenon requires an accelerated process of angiogenesis and invasion by trophoblasts, as well as overcoming the maternal immune system[1]. The mother responds in two ways: first through immune tolerance of the semi-allogenic fetus and second through immune system induction of trophoblast proliferation and invasion. The most dramatic changes are evidenced in widened spiral arteries with increased capacitance and decreased resistance, to facilitate the nutrient and gaseous exchange in need by the developing fetus

Placentation during early human pregnancy occurs when extravillous cytotrophoblasts from anchoring villi invade the decidualised endometrium and myometrium (interstitial trophoblasts) and also migrate in a retrograde direction along the spiral arteries (endovascular trophoblasts) transforming them into large diameter conduit vessels of low resistance. Endovascular trophoblast invasion has been reported to occur in two waves: the first into the decidual segments of spiral arteries at 8-10 weeks of gestation and the second into myometrial segments at 16-18 weeks of gestation[2]. This physiological transformation essential to normal placental function is characterized by a gradual loss of the normal musculo-elastic structure of the arterial wall and replacement by amorphous fibrinoid material in which trophoblast cells are embedded[3]. Human placentation therefore represents remarkable balance between concurrent degradation of the maternal decidual vasculature with highly coordinated angiogenesis presumably directed by the developing embryo.

Angiogenesis, the formation of new blood vessels from pre-existing endothelium, is a complex process necessitating the interactions of numerous cell types that lead to the coordinated development of a complex three-dimensional vascular structure in human placenta. Profound angiogenesis in the placenta is essential as high capacity transport is established between the maternal and fetal circulation. However, in the human, it is notable that little angiogenesis occurs in the maternal tissue while there is obvious capillary growth within the placental villi suggesting a role for locally acting growth factors and angiogenic factors in the regulation of vascular growth[4].

Among the most intensively studied angiogenic factors is the vascular endothelial growth factor family (VEGF) and placental growth factor (PlGF) VEGF immunoreactivity and mRNA encoding this growth factor have been localized in the human placenta[5]. VEGF is an endothelial-specific mitogen that plays a key role in angiogenesis. This process requires vasodilatation, increase in microvascular permeability, protease release, migration and proliferation of endothelial cells and subsequent lumen formation. All these processes are stimulated by VEGF which is chemotactic for endothelial cells. The wide range of important endothelial effects would suggest that this growth factor plays an essential role in both physiological and pathological angiogenesis. Its activities are mediated primarily by interaction with 2 high-affinity receptor tyrosine kinases: kinase-inert domain region (KDR) and fms-like tyrosine kinase-1 (Flt-1) that are selectively expressed on vascular endothelial cell surfaces[6].

Studies of circulating concentrations of VEGF in preeclampsia have reported conflicting results[7]. In studies that have measured free VEGF, not VEGF bound to proteins such as soluble Flt-1 levels were lower in preeclampsia than in controls of similar gestational age[8,9]. Measurements of total VEGF, including VEGF bound to proteins, have shown that concentrations of this angiogenic factor are modestly elevated in preeclampsia[10,11]. However, it appears that only free VEGF is biologically active and available to interact with cell surface receptors and possess relevant angiogenic activity.

Soluble Flt-1 (sFlt-1) has been shown to be increased in the placenta[12] and blood of women with preeclampsia[13]. Serum concentrations in women with normal or preeclamptic pregnancy fall sharply after delivery as would be expected if most circulating sFlt-1 during pregnancy were of placental origin. Levels were higher in preeclampsia with onset before 37 weeks than in preeclampsia of later onset; in severe as compared with mild precelampsia; and in preeclampsia with delivery of a small rather- than appropriate-for-gestational-age infant[9]. sFlt-1 concentrations were positively correlated with the degree of proteinuria, but inversely correlated with platelet count, neonatal birthweight, birthweight adjusted for gestational age, and gestational age of delivery[13]. In contrast, the circulating concentrations of free PlGF are reduced in preeclampsia[14]. Also, serum PlGF concentrations among women who delivered small-for-gestational-age (SGA) infants, but did not develop preeclampsia, were significantly lower than gestational-age matched controls with appropriate-for–gestational-age infants at 33 weeks, but not at 17 or 25 weeks[15].

In the continuing search for fundamental insights into placental angiogenesis, we have for the first time identified the mRNA expression and secretion of angiogenin, a single chain 14-kDa non-glycosylated polypeptide in normal placenta in a gestational dependent manner. Further investigations revealed overexpression of this angiogenic peptide in placentae of patients presenting with preeclampsia and fetal growth retardation. The role of these vasculogenic factors remains unknown at present but could be attributed to the ability to circumvent the poor oxygenation resulting from defective fetoplacental blood flow by autoregulation and could serve as positive feedback regulators to induce neovascularization in these compromised pregnancies.

References

1. Red-Horse K, Zhou Y,Genbarev O et al. Trophobloast differentiation during embryo implantation and formation of maternal-fetal interphase. J Clin Invest 2004; 114: 744-754.
2. Pijnenborg R, Bland JM, Robertson WB, Brosens I. Uteroplacental changes related to interstitial trophoblast migration in early human pregnancy. Placenta 1983; 4: 397-413.
3. Bernischke K, Kaufmann P. Pathology of the human placenta (Bernischke K, Kaufmann P, eds.) 3rd edition; Springer-Verlag Inc., New York, USA, 1995.
4. Hanahan D, Folkman J. Patterns and emerging mechanisms of the angiogenic switch during tumorigenesis. Cell 1996; 86: 353-364.
5. Clark DE, Smith SK, Licence D et al. Comparison of expression patterns for placenta growth factor, vascular endothelial growth factor (VEGF), VEGF-B and VEGF-C in the human placenta throughout gestation. J Endocrinol 1998; 159: 459-467.
6. Dvorak HF. Vascular permeability factor/vascular endothelial growth factor: a critical cytokine in tumor angiogenesis and a potential target for diagnosis and therapy. J Clin Oncol 2002; 20: 4368-4380.

7. Waite LL, Atwood AK, Taylor RN. Preeclampsia, an implantation disorder. Rev Endocr Metab Disord 2002; 3: 151-158.
8. Maynard SE, Min JY, Merchan J et al. Excess placental soluble fms-like tyrosine kinase 1 (sFlt1) may contribute to endothelial dysfunction, hypertension and proteinuria in preeclampsia. J Clin Invest 2003; 111: 649-658.
9. Levine RJ, Maynard SE, Qian C et al. Circulating angiogenic factors and the risk of preeclampsia. N Engl J Med 2004; 350: 672-683.
10. Kupferminc MJ, Daniel Y, Englender T et al. Vascular endothelial growth factor is increased in patients with preeclampsia. Am J Reprod Immunol 1997; 38: 302-306.
11. Bosio PM, Wheeler T, Anthony F et al. Maternal plasma endothelial growth factor concentrations in normal and hypertensive pregnancies and their relationship to peripheral vascular resistance. Am J Obstet Gynecol 2001; 184: 146-152.
12. Tsatsaris V, Goffin F, Munaut C et al. Overexpression of soluble vascular endothelial growth factor receptor in preeclamptic patients: pathophysiological consequences. J Clin Endocrinol Metab 2003; 88: 5555-5563.
13. Chaiworapongsa T, Romero R, Espinoza J et al. Evidence supporting a role for blockade of the vascular endothelial growth factor system in the pathophysiology of preeclampsia. Am J Obstet Gybnecol 2004; 190: 1541-1547.
14. Torry DS, Mukherjea D, Arroyo J et al. Expression and function of placenta growth factor: implications for abnormal placentation. J Soc Gynecol Invest. 2003; 10: 178-188.
15. Bersinger NA, Odegard RA. Second and third-trimester serum levels of placental proteins in preeclampsia and small-for-gestational-age pregnancies. Acta Obstet Gynecol Scand 2004; 83: 37-45.