Emerging Roles of Antiangiogenic and Angiogenic Proteins in Pathogenesis and Prediction of Preeclampsia

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Hypertensive disorders are a major cause of maternal and fetal death, especially in developing nations, with the pregnancy-specific disease preeclampsia-eclampsia responsible for most of this mortality. Preeclampsia, recognized by ancient Greeks, was only sporadically investigated until late last century, current literature still labeling this disorder a “disease of theories.” Thus, not surprisingly, we have started the new millennium unable to predict or prevent preeclampsia, and management strategies remain but supportive, with pregnancy termination still the only definitive “therapy.” This may be about to change, as focused research, mainly in the past decade, has resulted in dramatic progress regarding pathogenesis of disease manifestations and risk assessment, while investigators have begun designing and testing definitive therapy.¹ There are still a myriad of uncertainties and unanswered questions to address, but here we summarize the extent of 1 new and exciting chapter in preeclampsia research: the roles of angiogenic and antiangiogenic factors, to which an article in this issue by Rana and colleagues,² contributes.

A landmark report published in 2003 set the stage for all that followed.³ Dr Karumanchi’s laboratory, previously involved in renal cancer research, changed its focus to the kidney in preeclampsia. Using microarray chip technology, they probed gene expression profiles in placentas of women with preeclampsia and those with uncomplicated pregnancies. Of course many differences were noted, but one that caught the investigators’ attention was upregulation of the mRNA for the antiangiogenic protein soluble fms-like tyrosine kinase 1 (abbreviated as sFlt-1 or sVEGFR-1) in placentas from women with preeclampsia. Aware that de novo hypertension involved vasodilatation in vitro, further demonstrating that sEng increased vascular permeability in mice. But even more exciting was that the simultaneous overexpression of sFlt-1 and sEng in gravid rats resulted in severe hypertension, marked proteinuria, liver enzyme abnormalities, and circulating schistocytes, an animal model simulating most of the protean manifestations of severe preeclampsia in humans.⁷ Of interest, this second finding linked an antiangiogenic factor to another area of preeclampsia research, NO,² as sEng impairs transforming growth factor β1 (TGF-β1), whose concentrations were also increased in the placenta and maternal circulation during preeclampsia.⁷ Of interest, this second finding linked an antiangiogenic factor to another area of preeclampsia research, NO,² as sEng impairs transforming growth factor β–binding to the endothelium receptor, and should thus decrease endothelial NO synthase (eNOS) mediated vasodilatation. The investigators again showed that sEng, like sFlt-1, could explain why sera from women with preeclampsia inhibit both angiogenesis and arteriolar vasodilatation in vitro, further demonstrating that sEng increased vascular permeability in mice. But even more exciting was that the simultaneous overexpression of sFlt-1 and sEng in gravid rats resulted in severe hypertension, marked proteinuria, liver enzyme abnormalities, and circulating schistocytes, an animal model simulating most of the protean manifestations of severe preeclampsia in humans.

To sum up, the studies described above did not identify the etiology of preeclampsia, but the data did explain the patho-
genesis of key phenotypic features, including some related to its severest forms. In essence, the bench had provided for a logical approach to assess prediction, and eventually prevention or treatment. Indeed, commencing in 2004, the results in a number of reports (reviewed by Levine et al)\(^4\) suggest that measurements of circulating or urinary proteins associated with the angiogenic state (blood, sFlt-1; sEng, PlGF; urine, sEng, PlGF) reliably predict preeclampsia. The most striking data were those of Levine et al\(^4\) who combined sEng levels and the ratio sFlt-1:PlGF and succeeded in predicting preeclampsia (particularly severe disease) \(\simeq 10\) weeks before the onset of clinical signs and symptoms, with odd ratios \(\simeq 30\) in some instances. A note of caution, however, is that studies, to date, have been largely retrospective and cross sectional, and in those reporting the most striking results the sera analyzed had been stored for \(\simeq 10\) years.\(^4\) Thus, prospective observational studies are critically in order, and several are now in progress, including a World Health Organization protocol that aims at recruiting 10,000 participants.

One question that perplexed investigators was the following: The most plausible hypothesis regarding the initiating cause of preeclampsia, and thus the stimulus for excess production of antiangiogenic proteins, is the presence of abnormal placentalation. This process takes place between gestational week 11 to 18, but neither sFlt-1 nor sEng concentrations appear elevated during this period (though decrements in PlGF and sEng have been noted). Here is where the study by Rana et al\(^2\) may provide insight. These authors show that between week 11 to 13 and 17 to 20 sFlt-1 levels remain essentially stable, and circulating sEng actually decreases during uncomplicated gestations, whereas both values increase in women destined to develop preeclampsia. These findings, as well as data of others,\(^8\) imply that stimuli for sFlt-1 and sEng overproduction may well begin during placentalation, though more serial data would be needed to verify this. Incidentally, Rana et al\(^2\) assayed samples stored from 2 trials, one completed 10 years ago, the other with samples obtained many years later, and the similar values in the control groups finally provide data on the stability of the long stored samples.

Vattan et al.,\(^8\) and now Rana and colleagues,\(^2\) suggest that changes over time in circulating antiangiogenic and angiogenic protein levels can be used to identify patients who are at risk for developing preeclampsia. Obviously, large studies are required to determine whether these approaches can achieve the likelihood ratios required for a useful prediction test. Recall that tests with high false-positive rates are potentially harmful, especially when they lead to unnecessary interventions, whereas an excessive false-negative rate may lead the clinician to a false sense of security. There are two potential pitfalls to consider in the quest toward acceptable likelihood ratios. First, an “antiangiogenic state” may underlie other pregnancy complications such as growth restriction, and second, smaller increments in sFlt1 and/or sEng levels may cause preeclampsia phenotypes in patients with “prepared” endothelium such as women with diabetes, and/or chronic hypertension.

Now that we may have reconciled concerns that stimuli for antiangiogenic overproduction were not associated with abnormal placentalation, what might they be? Space precludes discussing the “usual suspects” like relative hypoxemia including genes stimulated by the hypoxic environment, as well as inflammation, including cytokines and antioxidants. Newer candidates as mediators of the excess antiangiogenic state are the presence of agonistic autoantibodies to the angiotensin I receptor, abnormalities in the immune system involving natural killer cells in the decidua,\(^10,11\) and perhaps thrombin.\(^12\) Time will declare some of these or other candidates as winners, but it is pleasing to see a disorder neglected through the ages, and a “disease of theories” in contemporary texts, receiving the scrutiny of such good scientists.

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### References

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