Progress Toward Identifying Potential Markers for Preeclampsia

Role of Agonistic Autoantibody to the Angiotensin II Type I Receptor

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As early as 20 weeks of gestation, preeclamptic women develop new-onset hypertension with proteinuria and display increased circulating factors, ranging from metabolic and proinflammatory to antiangiogenic in nature. These factors have been shown in various experimental models to possibly contribute to the development of hypertension in response to placental ischemia.1–4 A major focus of preeclamptic research has been the identification a molecular marker that could be used to predict early in gestation the development of this disease. Two potential factors associated with the development of preeclampsia are the imbalance of angiogenic factors (vascular endothelial growth factor/placental growth factor) and the antiangiogenic factor (soluble fms-like tyrosine kinase 1 [sFlt-1]), as well as agonistic autoantibody to the angiotensin II type I receptor (AT1-AA).3–5

The AT1-AA has been purified, and specificity for the second extracellular loop of the angiotensin II type I receptor (AT1R) has been demonstrated by Western blotting, colocalization, and coinmunoprecipitation experiments.5 The AT1-AA induces signaling in vascular cells, including activating protein 1, calcineurin, reactive oxygen species, and nuclear factor κB activation, which are blocked by an AT1R antagonist.5–9 In addition, the AT1-AAs appear to be responsible for other effects among different tissues, including stimulation of interleukin 6 production from mesangial cells, and most recently our laboratory has demonstrated AT1-AA activation of the endothelin pathway in human endothelial cells and in pregnant rats.9,10

Clinical studies indicate that both plasma and amniotic fluid concentrations, as well as placental sFlt-1 mRNA, are increased in preeclamptic patients.2 Moreover, increases in plasma levels of sFlt-1 in pregnant rodent models lead to pathophysiological alterations that mimic many of the characteristics observed in women with preeclampsia.2,3 Thus, these studies suggest that sFlt-1 may contribute to the pathophysiology observed in preeclampsia. However, the exact mechanism responsible for sFlt-1 overexpression has yet to be clearly elucidated (Figure).

Previous studies by Zhou et al11,12 demonstrated that AT1-AA from preeclamptic women induces sFlt-1 production via AT1R and calcineurin/nuclear factor of activated T-cell signaling. The authors demonstrated by injecting the IgG or affinity-purified AT1-AAs from women into pregnant mice caused hypertension, proteinuria, glomerular endotheliosis, placental abnormalities, intrauterine growth restriction, and elevated sFlt-1.12 The onset of these symptoms was prevented by an AT1R antagonist or an AT1-AA–neutralizing 7-amino acid epitope-binding peptide.12 Most recently, in agreement with the Xia laboratory, we have confirmed that AT1-AA infusion increased blood pressure and plasma sFlt-1 in pregnant rats.13

Although these studies suggest a potential interaction between AT1-AA and sFlt-1, a clear association among AT1-AA, sFlt-1, and severity of the disease in women has never been fully established. Much uncertainty about this relationship was only heightened by recent clinical studies by Stepan et al,14 who found that, whereas most preeclamptic patients expressed high sFlt-1 and the AT1-AA, in a population of patients characterized by reduced uterine perfusion and no other pregnancy complications, there was no association between the AT1-AA and sFlt-1. In these cases, sFlt-1 was not elevated when AT1-AA was frequently present.

In this issue of Hypertension, Siddiqui et al15 clearly demonstrate that the titer of AT1-AA not only correlates with the severity of the disease but that there was a strong correlation between AT1-AA activity and sFlt-1 in severe preeclampsia. In this study, the authors use a newly developed sensitive and high-throughput luciferase bioassay to determine the presence of the AT1-AA. In contrast to previous publications from our laboratories4–7,10,13 in which we used the cardiomyocyte contraction assay to detect the presence of AT1-AAs among preeclamptic women and several rat models of preeclampsia, Xia et al15 reported increased luciferase activity from IgG-treated CHO.AT1.luc cells, indicating AT1R activation mediated by elevated AT1-AAs. Both assays use the 7 amino acid blocking peptide inhibiting the antibody interaction with the epitope binding sequence of the AT1R.

Using this sensitive bioassay to quantify AT1-AA activity in patients, Xia et al15 provide compelling evidence that AT1-AA is present in nearly all women diagnosed with preeclampsia. Importantly, the authors distinguish greater AT1-AA activity in patients with severe preeclampsia compared with those with mild preeclampsia. However, because the AT1-AA was only measured at 1 stage of gestation, it is uncertain whether measurement of the AT1-AA could be used early in gestation as a marker for the disease. Furthermore, in contrast to previous
publications by Dechend et al.6,7 Xia et al15 demonstrate the presence of AT1-AA, average stimulation of 14±3% over basal, in half of pregnant nonhypertensive patients examined in the study. The increased sensitivity of this new bioassay could be one potential weakness that could lead to false positives in this patient population. Importantly, Xia et al15 report the AT1-AA in women with gestational hypertension in the absence of sFlt-1, thus indicating a possible association of the AT1-AA with other pregnancy-related hypertensive disorders. Future studies are critical in determining the presence of AT1-AAs among normal pregnant nonhypertensive women not only to corroborate their preliminary findings but also to determine the assay’s utility to measure the AT1-AA among preeclamptics. Thus, future studies using either of these bioassays to determine the AT1-AA early in gestation and possibly its relevance as a potential marker to identify women that could develop pregnancy-related hypertensive disorders are critical for this area research.

Although the findings of Xia et al15 demonstrate a significant correlation of AT1-AA activity with severity of the disease in humans and concurs with previous recent experimental studies demonstrating that AT1-AA induces features of preeclampsia, many unanswered questions still exist. Although we have reported that placental ischemia and inflammatory cytokines are important stimuli for AT1-AA, the antigenic stimulus for AT1-AA production is still unknown (Figure). Moreover, the pathway of production of the AT1-AA, such as T-cell dependent versus T-cell independent, has yet to be elucidated. Furthermore, it is unclear how early in gestation the onset of AT1-AA production occurs. Studies inhibiting the production of the AT1-AA in pregnant animal models of preeclampsia are also necessary to advance our understanding of the pathophysiological role of the autoantibody during pregnancy. A better understanding of the pathophysiology of AT1-AA production in preeclampsia may lead to novel therapeutic targets for the treatment of the disease and/or a marker for predicting patient risk of developing preeclampsia.

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Disclosures
None.

References
13. Parrish MR, Murphy SR, Keiser S, Ray LF, Dechend R, Martin JN, Granger JP, LaMarca B. Soluble fms-like tyrosine-1 (sFlt-1) production is enhanced during hypertension in response to tumor necrosis factor-alpha (TNF-α) and agonistic autoantibodies to the angiotensin II type I receptor (AT1-AA) [abstract]. Presented at the Central Association of Obstetricians and Gynecologists Meeting; October 25–28, 2009; Maui, Hawaii.

Figure. Potential role for AT1-AA in the pathophysiology of preeclampsia. Agonistic AT1-AAs stimulate in response to placental ischemia play an important role in the generation of reactive oxygen species, production of sFlt-1, and enhanced endothelin 1 and angiotensin II sensitivity, thereby contributing to the development of hypertension during pregnancy.
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