Progress Toward Identifying Potential Markers for Preeclampsia

Role of Agonistic Autoantibody to the Angiotensin II Type I Receptor

Babbette LaMarca

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 preeclampsic 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 coimmunoprecipitation 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 endothelial lysis, 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 preeclampsic 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

The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.

Correspondence to Babbette LaMarca, Departments of Obstetrics and Gynecology and Physiology, Division of Maternal Fetal Medicine, University of Mississippi Medical Center, 2500 North State St, Jackson, MS 39216-4505. E-mail bblamarca@physiology.umsmed.edu

Hypertension is available at http://hyper.ahajournals.org

DOI: 10.1161/HYPERTENSIONAHA.109.141465
lead to novel therapeutic targets for the treatment of the disease and/or a marker for predicting patient risk of developing preeclampsia.

Sources of Funding
This work was supported by an American Heart Association Scientist Development grant (0835472N).

Disclosures
None.

References
13. Parrish MR, Murphy SR, Keiser S, Ray LF, Dechend R, Martin JN, Granger JP, LaMarca B. Soluble Flt-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.
Progress Toward Identifying Potential Markers for Preeclampsia: Role of Agonistic Autoantibody to the Angiotensin II Type I Receptor
Babbette LaMarca

Hypertension. 2010;55:236-237; originally published online December 7, 2009;
doi: 10.1161/HYPERTENSIONAHA.109.141465

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2009 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/55/2/236

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/