Correspondence

Letter by Escudero et al Regarding Article, “Elevated Placental Adenosine Signaling Contributes to the Pathogenesis of Preeclampsia”

To the Editor:

We greatly enjoyed reading the study published by Iriyama and colleagues in which they increased placental adenosine by the placental-specific knockout of adenosine deaminase (ADA−/−), resulting in a preeclampsia-like syndrome in mice. Because we are very interested in this topic, it is gratifying to see data supporting a role for elevated placental adenosine as a cause rather than an effect of preeclampsia. The authors elegantly dissect mechanisms showing that the ADORA2B receptor is relevant to the demonstrated maternal and fetal changes. Further support for this pathway comes from an animal model of preeclampsia induced by autoantibodies to the angiotensin II type 1 receptor where increased placental adenosine forms part of the pathophysiology. Relevance to humans was indicated by a higher activity of the enzyme CD73 (which generates adenosine) and increased adenosine in placentas from preeclampsia.

It is tempting to consider these detailed mechanisms as perhaps the final common pathway to preeclampsia. However, some of these observations need to be reconciled with available literature. For instance, they did not find elevated adenosine concentrations in maternal plasma, which have been reported as a feature of human preeclampsia. Other factors that could increase local adenosine concentrations, including equilibrative nucleoside transporters (ENTs), have been reported by others but were not considered relevant in the current study.

What is also intriguing is when and how the apparent prosurvival signal mediated by ATP and adenosine is transformed into a deadly signal. The findings suggest an adenosine threshold, because the preeclampsia-like syndrome was present only when half of the progeny lack ADA in the placenta, but was not observed when 25% of progeny was expected to be ADA−/−. Part of the explanation may also include a shift from activity of proteins with high adenosine affinity (ie, ADORA2A or ENT1), toward those with low adenosine affinity (ie, ADORA2B or ENT2). This shift might result in the paradox of high adenosine concentrations associated with low adenosine–mediated response.

Another issue that needs to be reconciled is whether the impaired placental angiogenic process observed in mice is also present in human placentas, because current literature is contradictory. According to Iriyama’s report, potential mechanisms for impaired placental angiogenesis include adenosine-mediated release of sFlt-1, which would seem detrimental to placental vascularization. However, the potential proangiogenic role of adenosine in the placenta via synthesis and release of vascular endothelial growth factor is also present in preeclampsia. Therefore characterization of adenosine-mediated placental angiogenesis is needed.

Despite these discrepancies, we applaud this elegant report for the first time provides evidence linking adenosine with the pathophysiology of preeclampsia. We do believe, however, that it is unlikely that a single aberration of the adenosine pathway explains the role of adenosine or that the abnormalities of this pathway will be the common pathophysiological denominator for all preeclampsia. We encourage future research to generate a better understanding of the pleiotropic physiological and pathophysiological roles of adenosine during normal pregnancy and preeclampsia for which this elegant study is certainly a good start.

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Disclosures

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Carlos Escudero, MD, PhD
Vascular Physiology Laboratory
Group of Investigation in Tumor Angiogenesis (GIANT)
Department of Basic Sciences
Universidad del Bio-Bio
Chillán, Chile

Leslie Myatt, PhD
Center for Pregnancy and Newborn Research
University of Texas Health Science Center San Antonio
San Antonio, TX

James M. Roberts, MD
Magee-Womens Research Institute
Departments of Obstetrics, Gynecology and Reproductive Sciences, Epidemiology, and Clinical and Translational Science Institute
University of Pittsburgh, PA

References


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