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ADAM12: The Usual Suspect in Preeclampsia

Hemant Kulkarni[1,2]*

[1]*Texas Biomedical Research Institute, San Antonio, Texas, USA*
[2]*Lata Medical Research Foundation, Nagpur, India*

Abstract

Burgeoning evidence is now pointing towards a potential role of the *ADAM12* gene in preeclampsia. A closer scrutiny of this evidence, however, shows that many important questions remain unanswered. As a result, the genetic jigsaw of preeclampsia is a poser far from solved. Continued efforts are required to investigate this gene, especially in the context of its involvement in the transforming growth factor signaling pathway.

Introduction

Enquobahrie et al. [1] recently reported in the Journal that expression of the A Disintegrin and Metalloproteinase 12 (*ADAM12*) gene in the placenta is increased in preeclampsia as compared to normotensive women. This finding further substantiates an emerging theme from several other observations that *ADAM12* expression may be an early biomarker of preeclampsia – a condition as common as 3-7% of all pregnancies and one which is still associated with substantial fetal and maternal mortality [2-4]. In this context, as the epidemiological evidence in favor of a potential role of *ADAM12* in preeclampsia implants itself firmly in literature [5], it becomes important to understand the realities and ramifications of this association.

ADAM12 partakes in the transforming growth factor-β (TGF-β) signaling pathway [6,7] and is involved in the processing of growth factors, regulating the dynamic equilibrium of cytokine levels and signaling mediated by insulin-like growth factor receptors [8-11]. The ADAM12 protein comes in two alternatively sliced flavors – the shorter form is secreted (ADAMS12s) and detectable in serum while the longer form stays bound to the cell membrane [12]. ADAM12 regulates the cell-cell and cell-matrix interactions that are a hallmark of fertilization and uterine receptivity to blastocyst implantation [13,14]. However, which of the two forms of ADAM12 might be operational in the pathophysiology of preeclampsia is unclear. The obvious advantage of a serum-based biomarker such as ADAM12s is offset by two factors. First, the reduction of ADAM12s during the first trimester has not been consistently observed by all. There are studies that have shown that ADAM12s is reduced [15-17] or unchanged [18,19] in women with preeclampsia as compared to controls. Second, the reduction associated with ADAM12s during the first trimester is not specific to preeclampsia but can also be seen in other conditions such as aneupoidy, trisomy 21, trisomy 18 and gestational growth retardation [17,18,20-25].

On the other hand, whether and how the serum levels of ADAM12s correlate with the expression of the membrane bound form (especially in the placenta) of *ADAM12* is not clear. It has been found [26] that the maternal serum levels and the coelomic fluid levels of ADAM12s do correlate with each other suggesting a common syncytiotrophoblastic origin but direct evidence for a correlation (or a lack thereof) between the expression of soluble and membrane-bound forms is needed. In that regard it is interesting that the study by *Enquobahrie et al* [1] shows an upregulation of the placental *ADAM12*. This finding is in agreement with the recent observation that there occurs widespread DNA hypomethylation (and consequent upregulation of gene expression of several genes including the *ADAM12* gene) in women with preeclampsia. Interestingly, this observation brings out the possibility – a conjecture that needs to be tested in future studies – that there may be a simultaneous increase in the placental expression of *ADAM12* combined with a decrease in the serum ADAM12s levels due to a shift of operational balance in the alternative splicing mechanism. If this hypothesis is true, more genetic insights can be had from concurrent studies involving both the secreted and membrane-bound isoforms of ADAM12.

Together, the existing evidence cannot be considered to be adequate to recommend ADAM12s as a biomarker of preeclampsia at present. On the other hand, the consistency with which several authors have found *ADAM12* alterations in preeclampsia cannot be ignored. Considering the gestational threats proffered by preeclampsia, it is important that the search for its biomarkers must continue [27]. However, we must also realize that in a living organism no endogenous molecule acts on its own – the molecules are part of coordinated, synchronized and orchestrated signaling mechanisms. Some molecules, like the ADAM12, can appear to be commonly altered in specific conditions but the centrality of these molecules in the pathway should be studied in its entirety. These Usual Suspects must obviously be the first ones to be interrogated but their sleeping partners in crime must also be investigated or, at least, understood. We may be in for surprises since the central molecules in a pathway are only the tips of the iceberg – as researchers, we need to fathom the wholesomeness of the iceberg.

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***Corresponding author:** Hemant Kulkarni, 12023 Waterway Rdg, San Antonio, TX 78249, USA, Tel: 1-210-602-5537; Fax: 1-210-558-3177; E-mail: hkulkarn@txbiomedgenetics.org

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