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Decidual natural killer cells: A critical pregnancy mediator altered in preeclampsia

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Preeclampsia (PE) is a pregnancy specific disease that occurs in 5–10% of pregnancies worldwide [1,2]. The disease is characterized as hypertension after the 20th week of pregnancy associated with new-onset proteinuria, and/or thrombocytopenia, impaired liver function, renal insufficiency, pulmonary edema, or cerebral disturbances in the absence of proteinuria [3]. Chronic immune activation is another defining characteristic of PE that contributes significantly to the pathophysiology of the disease. Numerous immune cell types, including T cells, B cells, and natural killer (NK) cells have been implicated in contributing to the vascular dysfunction, intrauterine growth restriction and hypertension that occurs in PE.

A distinct population of NK cells, termed decidual NK (dNK) cells are the most abundant immune cell type present at the maternal-fetal interface during early pregnancy and placentation. Decidual natural killer cells (dNK) make up 70–90% of the uterine leukocytes and are the most abundant maternal leukocyte population during the first trimester in human pregnancy [4,5]. dNK cells are thought to have multiple roles in human pregnancy [5,6]. dNK cells interact closely with trophoblast cells and secrete cytokines that promote trophoblast growth and mediate trophoblast differentiation, invasion, and spiral artery remodeling [6,7]. dNK cells also have roles in the maintenance of angiogenic balance through secretion of VEGF and PlGF and maintenance of maternal-fetal tolerance throughout pregnancy. dNK cells recognize HLA antigens on fetal trophoblasts which protect them from cytotoxic targeting. In PE, a shift in the dNK phenotype occurs, however the regulatory mechanisms of dNK in PE are poorly understood.

In this article of *EBioMedicine*, Zhang, et al. examine the role of TGFβ1 in modulating dNK cell activation during PE [8]. The study reported increased populations of dNK, T regulatory cells (T_{Regs}) and higher levels of TGFβ1 in the decidua of preeclamptic women compared to normal pregnant control patients. Furthermore the increased TGFβ1 secreted by the T_{Regs} suppressed the cytotoxic and angiogenic function of dNK cells. Importantly, it was noted that the function of both the T_{Reg} and dNK populations were altered in PE. Other studies have also demonstrated altered function of T_{Regs} in PE [9], and the regulation of dNK cells by T_{Regs} has been studied in earlier periods of normal pregnancy [6,10]. Yet, less attention has focused on how the altered T_{Reg} population might lead to alterations in dNK cells, a critical regulator of angiogenesis and vessel remodeling in pregnancy.

The findings in this study demonstrate the need for additional research focused on these altered immune cell populations as potential therapeutic targets in PE. The delicate immune balance that is required for a healthy pregnancy poses some issues for targeting these cells. The complexity of communication and crosstalk between decidual cells requires a more clear understanding of the normal function of dNK cells in early *vs.* late pregnancy and the comparison of these changes in PE before we can move forward with targeting these cells. Clinical studies are needed to determine baseline cytotoxic and angiogenic function of dNK cells from normal and preeclamptic pregnancies. Additionally, experimental studies using *in vitro* and appropriate animal models of PE that mimic the phenotypic changes observed in clinical studies could be utilized to elucidate the mechanisms that are altered in PE. Basic science studies would initiate the identification of new targets and development of novel strategies that could eventually improve management and outcomes associated with PE.

This study by Zhang et al. has provided insight into what will likely be a complex network of communication and interaction between decidual cells (immune and non-immune) during the development and progression of PE [8]. The impact of aberrant function of T_{Regs} in this disease has translated into the abnormal phenotype of a dNK cells. The critical role of dNKs in the establishment and maintenance of pregnancy early on has now been expanded to realize that the proper activation of these cells is also critical later in gestation. The findings make even more of a case for understanding the role of dNKs throughout pregnancy and especially during pregnancy complications such as PE. It is certainly possible that dNK cells will make useful targets for therapeutics to ensure proper placentation, vessel remodeling, and pregnancy progression. The next focus in this area of research would be to gain an increased understanding of how this population is regulated so that we can take advantage of mechanisms to restore proper activation and balance for a successful pregnancy.

Conflict of interest

The authors declare no conflict of interest.

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Authors' contributions

DCC wrote the initial draft of the manuscript. DCC and KW edited and approved the final draft of the manuscript.

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