Dendritic cells in the circulation of women with preeclampsia demonstrate a pro-inflammatory bias

Objective:
Toll-like receptors (TLRs) are central components of the innate immune system that recognize both microbial ligands and host products released during tissue damage. Data from epidemiologic studies and animal models suggest that inappropriate activation of the immune system plays a critical role in the development of preeclampsia. This study evaluates in a systematic fashion the expression and function of TLRs in the circulation of patients with preeclampsia compared to healthy pregnant controls.

Methods:
We evaluated TLR expression and function in primary dendritic cells (DCs) of 30 patients with preeclampsia (gestational age 37-41 weeks) and 30 gestational age-matched healthy pregnant controls. DCs were stimulated with ligands engaging TLR1/2, TLR2/6, TLR3, TLR4, TLR5, TLR8 for myeloid (mDC) and TLR1/2, TLR2/6, TLR7, and TLR9 for plasmacytoid (pDC) populations. The expression of TLR-induced production of TNF-α, IFN-α, IL-6, and IL-12 were measured by multicolor flow cytometry.

Results:
We found substantial decreases in women with preeclampsia compared with healthy pregnant controls in TNF-α, IL-6, and IL-12 (p40) production in mDCs and in TNF-α and IFN-α production in pDCs in response to TLR3, TLR4 ligands in mDCs and TLR9 ligand in pDCs. These differences were highly significant after adjustment for heterogeneity between women with preeclampsia and healthy pregnant controls (e.g., gender, race, body mass index, number of comorbid medical conditions) using mixed-effect statistical modeling. Basal expression of TLR3, TLR4 and TLR9 (but not TLR1/2, TLR2/6, TLR5, TLR7, or TLR8) was significantly increased in DCs isolated from women with preeclampsia. Preeclamptic DCs also expressed significantly higher basal levels of cytokines (TNF-α, IL-6, IL-12 in mDCs and TNF-α, IFN-α in pDCs).

Conclusion:
Under basal conditions (in the absence of TLR ligand stimulation), DCs from preeclamptic individuals express higher levels of select TLRs (3, 4, and 9) and produce more pro-inflammatory cytokines as compared with healthy controls. As such, the ability of these cells to mount an inflammatory reaction in response to a TLR ligand is limited. These data demonstrate a dysregulated pattern of cytokine production in preeclamptic patients. Further studies are underway to determine whether these differences predate the clinical manifestations and whether they are causally related to the syndrome.