TIM-3/GALECTIN-9 IN NORMAL PREGNANCY AND IN EARLY-ONSET PREECLAMPSIA

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Introduction

T cell immunoglobulin domain and mucin domain (TIM)-3, which was initially identified on terminally differentiated Th1 cells, negatively regulates the T cell response by inducing T cell apoptosis. Multiple immune cells expressing TIM-3 including Th1, Th17, NK cells, NKT cells, dendritic cells, monocytes therefore it has been implicated both in activation and inhibition of immune responses. A growing body of evidence supports the critical role of TIM-3 receptor as modulators of the immune response in transplant tolerance. Identification of Galectin-9 (Gal-9) as a ligand for TIM-3 has established the Gal-9/TIM-3 pathway as an important negative regulator of Th1 immunity and tolerance induction. Data about the role of TIM-3/Gal-9 pathway in the pathogenesis of human diseases is emerging, but data about their role during human pregnancy is still not clear. The aim of our study was to investigate the expression of Galectin-9 and TIM-3 molecules and the possible role of Gal-9/TIM-3 pathway in healthy human pregnancy and in early-onset preeclampsia.

Methods of study

We involved 30 healthy pregnant women [first trimester (n=10); second trimester (n=10); third trimester (n=10)], 27 pregnant woman with early-onset preeclampsia and 15 non-pregnant control women in our study. We determined the TIM-3 receptor surface expression by cytotoxic T cells, NK cells and NK cell subsets and Gal-9 expression by regulatory T cells by flow cytometry. We measured the cytokine production and cytotoxicity of TIM3+ and TIM3- CD8 T and NK cells by flow cytometry. Serum Gal-9 levels were measured by ELISA.

Results

Our results show that the numbers of NK and CD8 T cells and their TIM-3 expression do not change during healthy pregnancy. Compared to non pregnant individuals, regulatory T cells show higher level of Galectin-9 expression as pregnancy proceeds, which is in line with the data obtained analyzing sera for soluble Gal-9. TIM-3+ CD8 T cells and NK cells show different cytokine production and cytotoxicity during pregnancy compared to non pregnant group. Analyzing peripheral lymphocytes of women with early onset preeclampsia, we detected decreased TIM-3 expression by CD3 T cells, CD8 T cells and NK cells compared with healthy pregnant women. We further demonstrated increased cytotoxic activity by CD8 T- and CD56dim NK cells in women with early-onset preeclampsia.

Conclusion

Our results indicate that the Gal-9/TIM-3 pathway could play an important role in the maintenance of healthy pregnancy. Furthermore the altered Gal-9 and TIM-3 expression could result in an enhanced systemic imflammatory response including the activation of Th1 lymphocytes and type-1 bias in early onset preeclampsia.

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