IMMUNE TOLERANCE

A mother's greatest gift is TIM3

Human embryos express paternal antigens that render the fetus semi-allogeneic, and to reduce the risk of pregnancy loss we have evolved mechanisms that promote maternal–fetal tolerance. Decidual natural killer (NK) cells are known to have regulatory functions during pregnancy, but the role of peripheral NK (pNK) cells in pregnancy is unclear. Now, Li and colleagues show that TIM3⁺ (T cell immunoglobulin and mucin domain-containing protein 3) pNK cells can protect against pregnancy loss.

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TIM3 is a regulator of T helper 1 (T_H1) cell immunity and NK cell functions. To investigate the role of TIM3 in maternal–fetal tolerance, the authors took blood from pregnant women. During the first trimester, TIM3⁺ NK cells transiently increased in number in peripheral blood. In contrast to TIM3[−] NK cells, TIM3⁺ NK cells had an immunosuppressive phenotype; they produced an increased amount of anti-inflammatory cytokines (transforming growth factor- β 1 (TGF β 1), IL-10 and IL-4), a decreased amount of pro-inflammatory tumour necrosis factor (TNF) and exhibited a lower degree of cytotoxicity.

To exert its immunoregulatory effects, TIM3 interacts with its ligand galectin 9. pNK cells isolated from blood taken during the first trimester of pregnancy and treated with recombinant galectin 9 had an increased production of anti-inflammatory cytokines, decreased production of TNF and showed reduced cytotoxicity. These effects were blocked by treatment with anti-TIM3 antibody. In addition, western blotting analysis and experiments with kinase inhibitors suggested that the galectin 9–TIM3 interaction induces an immunosuppressive phenotype through the activation of JUN N-terminal kinase (JNK) and AKT signalling pathways.

Importantly, pNK cells isolated from patients with recurrent miscarriage had a substantially decreased surface abundance of TIM3. Compared with TIM3⁺ NK cells from control donors, TIM3⁺ NK cells from patients with recurrent miscarriage produced lower levels of anti-inflammatory and higher levels of pro-inflammatory cytokines and had enhanced cytotoxicity. Furthermore, these patients had alterations in the accessibility of genes that encode for key inflammatory cytokines. Notably, the *TGFB1* and *IL10* genes were less accessible. TGF β 1 is important for promoting the differentiation of naïve CD4⁺ T cells into regulatory T (T_{reg}) cells. TIM3⁺ NK cells from donors with normal pregnancy were able to induce T_{reg} cell differentiation *in vitro* when co-cultured with CD4⁺CD25[−] T cells; however, TIM3⁺ NK cells from patients with recurrent miscarriage did not. Taken together, these data suggest that TIM3⁺ NK cells from patients with recurrent miscarriage have reduced immunosuppressive activity and this may contribute to allogeneic rejection of the fetus.

To confirm the importance of TIM3⁺ pNK cells, the authors treated normal pregnant mice and abortion-prone mice with anti-TIM3 antibody, which substantially reduced litter size and reduced resorption rate in both groups of mice. Furthermore, the adoptive transfer of TIM3⁺ pNK cells from control mice into abortion-prone mice reduced the rate of fetal loss. Last, the adoptive transfer of TIM3⁺ pNK cells from control mice into NK cell-deficient mice also reduced the rate of fetal loss.

In summary, this work suggests that a galectin 9–TIM3 signalling axis regulates pNK cell function during pregnancy to promote maternal–fetal tolerance. The authors suggest that TIM3⁺ pNK cells could be a potential biomarker for the prediction of recurrent miscarriage.

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“TIM3⁺ NK cells from patients with recurrent miscarriage have reduced immunosuppressive activity”

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