Experimental Maternal Cytokine Prophylaxis Protects from Fetal Neural Tube Teratogenesis Through an NK Cell Mediated Mechanism

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Background

It has been postulated that the maternal immune system provides surveillance for early fetal teratogenic events. However, little information exists regarding the types of maternal immune cells or cell signaling mechanisms that are needed for fetal protection.

Research Objectives

Given the abundance of NK cells at the maternal-fetal interface, we hypothesized that augmentation of maternal NK cell function provides protection against fetal teratogenesis.

Methods

We challenged this hypothesis in a murine model of valproic acid (VA)-induced fetal neural tube teratogenesis (NTT). VA-induced teratogenesis was induced in pregnant dams at E8. To evaluate protection from NTT’s, maternal NK cells were either selectively eliminated (mAb PK136) or functionally augmented (IFNg) prior to VA administration (E7). Litters were harvested on E14 and prevalence of NTT compared between each treatment group and untreated controls. The experiments were performed in a CD1 (outbred) model. Blood samples were taken prior to mating, prior to VA injection and at harvest. Flow cytometry was performed on these samples examining NK cell, T-cell, B-cell and Monocyte levels.

Results

• All NK cell-depleted litters were affected by fetal NTT. This was significantly higher when compared to litters of saline-treated age-matched control dams (100% vs 83.8%; p<0.05).
• Conversely, IFNg-augmented litters were less likely to be affected by NTT (66.7%). Animals given IFNg alone had no NTT and normal litter sizes.
• Dams given IFNg, PK136 (E7) and VA (E8) again had 100% of litters affected by NTT.

Limitations

• Mouse model may have translational limitations in humans.
• IFNg is a broad immune activator.
• Mechanism for how IFNg activates NK cells not yet elucidated in this model.

Conclusions

• Maternal cytokine prophylaxis provides protection from NTTs and may be a clinically relevant strategy. This protection appears to be mediated specifically by maternal NK cells. Further studies are needed to define the mechanisms by which maternal NK cells recognize and prevent aberrant fetal development.