Name of Trainee: Alice Lu (alice.lu@yale.edu)
Mentors: Akiko Iwasaki (akiko.iwasaki@yale.edu)
Type of Trainee: MD-PhD Student

Title: Maternal immune activation promotes the development of fetal neural tube defects
AY Lu-Culligan, LJ Yockey, S Pope, A Iwasaki. Yale School of Medicine.

Background: In utero infection by TORCH pathogens such as Zika virus are associated with poor neurodevelopmental outcomes such as neural tube defects (NTDs) in pediatric patients. However, it remains unclear which aspects of fetal damage are due to direct infection by the pathogen vs. indirect consequences of the maternal immune response to infection. Recently, maternal immune activation (MIA) has been linked to a number of neuropsychiatric disorders such as autism and schizophrenia. We hypothesized that exposure to MIA at earlier stages of gestation could lead to structural brain defects rather than behavioral abnormalities.

Methods: We developed a mouse model of MIA that leads to a high rate of structural birth defects such as NTDs in offspring. Pregnant mice were injected with either control PBS or double-stranded RNA to activate maternal antiviral responses and offspring were examined for prevalence of NTDs. Tissues at the maternal-fetal interface, including fetal brain, were analyzed by RNA-seq and stained for immune markers. Experiments using knockout mice and antibody-mediated depletion of immune cell populations were performed to determine which pathways modulate risk for the development of birth defects in offspring following MIA.

Results: While type I interferon signaling is known to impact susceptibility to fetal demise, Ifnar1−/− mice were nonetheless vulnerable to NTD development. Antibody-mediated depletion of adaptive immunity (T and B cells) or NK cells during MIA was not able to rescue NTD development in poly(I:C)-treated pregnancies. We found that the activation of antiviral maternal immunity in our model leads to distinct increases in cytokine and chemokine levels circulating in maternal serum and a major restructuring of the maternal-fetal interface. Neural progenitors are directly impacted by maternal antiviral responses with a decrease in proliferation but no change in apoptosis at the fetal neural tube following exposure to MIA.

Conclusions: Clinical and epidemiological data have long suggested a potential role for maternal immune responses in mediating the pathogenesis of structural birth defects, including those seen as part of TORCH syndrome; this work provides insights as to how pathogen-independent activation of antiviral maternal innate immunity may lead to structural anomalies in offspring.

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