Maternal Immune Activation alters Hematopoietic Stem Cell Development in Murine Placenta and Fetal Liver

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Maternal immune activation (MIA) increases the risk for schizophrenia and symptoms of autism spectrum disorders (ASD) in the offspring. In pregnant mice, MIA can be induced by respiratory infection or by the administration of poly(I:C), a synthetic, double-stranded RNA that triggers an anti-viral inflammatory response (Shi et al., 2003). A single intraperitoneal injection of poly(I:C) on embryonic day (E)12.5 induces behavioral deficits in the offspring that are associated with schizophrenia and ASD. The cytokine IL-6 is critical in mediating the behavioral and transcriptional changes observed in these offspring (Smith et al., 2007). In addition to behavioral deficits, the adult offspring display dysregulated peripheral immunity. Elevated levels of IL-17 and IL-6 are produced by CD4+ T cells from lymph nodes and spleens of adult MIA offspring. Similar abnormalities are observed in CD4+ T cells isolated from spleens of young and newborn MIA offspring. Shortly after MIA, cytokine levels in the placenta, maternal serum, amniotic fluid and fetal brain are altered. Recent reports demonstrate that this time of poly(I:C) injection, E12.5, marks the onset of placental hematopoietic stem cell (HSC) expansion (Mikkola et al., 2005) as well as HSC seeding of the fetal liver (Mikkola et al., 2006). Embryonic HSCs express cytokine and toll-like receptors and may therefore respond to poly(I:C) directly or to poly(I:C)-induced proinflammatory cytokines (McKinstry et al., 1997; Nagai et al., 2006). Thus, MIA may initiate the dysregulation of peripheral immunity in the offspring by affecting the early development of the immune system at key sites during embryogenesis. Studying the effects of MIA on the placenta and fetal liver, important HSC niches, may therefore elucidate the genesis of peripheral immune dysregulation.

To test our hypothesis that MIA alters HSC development, we are examining the effects of MIA on the abundance, differentiation and transcriptional programming of HSCs from the placenta and fetal liver at 24 and 72 hours post poly(I:C) injection. Preliminary data reveals an increase in CD41+ placental HSCs from E12.5 to E15.5. However, compared to saline controls, poly(I:C) placentas harbor fewer CD41+ HSCs on E15.5. Similarly, poly(I:C) reduces the *in vitro* differentiation of the murine R1 embryonic stem cell line into HSCs . ELISAs show that, compared to saline controls, sera from poly(I:C) placentas have upregulated IL-6 while poly(I:C) fetal livers have upregulated IL-6 and IL-17. Thus, poly(I:C) and/or inflammatory cytokines may affect HSC development during embryogenesis.

We have recently sorted CD34+/c-kit+ HSCs from the placenta and fetal liver of control and MIA offspring and are examining differential lineage priming of HSCs using markers associated with particular hematopoietic multipotent progenitors. We will also test the effects of poly(I:C) and inflammatory cytokines on isolated placental and fetal liver HSCs *in vitro*. By evaluating the effects of MIA on embryonic HSC self-renewal, differentiation, homing, and premature exhaustion of the HSC pool, we hope to gain insights into the long-term implications of MIA on immune dysregulation in schizophrenia and ASD.

References

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