

The Role of Inflammatory Cytokines in Altered Fetal Neural Progenitor Proliferation and Differentiation

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Infection and inflammation during pregnancy are correlated with adverse neurological outcomes in the child. A growing body of research suggests that inflammatory mediators can directly alter the behavior of neural progenitor cells (NPCs) in the adult brain. **Objective:** The goal of this study is to investigate the effect of maternal inflammation on fetal neural NPC proliferation and differentiation and to determine if specific cytokines are responsible for alterations in normal fetal neurogenesis. **Methods:** Pregnant rats were given intraperitoneal LPS on E13, and injected with BrdU on E16 to label neuronal progenitors in S-phase. On postnatal day 7 (P7) the fraction of BrdU+ neurons in the cortex were measured in pups. To determine the effect of selected cytokines on progenitor proliferation and differentiation *in vitro*, rat and mouse fetal NPCs were cultured with cytokines, and the fraction of S-phase cells were examined by BrdU labeling. **Results:** P7 rat pups from dams exposed to LPS on E13 and labeled with BrdU on E16 show a reduction in the number of neurons in cortical layer V that were born on E16. In both rat and mouse fetal progenitor cultures, treating cells with TGF β reduces the mitotic index, measured by BrdU incorporation. In rat cultures TGF β also decreases the production of cells with a neuronal phenotype, while in mouse cultures TNF α , and not TGF β , reduces neuronal differentiation, and MCP-1 increases the fraction of cells with a glial phenotype. **Conclusions:** Our BrdU birth-dating data suggest that maternal inflammation triggered at E13 results in a reduction in cortical neuron birth in the fetus at E16. *In vitro* treatment of NPCs with different cytokines show that TGF β is capable of inhibiting NPC proliferation and that TGF β and TNF α can inhibit differentiation of progenitors into neuronal cells. We are currently investigating the cytokine profile in maternal serum and fetal brain to see if these cytokines are increased, and whether treatment of dams with TGF β and/or TNF α is sufficient to reproduce alterations in fetal neurogenesis.

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