Cytokines Make an Indelible Impression on Neural Stem Cells

Elise C. Cope[1] and Elizabeth Gould[2,*]
[1]Department of Biomedical Sciences, Florida State University College of Medicine, Tallahassee, FL 32306, USA
[2]Department of Psychology, Princeton Neuroscience Institute, Princeton University, Princeton, NJ 08544, USA
*Correspondence: goulde@princeton.edu
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Infections during pregnancy have been associated with increased risks of neuropsychiatric disorders in offspring, although the underlying mechanisms have not been determined. Gallagher et al. (2013) show that maternal exposure to the infection-induced inflammatory cytokine IL-6 produces lasting effects on forebrain stem cell pools of offspring during embryogenesis and throughout life.

For many decades, a link between maternal infection during pregnancy and a predisposition to develop mental illness in the offspring has been debated. Evidence suggests that prenatal infection by diverse microbial pathogens, including viruses, bacteria, and parasites, can increase the incidence of neuropsychiatric diseases, such as schizophrenia (Boksa, 2008). Although not without controversy, enough studies support this association to warrant attention and further investigation. Some infectious agents, such as the rubella virus, are known teratogens and can affect fetal development through direct infection. Other contagions, however, likely have an indirect effect on embryogenesis. Given the vast array of pathogens that seem to predispose the fetus to develop mental illness later in life, it seems likely that a factor involved in the maternal response to infection may be a common mechanism. In this regard, cytokines are likely candidates. Cytokine levels increase during infection and elevated cytokine levels in pregnant women appear to be a risk factor for the development of mental illness in the offspring (Miller et al., 2011). If prenatal cytokines contribute to the emergence of mental illness in offspring at a time years after birth, they must do so by inducing long-lasting changes. In this issue of *Cell Stem Cell*, Gallagher and colleagues (2013) provide an example of such a change, identifying a role for interleukin 6 (IL-6), an inflammatory cytokine that is increased during maternal infection, in regulating forebrain neural precursors during embryogenesis and through adulthood. This work may suggest a general mechanism whereby maternal infection increases the risk of mental illness in progeny.

In this study, the authors found that a single injection of exogenous IL-6 during pregnancy produced long-lasting alterations in the size, composition, and localization of neural progenitor pools in the forebrains of fetal mice. These changes, demonstrated using immunolabeling for various markers of proliferating cells in vivo and in vitro, persisted well into adulthood of the progeny. In the mouse, most adult-born subventricular zone (SVZ) stem cells proliferate, migrate, and undergo differentiation into different types of olfactory bulb interneurons (Young et al., 2007). A maternal surge in IL-6 not only resulted in a surprising 2-fold enhancement of olfactory bulb neurogenesis in adulthood, but it also altered the proportionate phenotypes of these adult-born cells by exclusively increasing the number of calretinin-positive olfactory neurons. The authors then performed in utero electroporation-based lineage tracing experiments, inducing expression of a fluorescent protein in embryonic neural progenitor cells and their daughter cells. Using this approach, they showed that embryonic exposure to IL-6 enhanced the number of postnatal progenitors contributed by the developing dorsal cortex, doubling the number of fluorescent cells in the adult SVZ.

The researchers went on to show that the IL-6-induced deregulation of stem cell and progenitor cell proliferation is not the result of a broad inflammatory response, as maternal injection of the proinflammatory agent interferon-γ does not produce similar changes (Gallagher et al., 2013). Since IL-6 is generally thought of as an inflammatory cytokine, these results led the authors to explore the noninflammatory mechanisms that IL-6 might employ to alter forebrain stem cell pools. While it has been previously reported that there are fewer proliferating cells in the adult SVZ in the absence of IL-6 (Bowen et al., 2011), Gallagher et al. (2013) provide evidence that IL-6 directly promotes expansion of embryonic neural progenitor cells in the cortex and ganglionic eminence. The authors not only showed an effect of exogenously administered IL-6, but they also demonstrated a novel function for this cytokine during normal forebrain development. Using transgenic mice as well as a series of carefully constructed in vitro studies of forebrain progenitor cells, they showed that IL-6 is secreted by these progenitors during development and acts in an autocrine/paracrine manner to regulate the composition of the neural progenitor cell pool. They further showed that this IL-6-mediated regulation occurs through direct activation of the heterodimer gp130/IL-6 receptor complex on embryonic forebrain stem cells. Thus, the transient maternal surge of IL-6 produced by exogenous administration disrupts normal neural progenitor cell homeostasis by providing excess ligand. Consistently, IL-6 injection caused hyperactivation of this endogenous signaling pathway, resulting in enhanced downstream activation of the JAK-STAT pathway in the stem cell progeny. Ultimately, these changes had a profound and lasting impact on embryonic and subsequent adult stem cell pools by enhancing the number of self-renewing, mulitpotent stem cells (Figure 1).

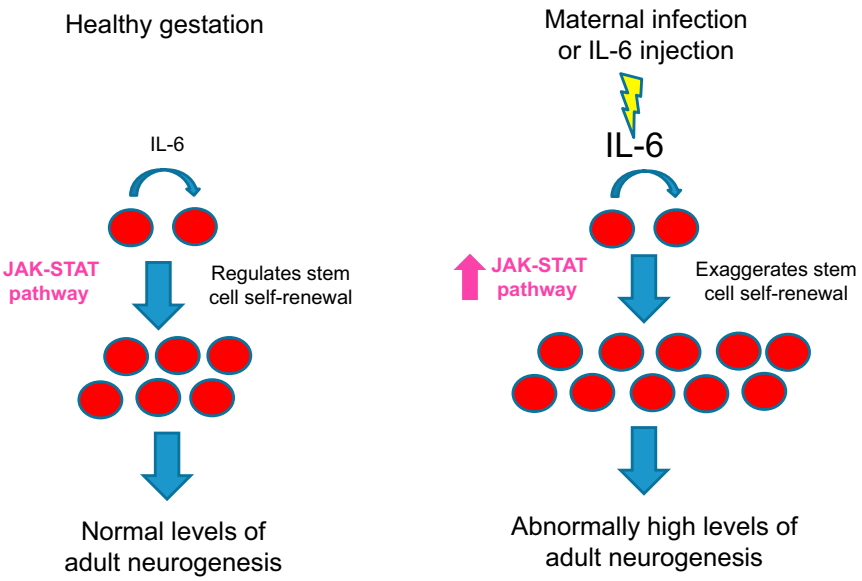

Figure 1. IL-6 Injection Persistently Enhances Adult Neurogenesis
During healthy fetal development (left), IL-6 is released by stem cells (red circles) where it has an autocrine/paracrine effect and regulates stem cell self-renewal. Physiologic levels of IL-6 activate the JAK-STAT pathway to regulate embryonic production of forebrain stem cells, which contribute new neurons to the olfactory bulb throughout adulthood. In the presence of excess IL-6 as a result of experimental injection or maternal infection (right), the JAK-STAT pathway is hyperactivated and greater numbers of stem cells are produced. The expanded stem cell pool generates more of one neuronal subtype throughout adulthood, persistently altering both the quantity and quality of adult neurogenesis.

Prenatal perturbations, such as alcohol and stress exposure, have been shown to exert a lasting influence on postnatal and adult neurogenesis in the hippocampus (Coe et al., 2003; Uban et al., 2010) of progeny. Maternal IL-6, however, did not measurably alter cell proliferation or neurogenesis in the hippocampus of offspring, suggesting inherent differences between these two populations of stem cells. Stem cells of the hippocampal subgranular zone arise from different embryonic progenitors than the stem cells of the SVZ (Li et al., 2013), and these two populations produce discrete classes of neurons with different phenotypes in the adult brain. The current work provides further evidence that these stem cells pools are intrinsically different and that the mechanisms governing their establishment and maintenance are distinct.

These findings raise questions about the behavioral consequences of IL-6-induced changes in forebrain progenitor cell composition. While not directly examined in this study, previous work has linked prenatal IL-6 exposure to schizophrenia-like behaviors in adult mice (Smith et al., 2007). It remains unclear whether these behaviors are driven by alterations in forebrain neural progenitors, and, in the case of mice, by changes in the population of adult-generated neurons in the olfactory bulb. Although it may seem intuitive that functional deficits would result from reduced numbers of neural progenitor cells, IL-6 might exert a detrimental influence through increasing the number of newborn neurons. The extent to which the prenatal IL-6-induced effects observed in mice mimic the effects of a gestational cytokine surge in humans remains unknown. Even though the significance of adult neurogenesis in the human olfactory bulb remains controversial (Bergmann et al., 2012), it is possible that the results of Gallagher et al. (2013) obtained in mice hint at a similar cytokine-driven mechanism that has a lasting effect on progenitor cells in other brain regions in humans, including ones likely to be compromised in neuropsychiatric disease.

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