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Brief Commentary

How cytokines leave their mark: The role of the placenta in developmental programming of brain and behavior

Staci D. Bilbo *

Duke University, Durham NC 27708, USA

Every year pregnant women are urged to receive their "flu" vaccines, as immune changes during pregnancy may lend them especially vulnerable to infection. Prior to the twentieth century, the primary causes of death and morbidity were infectious diseases, notably influenza and tuberculosis. With modern medicine, these deadly diseases have been steadily replaced with chronic diseases, including heart disease, cancer, and neuropsychiatric disorders (e.g., depression). Accordingly, a large shift in biomedical research has changed the focus away from communicable pathogen transmission and towards the identification of factors that precipitate vulnerability to chronic, costly diseases. Diet, stress, and genetics are most often viewed as the leading culprits.

In this issue of *Brain, Behavior, and Immunity*, Hsiao and Patterson (2011) elegantly establish that infections, despite the low risk of death, nonetheless leave their enduring mark upon us. Their paper adds to a growing literature on fetal programming, in which experiences during the perinatal period may modulate or "program" the normal course of development. This programming causes changes in newborns that persist as they mature into adolescents or adults, including disease resistance and psychopathology risk that may not appear for years, (Barker et al., 1995; Bilbo and Schwarz, 2009). The authors expand on their previous findings that IL-6 is a critical mediator of enduring pathological and behavioral changes in mice exposed prenatally to maternal viral infection or to the viral mimetic, poly I:C. These behavioral changes are striking in their similarity to the schizophrenia and autism literatures (Smith et al., 2007).

The authors' primary goal was to trace the path by which maternal infection transduces a cytokine signal to the fetal brain, with a focus on the placenta as the physiological interface between mother and fetus. This was no easy task – there are two immune systems at play that continually change throughout pregnancy. The placenta has a dual origin, with both fetal and maternal compartments, each with its own population of resident leukocytes (Hauguel-de Mouzon and Guerre-Millo, 2006). The authors used a clever knockout strategy to identify immune cells within the maternal decidua as the key physiological component. The novel finding was that without the maternal cells' ability to produce IL-6, the fetal consequences of poly I:C exposure were completely absent. The authors rightly concluded that some type of leukocyte in the fetal compartment of the placenta responds to an elevated cytokine signal from the maternal compartment. This response leads to downstream modification of growth factors, such as insulin-like growth factor, (IGF-I), that are important for fetal development. Therefore, the fetal immune response faithfully mimics the maternal immune response, presumably "programming" the offspring for life (and in this case, pathology). Of course, this finding begs an answer to the obvious question: *Why does the placenta not confer greater protection of the fetus*? The fact that the initial inflammatory stimulus lies within the maternal compartment may help answer this question. That is, a balance is clearly struck during pregnancy between the needs of the mother (in this case, the need to fight the infection) and the needs of the fetus (which remain unclear in terms of immune signaling). However, we do know that pro-inflammatory cytokine expression is a normal (and necessary) component of blastocyst implantation and placental growth (Hauguel-de Mouzon and Guerre-Millo, 2006), just as it is for fetal brain growth (recently reviewed by Deverman and Patterson (2009)). Thus, because cytokines are critical for *normal development*, they are perfectly positioned to play a pivotal role in *abnormal development*.

So where do we go from here? Infections are here to stay, and anti-cytokine therapy is risky for pregnant women given their known (and unknown) physiological functions, such as those involved in protective immunity. However, before allowing these findings to strike fear into the minds of pregnant women everywhere, a broader perspective is needed. Unlike animal studies that often produce a unilateral treatment effect and therefore are useful in discovering mechanisms, only a small percentage of infants delivered from humans exposed to harmful microorganisms during pregnancy develop psychopathology. Why is this the case? Exactly how do placental growth factors affect the brain of the developing fetus? Much remains to be explored. One interesting topic the authors did not investigate is the sex bias that occurs in both autism and schizophrenia (males > females). Many of the genes expressed in the fetal compartment of the placenta are sex-specific (Clifton, 2010). Furthermore, there are sexually dimorphic responses within the placenta to environmental factors such as stress and high fat diets (Pankevich et al., 2009), suggesting the same may be true for infections. The finding of Hsiao and Patterson on the impact of viral infection on IGF-I was very interesting because of the emerging literature on fetal programming of adult obesity and the metabolic syndrome (Simmons, 2008). These data suggest that maternal infection, and perhaps systemic

* Fax: +1 919 660 5798.
E-mail address: staci.bilbo@duke.edu

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inflammation in general, may impact a broad array of adult health outcomes due to considerable convergence within cytokine and hormone signaling pathways (e.g., IGF-I, leptin; Kelley, 2004). For instance, the pro-inflammatory consequences of early-life infection may not lead to schizophrenia, which is good. Instead, it might be a propensity towards metabolic syndrome, which is not so good. Perhaps most important is the need to understand which co-occurring maternal factors, like stress or poor nutrition, can impact cytokine transmission within the placenta, and how these environmental stimuli interact with postnatal and later life events such as maternal care, subsequent infections, stress, or trauma. In sum, which combinations of factors confer greater risk or resilience to later pathology? A consideration of cytokines from the immune system and their inflammatory cousins should be front and center in this discussion.

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