

## Journal Club

**Editor's Note:** These short reviews of a recent paper in the *Journal*, written exclusively by graduate students or postdoctoral fellows, are intended to mimic the journal clubs that exist in your own departments or institutions. For more information on the format and purpose of the Journal Club, please see [http://www.jneurosci.org/misc/ifa\\_features.shtml](http://www.jneurosci.org/misc/ifa_features.shtml).

## Maternal Infection and the Offspring Brain

Amaicha Mara Depino

European Molecular Biology Laboratory, Mouse Biology Unit, 00016 Monterotondo, Italy

Review of Meyer et al. (<http://www.jneurosci.org/cgi/content/full/26/18/4752>)

Infections are a common complication of pregnancy that can lead to miscarriage and stillbirth. Epidemiological studies have associated infections caused by virus and bacteria (e.g., influenza, diphtheria, pneumonia, varicella-zoster) with adult brain disorders, including schizophrenia, autism, mental retardation and cerebral palsy. This association is not limited to a single etiological agent, suggesting that it may be mediated by factors that are common to all infections. The primary host response to infection is inflammation: the recruitment of immune cells that, in turn, release cytokines and other immunological molecules on site and to the blood stream. Cytokines released by the maternal immune system can cross the placenta and enter the fetal circulation. It is well known that cytokines can modulate neuronal proliferation, survival, differentiation, and function. Thus, cytokines released by the maternal immune system (and/or the placental or fetal immune system) in response to infection may be responsible for the interaction between maternal infection during pregnancy, altered neuronal development, and mental diseases.

The recent *Journal of Neuroscience* paper by Meyer et al. (2006) tested the hypothesis whether the effects of infection during pregnancy depend on the stage of

development of the fetus and/or the maternal inflammatory response. To this aim, a synthetic analog of double-stranded RNA (polyriboinosinic-polyribocytidylic acid, PolyI:C) was injected in mouse dams at two stages of pregnancy, on gestation day 9 (GD9; mid-gestation) and GD17 (late gestation). PolyI:C is used experimentally to model viral infections because it stimulates the antiviral activities of the innate immune system (including cytokine production and induction of fever), without the confounding effects of viral infection.

PolyI:C challenge resulted in pronounced elevation of both proinflammatory and anti-inflammatory cytokines in the maternal serum [Meyer et al., their Fig. 7 (<http://www.jneurosci.org/cgi/content/full/26/18/4752/F7>)] that were accompanied by changes in cytokine protein levels in the fetal brain [Meyer et al., their Fig. 8 (<http://www.jneurosci.org/cgi/content/full/26/18/4752/F8>)]. The changes in cytokine mRNA levels in the fetal tissue showed that fetal brain cells can sense maternal infection at both gestational periods, but an increase in fetal cytokine expression only was observed at GD17 [Meyer et al., their Fig. 9 (<http://www.jneurosci.org/cgi/content/full/26/18/4752/F9>)]. Some proinflammatory cytokines (e.g., TNF- $\alpha$  and IL-1) can induce neuronal differentiation and survival *in vitro*. However, the pattern of expression of cytokine receptors and intracellular signaling pathways during brain development is largely unknown. Thus, we can only speculate about the consequences of

changes in cytokine levels on the fetal brain.

Meyer et al. [their Figs. 3 (<http://www.jneurosci.org/cgi/content/full/26/18/4752/F3>), 4 (<http://www.jneurosci.org/cgi/content/full/26/18/4752/F4>), and 5 (<http://www.jneurosci.org/cgi/content/full/26/18/4752/F5>)] showed, in fact, that the timing of prenatal infection affected the hippocampus. Juvenile brains from mice subjected to maternal inflammation at GD9 showed reduced Reelin expression and neurogenesis. Mice exposed to PolyI:C at GD17, on the contrary, showed no significant reduction in Reelin, but had reduced neurogenesis in the outer granular layer of the dentate gyrus (DG) and increased apoptosis in the DG. Reduced Reelin immunoreactivity in postmortem brains is associated with several neuropsychiatric diseases with a presumed neurodevelopmental origin (schizophrenia, bipolar disorder, and depression). Increased apoptosis in postmortem brains has been associated with autism. On the other hand, the changes induced in neurogenesis show that early inflammation can result in long-lasting effects on neuronal turnover. Whether this phenomenon is also common in human diseases will be interesting to examine.

Cytokines can act on central neurons that affect learning and behavior. After midgestational inflammation, adult offspring showed reduced exploration of the center of the open field [Meyer et al., their Fig. 1 (<http://www.jneurosci.org/cgi/content/full/26/18/4752/F1>)]. The lack of differences among treatments during the first 5 min of the test, however, suggests

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Correspondence should be addressed to Amaicha Mara Depino, European Molecular Biology Laboratory, Mouse Biology Unit, Campus "A. Buzzati-Traverso," Via Ramarini 32, 00016 Monterotondo (Rome), Italy. E-mail: depino@embl.it.

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that this was not attributable to increased anxiety-related behavior. In fact, Meyer et al. (2005) characterized the behavioral alterations of adult offspring challenged at GD9 and suggested multiple psychotic-like behavioral deficits. The behavioral consequences of infection at late pregnancy are much less known. Meyer et al. [their Fig. 2 (<http://www.jneurosci.org/cgi/content/full/26/18/4752/F2>)] showed that inflammation at GD17 resulted in perseverative memory. However, Zuckerman and Weiner (2005) showed opposite effects (i.e., increased switching) in rats challenged with PolyI:C at GD17. The use of additional behavioral tests and the study of the neuronal basis of these behavioral alterations would help to distinguish between the long-term consequences of midgestational and late-gestational immune activation on adult brain function.

The interaction between genes and environment guides development. Meyer et al. (2006) underline the importance of timing of this interaction on the long-term consequences to the animal. That such a common phenomenon (i.e., infection during pregnancy) can have different maladaptive consequences on the adult organism, places cytokines as a putative etiological factor for a variety of diseases. The data linking cytokine expression during development and adult brain pathology is, however, correlative. The use of

different cytokine receptor knock-out mice would help to reveal whether (and which) cytokines mediate the effects of maternal infection on brain development. How could cytokines induced by prenatal infection lead to adult neuropathology?

Peripheral cytokine elevation induces a set of behavioral and physiological changes collectively known as “sickness behavior.” Although PolyI:C treatment does not result in prolonged sickness, the possibility that acute inflammation in the dams is sufficient to precipitate later maternal care changes cannot be entirely excluded. In fact, maternal behavior can modulate Reelin expression, neurogenesis, apoptosis in the hippocampus and anxiety-related behavior in adulthood (Weaver et al., 2006 and references therein). Characterization of maternal care after infection and/or cross-fostering studies would allow the distinction between the effects of prenatal infection and the perinatal maternal influence. Moreover, further experiments could reveal whether the molecular mechanisms that mediate long-term consequences of maternal care (e.g., DNA methylation) also cause late effects of prenatal inflammation.

Cytokines can activate the hypothalamic–pituitary–adrenal axis resulting in increased glucocorticoid levels in the peripheral bloodstream. Prenatal or early

life stress can trigger disruptions of fetal neurodevelopment and result in adult anxiety-related behavior in rodents (Weinstock, 2005). The use of different cytokine or glucocorticoid receptors knock-out mice would allow to characterize the role of each of these molecules during prenatal infection, and to reveal whether infection and mental stress share common pathways that can affect brain wiring.

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