Experimental Neurology xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Experimental Neurology

journal homepage: www.elsevier.com/locate/yexnr

Beyond infection - Maternal immune activation by environmental factors, microglial development, and relevance for autism spectrum disorders

Staci D. Bilbo [a,*], Carina L. Block [b], Jessica L. Bolton [c], Richa Hanamsagar [a], Phuong K. Tran [a]

[a] Pediatrics and Neuroscience, Harvard Medical School, Lurie Center for Autism, Massachusetts General Hospital for Children, Boston, MA 02126, United States
[b] Psychology and Neuroscience, Duke University, Durham, NC 27708, United States
[c] Pediatrics and Anatomy/Neurobiology, University of California-Irvine, Irvine, CA 92697, United States

ARTICLE INFO

Article history:
Received 23 January 2017
Received in revised form 26 June 2017
Accepted 5 July 2017
Available online xxxx

Keywords:
Developmental programming
Air pollution
Environmental toxins
Neurodevelopmental disorders

ABSTRACT

Immune molecules such as cytokines and chemokines and the cells that produce them within the brain, notably microglia, are critical for normal brain development. This recognition has in recent years led to the working hypothesis that inflammatory events during pregnancy, e.g. in response to infection, may disrupt the normal expression of immune molecules during critical stages of neural development and thereby contribute to the risk for neurodevelopmental disorders such as autism spectrum disorder (ASD). This hypothesis has in large part been shepherded by the work of Dr. Paul Patterson and colleagues, which has elegantly demonstrated that a single viral infection or injection of a viral mimetic to pregnant mice significantly and persistently impacts offspring immune and nervous system function, changes that underlie ASD-like behavioral dysfunction including social and communication deficits. Subsequent studies by many labs – in humans and in non-human animal models - have supported the hypothesis that ongoing disrupted immune molecule expression and/or neuroinflammation contributes to at least a significant subset of ASD. The heterogeneous clinical and biological phenotypes observed in ASD strongly suggest that in genetically susceptible individuals, environmental risk factors combine or synergize to create a tipping or threshold point for dysfunction. Importantly, animal studies showing a link between maternal immune activation (MIA) and ASD-like outcomes in offspring involve different species and diverse environmental factors associated with ASD in humans, *beyond infection*, including toxin exposures, maternal stress, and maternal obesity, all of which impact inflammatory or immune pathways. The goal of this review is to highlight the broader implications of Dr. Patterson's work for the field of autism, with a focus on the impact that MIA by diverse environmental factors has on fetal brain development, immune system development, and the pathophysiology of ASD.

Contents

* Corresponding author at: Lurie Center for Autism, MassGeneral Hospital for Children, Pediatrics and Program in Neuroscience, Harvard Medical School, Lab: Charlestown Navy Yard Building 114, 114 16th Street (Mail Stop 114-3400), Charlestown, MA 02129, United States.
E-mail address: sbilbo@mgh.harvard.edu (S.D. Bilbo).

http://dx.doi.org/10.1016/j.expneurol.2017.07.002
0014-4886/

1. Introduction

Autism spectrum disorder (ASD) is a complex continuum of neurodevelopmental disorders with early childhood-onset. These disorders, for which there is presently no cure and only limited treatments, are typically associated with significant lifelong cognitive, social, communication and behavioral impairments for the individual (Birtwell et al., 2016; Magiati et al., 2016). The prevalence of ASD has been progressively increasing, and is more common than previously thought (Centers for Disease Control and Prevention, 2014). Though a component is certainly genetic, hundreds of diverse genes are now linked to ASD, each of which contributes to only a very small percentage of the affected population. The heterogeneous clinical and biological phenotypes observed in ASD strongly suggest that in genetically susceptible individuals, environmental risk factors also combine or synergize to create a tipping or threshold point for dysfunction. Multiple prenatal/maternal exposures, most notably infection, have been linked to an increased risk of ASD in offspring (Ashwood and Van de Water, 2004; Becker, 2007; Blaylock and Strunecka, 2009; Lauritsen et al., 2005; Volk et al., 2014). A large body of work by the highly influential Dr. Paul Patterson, and colleagues, has illustrated some of the mechanisms by which maternal immune activation (MIA) with viral infection or viral mimetics can persistently alter offspring immune function, disrupt fetal brain development, and induce the onset of ASD-like behaviors in animal models. The immune system is our interface with the environment, and a role for immunological involvement in at least a subtype of ASD has been hypothesized for some time (Money et al., 1971). Family studies document a significant relationship between familial autoimmune disorders and ASD (Comi et al., 1999; Molloy et al., 2006a; Molloy et al., 2006b; Sweeten et al., 2003a; Sweeten et al., 2003b). Results from post-mortem and neuroimaging studies utilizing PET/MRI have identified stable and persistent inflammation in the brains of some subjects with ASD compared to control subjects (Pardo et al., 2005; Suzuki et al., 2013; Vargas et al., 2005). Findings from multiple animal models have demonstrated marked immune abnormalities that correlate with abnormalities in behavior (Bauman et al., 2013; Bauman et al., 2014; Borrell et al., 2002; Braunschweig et al., 2012; Brimberg et al., 2016; Dalton et al., 2003; Malkova et al., 2012; Martin et al., 2008; Shi et al., 2003; Singer et al., 2009; Smith et al., 2007a). These studies involve different species and diverse environmental factors associated with ASD in humans, *beyond infection*, including toxin exposures, maternal stress, and maternal obesity, all of which impact inflammatory or immune pathways (Krakowiak et al., 2012; Volk et al., 2014; Zerbo, 2015). The goal of this review is to highlight the broader implications of Dr. Patterson's work for the field of autism, with a focus on the impact that MIA by diverse environmental factors may have on fetal brain development, immune system development, and the risk of ASD.

2. The immune system is a regulator of normal brain development

Immune molecules are critical for normal brain development (Bilbo and Schwarz, 2012; Deverman and Patterson, 2009; Schwarz and Bilbo, 2012). A novel role for major histocompatibility (MHC) class I proteins in activity-dependent synapse formation within the visual cortex was identified over two decades ago (Corriveau et al., 1998), and a role for complement proteins in synapse elimination was described several years later (Stevens et al., 2007), two pivotal findings that fundamentally changed our concept of "immune privilege" within the healthy brain. Several chemokines and cytokines have now been identified for their critical roles in neuronal and glial cell migration, differentiation, synaptic maturation, and many other processes (Deverman and Patterson, 2009; Nawa and Takei, 2006). Time-dependence and regional specificity has been demonstrated for cytokines during brain development (Pousset, 1994), suggesting distinct roles for individual cytokines in the development of specific brain circuits. For instance, interleukin (IL)-1β is expressed at high levels throughout the late prenatal/early postnatal hippocampus and cortex, but at very low (constitutive) levels in the adult (Giulian et al., 1988; Schmitz and Chew, 2008). Microglia, the primary immune and cytokine-producing cells of the central nervous system (CNS), are also important for normal brain development via the phagocytosis of extraneous synapses (Paolicelli et al., 2011; Schafer et al., 2012) and apoptotic cells (Sierra et al., 2010), and for aspects of axonal growth and angiogenesis (Rakic and Zecevic, 2000; Streit, 2001). Microglia colonize the fetal brain as primitive myeloid precursor cells from the yolk sac, starting around embryonic (E) day 9 in the rodent and late 1st trimester in humans (Chan et al., 2007; Ginhoux et al., 2010). They enter the parenchyma via the blood stream and ventricles, and are initially clustered around subcortical regions such as the hippocampus and corpus callosum (Cuadros and Navascues, 1998; Wang et al., 2002; Xu et al., 1993). From there, microglia migrate throughout the brain where they continue to proliferate throughout the first postnatal weeks in humans and rodents. They are long-lived cells that are now accepted to be self-renewing, e.g. without contribution from the hematopoietic cells in the periphery under normal conditions (Elmore et al., 2014; Schulz et al., 2012). Microglia largely appear thick, reactive or amoeboid during the early perinatal period, in contrast to the ramified morphology found in adults (Fujita et al., 1981; Ling and Wong, 1993; Rezaie and Male, 2002), though little is known about what this means for function. Interestingly, the developmental peak in cytokine concentrations within distinct brain regions depends on the presence of amoeboid microglia in the rat (Giulian et al., 1988). Due to the critical role that immune molecules play in normal brain development, many, notably Dr. Patterson (Deverman and Patterson, 2009), have hypothesized that aberrant expression of these molecules in response to immune activation is harmful for neural development. That is, it is *because* immune molecules and glia are critical for normal development that they are also implicated in abnormal development (Bilbo and Schwarz, 2009, 2012).

3. Immune activation and neural dysfunction

We now recognize that immune activation or abnormalities within the brain may play a pivotal role in the etiology and/or progression of neuropsychiatric conditions as diverse as Alzheimer's disease, schizophrenia, ASD, and depression. The link between influenza virus in pregnancy and increased risk for ASD and other neurodevelopmental disorders such as schizophrenia has been documented for many years (Brown, 2012; Canetta and Brown, 2012). Severe bacterial infections in pregnancy, in particular those associated with fever, are similarly associated with increased risk of ASD in children (Atladottir et al., 2010). Very recent data show the association extends to parasites, as low circulating maternal immunoglobulin (Ig) levels against *Toxoplasma gondii*, a common parasite, is linked to increased odds of ASD in offspring, whereas high levels of Ig predict the opposite, suggesting a protective effect of adequate maternal Ig (Spann et al., 2017). Conversely, fetal brain-specific antibodies have been identified in a subset of mothers of autistic children in several different studies (Brimberg et al., 2016; Careaga et al., 2013; Fox-Edmiston and Van de Water, 2015; Piras et al., 2014; Rossi et al., 2014). These same isolated antibodies produce ASD-like symptoms in naïve rhesus monkey offspring following injection of the mothers during pregnancy (Bauman et al., 2013). These data strengthen the intriguing evidence that autoimmune disorders are more common in individuals and first degree relatives with ASD, broadly suggesting a critical role of immune dysregulation.

The developing CNS may be especially vulnerable to inflammatory disruption (Rodier, 1980), in large part due to its remarkable plasticity within discrete critical windows, perturbations of which may produce effects on brain and behavior that manifest much later in life, or persist throughout an organism's life span (Cai et al., 2000; Pang et al., 2003; Richardson-Burns and Tyler, 2004; Urakubo et al., 2001; Yu et al., 2004). For instance, the neural circuitry underlying sensory systems such as vision and audition require environmental input during discrete developmental windows for adult function to emerge intact – disruption

Please cite this article as: Bilbo, S.D., et al., Beyond infection - Maternal immune activation by environmental factors, microglial development, and relevance for autism spect..., Exp. Neurol. (2017), http://dx.doi.org/10.1016/j.expneurol.2017.07.002