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Brain Research

Review

Interactions of innate and adaptive immunity in brain development and function

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ARTICLE INFO

Article history:
Accepted 30 July 2014
Available online 7 August 2014

Keywords:
Neuroimmunology
Microglia
Innate and adaptive immunity
Autism spectrum disorder
Rett
Syndrome

ABSTRACT

It has been known for decades that the immune system has a tremendous impact on behavior. Most work has described the negative role of immune cells on the central nervous system. However, we and others have demonstrated over the last decade that a well-regulated immune system is needed for proper brain function. Here we discuss several neuro-immune interactions, using examples from brain homeostasis and disease states. We will highlight our understanding of the consequences of malfunctioning immunity on neurodevelopment and will discuss the roles of the innate and adaptive immune system in neurodevelopment and how T cells maintain a proper innate immune balance in the brain surroundings and within its parenchyma. Also, we describe how immune imbalance impairs higher order brain functioning, possibly leading to behavioral and cognitive impairment. Lastly, we propose our hypothesis that some behavioral deficits in neurodevelopmental disorders, such as in autism spectrum disorder, are the consequence of malfunctioning immunity.

This article is part of a Special Issue entitled SI: Neuroimmunology in Health And Disease.

Contents

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http://dx.doi.org/10.1016/j.brainres.2014.07.050
0006-8993/

1. Introduction

The immune and nervous systems are complex systems that rely heavily on the interactions of multiple cell types for normal development and function. In the immune system, host-defense and long-term memory immunity are accomplished by the coordinated efforts of the innate and adaptive arms. The innate arm of the immune system provides a general first line of defense against pathogens, and includes phagocytes such as macrophages (brain resident macrophages are referred to as microglia) and granulocytes such as neutrophils. The adaptive arm, which includes T and B cells, is used to provide memory for subsequent pathogen challenges. In the nervous system, behaviors are output of integrated neural circuits that are balanced by excitatory and inhibitory neurons, supporting glia, and constant dialog between cells. In both systems inter-cellular communications yield astounding complexity, and it is perhaps more astonishing then to consider that the systems do not exist in isolation but actually rely upon each other for normal function.

The immune and nervous systems are intimately connected and each can directly influence the behavior of the other. The brain can influence immune function via glucocorticoids (Besedovsky et al., 1986) and catecholamines (Kipnis et al., 2004a; Flierl et al., 2008), as well as direct stimulation of lymphoid organs (Nance and Sanders, 2007; Rosas-Ballina et al., 2011). The immune system can likewise influence brain function by multiple mechanisms; this is quite obvious to anyone experiencing sickness behavior from infection (Hart, 1988; Dantzer and Kelley, 1989). It is thought that sickness behavior, although uncomfortable, is beneficial for clearing infections (Dantzer et al., 2008). Changes in behavior including social withdrawal, loss of appetite, lethargy, amongst others, result from elevated levels of pro-inflammatory molecules, most notably tumor necrosis factor (TNF), interlukin-1β (IL-1β), and IL-6 (Dantzer, 2001). These molecules are produced by circulating immune cells and macrophages and affect neuronal function and behavior (Bluthe et al., 2000; Balschun et al., 2004). In addition to soluble molecules, microglia directly interact with neurons and maintain a proper excitatory/inhibitory balance (Pascual et al., 2012; Zhan et al., 2014). Disrupting these tightly controlled interactions or the imbalance in immune molecules can cause a pro-inflammatory skew and produce life-long changes in neuronal function and behavior (Hsiao and Patterson, 2012; Zhan et al., 2014). Neurodevelopment continues well after birth (Lebel and Beaulieu, 2011) and offers a large time window for immune influence. Although the mechanisms of how the immune system shapes neuronal function and behavior are just beginning to be uncovered (Kipnis et al., 2012), immune dysregulation is most evident in common neurodevelopmental disorders.

2. Pro-inflammatory skew in autism spectrum disorder

Autism spectrum disorder (ASD) is a common clinical diagnosis for a heterogeneous group of neurodevelopmental disorders that are estimated to affect 1 in every 68 children (Baio, 2014). The diagnosis is clinically described by dysfunction in social behavior and language, abnormal response to sensory input, and often include repetitive behavior and cognitive disabilities (American Psychiatry Association, 2013). Direct genetic alterations can account for only approximately 10% of all ASD (Abrahams and Geschwind, 2008). Therefore, it is likely that a combination of genetic and alternative variables, such as environmental factors and immunity, contribute to the etiology of ASD.

A pro-inflammatory phenotype can be measured in numerous tissues from patients with ASD. In the brain, microglia have an activated morphology in several regions, most notably the frontal cortex and cerebellum, by postmortem analysis of brains from ASD patients (Vargas et al., 2005; Morgan et al., 2010). The age range of these cohorts spanned 40 years suggesting an early and prolonged chronic state of inflammation in ASD (Vargas et al., 2005). This pro-inflammatory phenotype is not limited to the CNS and was observed in peripheral immune cells. T cells isolated from autism patients were hyperexcitable, having an exaggerated response when stimulated *ex vivo* with the mitogen phytohaemagglutinin (Ashwood et al., 2011b). Several clinical studies also measured elevated pro-inflammatory molecules, such as IL-6 (Ashwood et al., 2011a, 2011c; Brown et al., 2014), and decreased anti-inflammatory molecules, such as transforming growth factor (TGF)-β (Okada et al., 2007; Ashwood et al., 2008), in the plasma, suggesting an overall pro-inflammatory skew.

As it stands now, pro-inflammatory profiles and ASD remain correlative and no causation has been proven. Several studies determined a correlation with diseases of the immune system and ASD (Ashwood et al., 2011a, 2011c; Brown et al., 2014). It has yet to be determined if a pro-inflammatory skew can cause ASD, however, there was an increased risk for ASD in families with maternal history for autoimmune disease ((Atladottir et al., 2009); also see McDougle et al., 2015 for a more comprehensive review of studies linking familial autoimmune disorders and ASD (McDougle et al., 2015)) and evidence of increased gut permeability and gastrointestinal disorders in ASD patients (Buie et al., 2010; de Magistris et al., 2010; Kohane et al., 2012; Hsiao, 2014; McElhanon et al., 2014). Possibly related to these gut phenotypes, disturbances in normal gut microbiota, or dysbiosis, have been described in patients with ASD (Finegold et al., 2010; Kang et al., 2013). The healthy gut hosts a symbiotic microbiota that has been shown to be necessary for the proper development of the immune system (Kamada et al., 2013). Although neonates are more susceptible to infection at this critical developmental point, establishment of a normal microbiota is important and neonates actively suppress inflammation via $CD71^{+}$ erythroid cells to assure proper gut colonization (Elahi et al., 2013). The colonization of symbiotic bacteria is necessary for healthy intestinal homeostasis and can contribute to diseases of the gut as well as the CNS (Maloy and Powrie, 2011; Mortha et al., 2014; Wang and Kasper, 2014). The role of the gut microbiota in a gut-brain-behavior axis is only beginning to emerge (Rook et al., 2014). Dysbiosis in mice alone can lead to similar neurodevelopmental behavioral dysfunction observed in ASD. Germ-free mice had social deficits that can be corrected by colonization