Editorial: Neuroinflammation in the developing brain

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Neuroinflammation is the response of the central nervous system (CNS) to elements that interfere with tissue homeostasis and represents a common denominator in virtually all neurological diseases. The main reactive cellular components of the CNS include mast cells, microglia, astrocytes, and possibly oligodendrocytes (Skaper *et al*., 2017). Microglia, the resident myeloid cells of the CNS, are not only responsible for maintaining immune homeostasis, but are also indispensable for CNS development and neuronal cell activity (Casano and Peri, 2015; Prinz and Priller, 2017). In recent years, increasing evidence has highlighted the crucial role of microglial cells in brain development, and several studies have explored how these cells participate in shaping the developing CNS. In this context, perturbations or hyperactivation of microglia due to pre- or postnatal infections or non-infectious pro-inflammatory conditions may negatively affect developing neural circuits and increase the risk of neurodevelopmental disorders characterized by cognitive disability, and social and behavioral deficits (Sominsky *et al*., 2018). This special issue collects both reviews and original research articles that seek to describe how neuroinflammation, microglia and cytokine abnormalities influence brain development and the etiology of neurodevelopmental disorders.

Guidolin *et al* provide an overview of the role of cytokines and their signaling pathways in the organogenesis of the CNS. Developmental processes underlying the genesis of the CNS are regulated by transcription factors as well as by extracellular signals, including cell-cell interaction and signals provided by the extracellular matrix. Among extracellular signals, cytokines, mostly produced by microglia, play a significant role at all stages of CNS development, including induction of neuroepithelium, proliferation and self-renewal of neural progenitor cells, generation of morphogenic gradients and regulation of the synaptic pool. Perturbation of cytokine production, for example as a consequence of maternal infections, environmental factors (*e.g.*, pesticides, air pollutants, dietary components), or prenatal hypoxia can significantly impact fetal brain development. Thus, a better knowledge of the cytokine

imbalance underlying neurodevelopmental disorders is critical for prevention and, possibly, treatment of these diseases.

Microglia have essential roles in intricate and multi-step processes during brain development. Konishi *et al* provide a comprehensive review of the 'bidirectional' roles of microglia during normal CNS development. Microglia, distributed throughout the brain parenchyma during development, participate in various neuronal developmental events, including phagocytosis of apoptotic cells and excess newborn neurons, supporting neurogenesis, cell migration, axonal growth, synapse formation and remodeling, and mediating cell death and survival (Tay *et al*., 2017). Microglia exert dual functions during each of these events by eliminating unnecessary cells, axons, and synapses, and supporting the neighboring ones, and by promoting phagocytosis and secretion of a variety of molecules, to form refined neural circuits. Understanding the molecular mechanisms involved in these processes is essential for preventing developmental brain disorders caused by microglia dysfunctions.

Arcuri *et al* discuss the role of parenchymal and non-parenchymal immune cells in regulating CNS functions. Parenchymal resident immune cells, namely microglia and mast cells, monitor CNS parenchyma and perform important physiological functions autonomously from the periphery, but they are also capable of becoming activated in pathological conditions. In particular, microglia regulate synaptic pruning, neuronal survival and neurogenesis; mast cells, positioned near the hippocampus, influence neuronal activities through the secretion of numerous neuromodulators (*e.g*., serotonin) and other molecules (*e.g*., histamine, cytokines) that affect memory, anxiety, learning and neurogenesis. Non-parenchymal immune cells, located at the CNS border, in subarachnoid space, choroid plexus and lymphatic vessels, are sensitive to external stimuli and influence parenchymal immune cells by secreted factors or by direct interactions. The two systems can interact with each other, but the extent of this cross-talk remains unclear.

Recent evidence indicates a critical role for microglia and astrocytes in oligodendrogenesis, mediated by the production of cytokines, growth factors and other components important to drive oligodendrocyte differentiation and maturation (Miron, 2017). Understanding the complex immune cell-oligodendrocyte interaction can increase our knowledge of diseases caused by incomplete or erroneous myelination. Gingele *et al* investigate how microglia of different activation states (*i.e.*, M0, M1, and M2-like subtypes) influence oligodendrocyte lineage cells indirectly via astrocytes. Authors analyze growth factor expression in astrocytes and the effect on proliferation, differentiation, and migration of oligodendrocyte precursor cells (OPCs). They

show that treatment of astrocytes with supernatants from pro-inflammatory M1-like microglia results in upregulation of gene transcripts of growth factors which predominantly induce OPC proliferation, differentiation, and survival and are crucial for remyelination. In contrast, M0- and M2-like microglia have only marginal effects on gene expression of these factors in astrocytes. This suggests that M2-like microglia are unlikely to exert remyelination supportive effects indirectly via astrocytes, but rather via direct effects on OPCs.

Recent studies indicate that mitochondrial functions, glucose availability and glycolytic rate influence microglia activation and neuroinflammation (Ghosh *et al*., 2018). Saito *et al* examine the literature surrounding the possible role that adenosine monophosphate-activated protein kinase (AMPK), which regulates energy homeostasis, could have in the regulation of energy balance of microglia during neuroinflammation and neurodegeneration in the developing as well as mature CNS. In this context, the authors consider this molecule as a candidate for regulation of pro- and anti-inflammatory microglia responses.

The developing brain in the perinatal period is highly vulnerable and extremely sensitive to inflammatory challenges of infectious and non-infectious nature that can affect immune cell functions. In this context, accumulating evidence shows that maternal obesity, metabolic disorders, and high-fat diet induce a chronic low-grade inflammation, which is associated with adverse offspring health and neurodevelopmental outcomes (Bilbo and Tsang, 2010; Kang *et al*., 2014). Edlow *et al* examine a novel concept about the similarity in immune response between placental macrophages and brain microglia. Authors isolate $CD11b^+$ microglia and placental cells from embryos of lean and obese mouse dams. They demonstrate that maternal obesity primes $CD11b^+$ microglia and placental macrophages to overproduce the pro-inflammatory cytokine TNF-α in response to lipopolysaccharide stimulation. This effect is most pronounced in male fetal microglia and placental macrophages, suggesting the male predominance of certain neurodevelopmental disorders linked to maternal obesity (*e.g.*, cognitive disfunction, autism spectrum disorder and ADHD).

In uncomplicated pregnancy there is a normal systemic inflammatory response, which becomes exaggerated in pregnancy complications, such as pre-eclampsia (Redman and Sargent, 2003). While the adverse effect of pre-eclampsia on maternal and fetal health is recognized, the long-term impact of this condition on the risk of neurodevelopmental disorders, such as autism spectrum disorder, in exposed offspring is a topic of debate. Maher *et al* present a comprehensive review examining recent evidence suggesting a relationship between maternal pre-eclampsia-induced inflammation and neurological outcomes in offspring. Data analyzed support the idea

that fetal exposure to pre-eclampsia-induced maternal inflammation may increase the risk of neurodevelopmental disorders and perhaps also the risk of these disorders in genetically predisposed offspring. Furthermore, the authors raise an important unaddressed question about the potential impact of antihypertensive pharmacological treatments during pregnancy on the observed association.

Nguyen *et al* present a narrative review that integrates clinical and preclinical studies focusing on punctate white matter lesions in neonates, a specific form of focal non-cystic white matter injury, detected by high resolution MRI. These focal lesions, frequently detected in the preterm and full-term infants, may result from inflammatory or ischemic processes or from neuroinflammation following pre and/or postnatal infections. These lesions are characterized by loss of astrocytes and neurofilaments, neuronal amyloid precursor protein accumulation, and a dense accumulation of activated microglia, and in preterm infants can be associated with neurodevelopment disorders. The authors highlight the importance of imaging techniques to screen brain lesions in critically-ill infants, considering that, in some cases, these may determine their prognosis and outcome.

During adolescence the immature brain is extremely vulnerable to the effects of alcohol and other drug abuse (Winters *et al*., 2012). Ethanol consumption in adolescence affects brain plasticity and causes structural and functional changes in immature brain areas (prefrontal cortex and limbic system) that result in cognitive and behavioral deficits (Pascual *et al*., 2018). Guerri *et al* review the action of alcohol and drug abuse (cannabis, cocaine, opioids, amphetamines, anabolic androgenic steroids) in the adolescent brain and focus on the impact on both cognition and behavioral dysfunction, including predisposition to drug abuse in later life. Authors also describe the molecular and cellular mechanisms at the basis of neuroimmune dysfunction due to alcohol and drug abuse in adolescence, suggesting the therapeutic potential of anti-inflammatory targets to prevent the long-term consequences of drug abuse.

In summary, this special issue will include both literature reviews and original research articles on the state of our knowledge of the mechanisms by which neuroinflammation and microglia influence brain development in both healthy and pathological contexts. Moreover, it will highlight the impact of a dysregulated immune response in the etiology of neurodevelopmental alterations.

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