Editorial: White blood cells matter in neonatal white-matter injury

By Xiaoyang Wang* and Carina Mallard*†,1

*Department of Neuroscience and Physiology, Sahlgrenska Academy at University of Gothenburg, Sweden; and †Centre for the Developing Brain, Department of Perinatal Imaging and Health, King’s College London, United Kingdom

RECEIVED JUNE 5, 2015; REVISED JULY 6, 2015; ACCEPTED JULY 12, 2015. DOI: 10.1189/jlb.3CE0615-242R

See corresponding article on page 21

Neonatal brain injury remains a common occurrence in preterm infants, and with the enhanced survival of extremely preterm infants, the rates of neonatal brain injury are likely to increase in the future. The most common neuropathological finding in preterm infants is diffuse injury to the cerebral white matter. The etiology of preterm birth and white-matter injury is often unclear; however, placental insufficiency/fetal hypoxia and infection/inflammation are important risk factors. Fourteen years ago, it was first suggested that white blood cells might play a significant role in neonatal whiter-matter injury [1]. However, it was not until more recently that several studies have been performed to support further the link between peripheral immune cells and neonatal white-matter injury.

Introduction

In this issue of Journal of Leukocyte Biology, Ortega and colleagues [2] used a mouse model of chronic hypoxia, similar to the model established in rats [3], to investigate further the importance of immune reactions in neonatal brain injury. They demonstrate that a period of chronic hypoxia during the early neonatal period in mice induces a persistent loss of myelin, weeks after the end of the hypoxic exposure. The reduction in myelin correlates with long-term motor impairment, and the authors suggest that the myelin deficit arises from maturational dysfunction of oligodendrocyte marker O1-positive cells rather than reduced proliferation capacity of these cells. These results agree with the current understanding of the development of white-matter injury in preterm infants, where arrest of preoligodendrocytes (i.e., O1-positive cells) maturation is believed to be an important mechanism that gives rise to myelination failure [4]. Intriguingly, the authors found increased numbers of CD4⁺ T cells in the brain, indicating infiltration of peripheral adaptive immune cells. When CD4⁺ T cells were isolated from splenocytes, they were found to be autoreactive to the myelin antigen MBP, which suggests a dynamic interplay between the CNS and the adaptive immune system during the progression of neonatal white-matter injury.

Neonates used to be considered to be immune deficient, but it is now widely accepted that even preterm infants can indeed raise an immune response. With the discovery of different T cell populations, it has become evident that immune responses in the newborn are biased toward a Th2/regulatory T cell reaction. However, the adaptive immune system is at a relatively early developmental stage compared with the innate immune system at this age. Thus, in neonates, it appears that there is significant contribution of the innate and adaptive immune systems in response to infection/injury [5], including neonatal brain injury [6, 7] (Fig. 1). However, despite its relative immaturity, the adaptive immune arm seems to play a significant role, as blockade of lymphocyte trafficking by use of FITC20 (fingolimod), a sphingosine-1-phosphate receptor agonist, prevents inflammation-sensitized hypoxic-ischemic brain injury in newborn rats [8]. A recent study observed peripheral activation of brain antigen-recognizing T cells, several months after acute hypoxia-ischemia-induced neonatal brain injury, which might favor the notion that the brain injury in the chronic stage, at least partly, causes infiltration of self-antigen-reactive T cells [9]. Such autoreactive T cells are very likely playing a different role than autoreactive T cells in multiple sclerosis cases, where these T cells dominate the multiple sclerosis pathology.

In the current study, the autoreactivity is specific to the MBP myelin antigen and not to the other 2 common myelin proteins (myelin oligodendrocyte glycoprotein and proteolipid protein). All of these myelin peptides appear at similar developmental stages in the brain, so the autoreactive response is unlikely a result of differences in their expression in the white matter. One possibility is that the chronic hypoxia model causes consistent stimulation and/or release specifically of MBP, which triggers an autoimmune response in splenocytes. However, these findings need to be confirmed further by animal studies that use different experimental models and by studying human autoimmune antigens in newborn infants with white-matter injury.

Important questions that remain to be answered concern the exact relationship between white-matter injury and the adaptive immune response. It remains to be demonstrated whether the MBP

Abbreviations: MBP = myelin basic protein

1. Correspondence: Sahlgrenska Academy, University of Gothenburg, Box 432, Gothenburg, Sweden. Email: carina.mallard@neuro.gu.se
autoactive CD4+ T cells in the brain are just a side effect of the brain injury or if they are the initiator of white-matter injury. For example, would adoptive transfer of autoactive T cells from perinatal chronic hypoxia mice to control mice cause brain injury? How important is the contribution of self-reactive CD4+ T cells to the maturation arrest of the preoligodendrocytes? What is the route of CD4+ T cell entry into the neonatal brain? Is the blood-brain barrier permeability increased by hypoxia, thus allowing transfer of cells into the CNS? In light of the new discovery of lymphatic vessels in the CNS [10], do such lympho-cytic vessels also exist in the neonatal brain? If so, how much does the lymphatic system contribute to neonatal brain injury?

How translational are these results to human newborns, especially preterm infants? The ontogeny of the adaptive immune system is different in mice compared with humans [11]. For example, we know that mature α/β T cells only increase in number after birth in mice, whereas the first mature α/β T cells are present already during the 1st trimester in humans.

Another important question that needs to be asked is what role neonatal immunity, inflammation, and cytokines play in the normal physiologic development of the CNS—and especially, in the case of preterm birth—in the early developmental stages. Immune responses, both locally in the brain as well as in peripheral tissues, are known to be important for many aspects of brain development, including neural cell differentiation, cell migration, synapse formation and pruning, and programmed cell death. In relation to this, we should keep in mind that in the perinatal period, both the immune system and the brain are still developing, and when an injury occurs in the brain, this injury can have a significant impact on further development of the CNS. If there is indeed an interaction between the innate immune system and CNS development, it is important to understand how brain injury influences the developmental processes of both of these systems. The injury might trigger brain cell development and differentiation toward pluripotency, depending on the type of injury that occurs. A deeper understanding of the interplay between neonatal immunity and the CNS and between innate immunity and adaptive immunity under normal and injured conditions will certainly deepen our understanding of the pathologic conditions that occur in newborn infants.

There are obviously still many more unknowns regarding the role of immune cells in the development of neonatal white-matter injury, and there are many aspects of this proposed relationship that still need to be investigated. However, based on current knowledge in the field and the data from the study by Ortega and colleagues [2], it is becoming evident that in neonatal white-matter injury, white cells do matter; the question now is in what way they matter. A deeper understanding of this relationship will pave the way toward the development of effective neuroprotective interventions in newborns.

REFERENCES


KEY WORDS: CNS·CD4+ T cells·neonatal brain injury
Editorial: White blood cells matter in neonatal white-matter injury

Xiaoyang Wang and Carina Mallard

*J Leukoc Biol* 2016 99: 4-6
Access the most recent version at doi:10.1189/jlb.3CE0615-242R

References
This article cites 10 articles, 1 of which can be accessed free at:
http://www.jleukbio.org/content/99/1/4.full.html#ref-list-1

Subscriptions
Information about subscribing to *Journal of Leukocyte Biology* is online at
http://www.jleukbio.org/site/misc/Librarians_Resource.xhtml

Permissions
Submit copyright permission requests at:
http://www.jleukbio.org/site/misc/Librarians_Resource.xhtml

Email Alerts
Receive free email alerts when new an article cites this article - sign up at
http://www.jleukbio.org/cgi/alerts