Published in final edited form as:

J Neuroimmune Pharmacol. 2013 March ; 8(1): 4–6. doi:10.1007/s11481-013-9437-9.

Microglial-neuronal interactions during neurodegenerative diseases

Carol Colton

Neurology, Duke University Medical Center, Durham, NC 27710

Abstract

The impact of the brain's immune response to disease is no longer relegated to a secondary event of limited interest. Multiple types of brain and spinal cord injuries and diseases show varying immune phenotypes over the time course of the disease. The collection of articles illustrates the wide reach of brain immunity and provides research papers and reviews that illustrate this point. These articles have added both new information and new directions to consider, and I would like to thank all of the participants for their insightful contributions to the field.

Drs. Kaur and Ling are pioneers in the field of microglia and brain immunity (Kaur et al., 1989; Kaur and Ling, 1991; Ling et al., 1991). Their early studies provided important contributions to our understanding of microglia and served to stimulate recognition that microglia are critical to the brain. They continue to provide new and valuable insights as shown in this issue. They and their colleagues at the National University of Singapore have focused on how microglia contribute to the response to hypoxia. They review how microglia respond under hypoxic stress conditions and how this response impacts oligodendrocytes in white matter tracts, in the cerebellum and in the retina during development (Kaur et al., 2012). The impact of immunity on development and early life is further supported in the study by Dr. Irene Kneusel, Maternal and prenatal exposure to pathogens has been shown to affect microglial-mediated inflammation and to influence later life aging processes and/or brain disease (Bilbo, 2010; Bland et al., 2010). Dr. Knuesel along with Amrita Madhusudan and Prisca Vogel from her lab examined TLR3 activators such as the single stranded RNA mimetic, polyinosinic:polycytidylic acid (PolyI:C). In this issue, they review the effects of age on microglia and discuss their data on prenatal immune challenge late in gestation. Late stage exposure to PolyI:C not only impacts developing neurotransmitter systems by altering *N*-methyl-D-aspartate (NMDA) receptors but also alters Reelin expressing neurons (Ratnayake et al., 2012). These changes are translated to significant memory deficits (Madhusudan et al., 2012).

Because the brain has among the highest lipid content of any tissue in the body, the potential for lipids and lipid metabolites to influence brain immunity is very high. A number of lipid products play direct roles in modulating inflammation by altering microglia or dendritic cell function. In this special collection of articles, we present two ways in which lipids regulate inflammatory events. In the study from Dr. Ji's lab at Duke University, the focus is on spinal cord microglia and how their modulation contributes to reduction of pain. Interestingly, a lipid mediator derived from omega-3 polyunsaturated fatty acids and more specifically from eicosapentaenoic acid is a primary factor in pain reduction (Sommer and Birklein, 2010; Ji et al., 2011). This mediator is called resolvin E-1 and is known to be an immunosuppressive

Corresponding Author: Carol A. Colton, Box 2900, Neurology, Duke University Medical Center, Durham, NC 27710, 919 668 2758, carol.colton@duke.edu.

Conflict of Interest: The author declares there is no conflict of interest.

agent that also affects dendritic and T-cells. The impact of lipid mediators in brain and spinal cord inflammation adds an important and new dimension to the field. That some of these lipid derivatives can act as suppressors of microglia and other immune cells is an exciting direction for microglial studies and clearly has clinical potential (Xu et al., 2012). Drs. Kathleen and Tom Montine and colleagues focus on arachidonic acid derived products, and in particular, prostaglandin E2 (PGE2). PGE2 is a well-known and critical mediator of inflammation and has been proposed as a cytotoxic factor in Alzheimer's disease (Montine and Morrow, 2005). PGE2 works through 4 different G-protein coupled receptors called EP1, EP2, EP3 or EP4 (Andreasson, 2010). Their studies presented in this issue focus on the role of EP-1 and the induction of calcium signaling through this receptor. These data help to resolve controversies in the field over the direct or indirect toxicity of EP1 activation (Li et al., 2012).

Similarly to other cells, microglia express ion channels that are part of the signaling mechanisms during immune activation (Kettenmann et al., 2011). Dr. Lyanne Schlichter has provided valuable information on the types and functions of channels in microglia. She and her colleagues focus on a specific sub-type of microglial channel, the calcium -activated potassium channels, SK3 and SK4, and the action of a neuroprotective agent, riluzole, on these channels. SK channels are implicated in LPS mediated activation and cell death. Exactly how riluzole works has not been clear. Interestingly, Schlichter's data suggest that the neuroprotective role of riluzole treatment may not be due to prevention of expression of LPS-activated pro-inflammatory cytokines. Rather, part of its actions may be via up-regulation of alternative activation genes and increased BDNF production (Liu et al., 2012).

Dr. Kathleen Maguire-Zeiss provides a critical view of the relationship between α -synuclein, oxidative stress and immunity. She and her colleagues at Georgetown University Medical School have generated an interesting mouse model to study the oxidative response to α -synuclein. The Maguire-Zeiss mouse combines the overexpression of human α -synuclein under the (TH) promoter with a reporter system for activation of the antioxidant response element (ARE). This unique mouse has provided information on specific antioxidant genes that are altered by α -synuclein overexpression. When microglia from these mice are exposed to dopamine-modified α -synuclein (which forms aggregates), they change their immune activity to an anti-inflammatory profile. The data shown in this article re-enforces the concept that oxidative stress and microglial activity intertwine in complex patterns, and paves the way for greater insight into α -synuclein-driven pathology (Beraud et al., 2012).

The original view that microglia's immune activity damages the brain is clearly changing throughout the field. Dr. Italo Mochetti, also from Georgetown University Medical School, provides a comprehensive review on chemokines in HIV infection and particularly in HIV-associated dementia (HAD). HAD has been an interesting puzzle since this neurodegenerative disease process does not develop in the brain until many years past the initial infection. Mochetti and his colleagues discuss in detail how indirect neuronal toxicity may be produced in HAD and again, emphasize the complexity of the immune reaction in the brain during disease (Mochetti et al., 2012). Drs. Leonid Tarassishin, Sunhee Lee and colleagues continue the emphasis on responses of the brain to virus. Dr. Lee's lab has focused on the transcription factor, interferon regulatory factor 3 (IRF3) and provides a comprehensive review of its actions. Viral infection of the brain initiates a series of protective responses that include activation of Type 1 interferon and interferon-stimulated genes (Paul et al., 2007). IRF3 acts as a focal point for multiple pathways initiated by viral actions, particularly in HIV. Based on their recent *in vitro* data, they also show that overexpression of IRF3 reduces pro-inflammatory responses and can rescue neurons from immunotoxicity. Furthermore, expression of IRF3 in microglia results in a phenotype switch

from an M1 to M2 alternative activation state (Tarassishin et al., 2012). Finally, Colton continues the discussion started in an earlier special edition of the journal on brain immunity. While microglia are clearly the major immune cell of the brain, peripheral cells preside in the perivascular spaces and in the CSF. Of these “peripheral cells”, dendritic cells (DCs) play an important role in the normal and diseased brain (Carson et al., 2006). Whether microglia can serve as the parent cell for brain DCs or if they arise solely from outside of the brain is also an interesting and potentially important question to brain disease (Colton, 2012).

Acknowledgments

I would like to thank Robin Taylor, Managing Editor and Dr. Howard Gendelman, Editor-in- Chief of the Journal of Neuroimmune Pharmacology for their help and encouragement during the preparation of this special edition.

References

- Andreasson K. Emerging roles of PGE2 receptors in models of neurological disease. Prostaglandins & other lipid mediators. 2010; 91:104–112. [PubMed: 19808012]
- Beraud D, Hathaway HA, Trecki J, Chasovskikh S, Johnson DA, Johnson JA, Federoff HJ, Shimoji M, Mhyre TR, Maguire-Zeiss KA. Microglial Activation and Antioxidant Responses Induced by the Parkinson's Disease Protein alpha-Synuclein. Journal of neuroimmune pharmacology : the official journal of the Society on NeuroImmune Pharmacology. 2012
- Bilbo SD. Early-life infection is a vulnerability factor for aging-related glial alterations and cognitive decline. Neurobiology of learning and memory. 2010; 94:57–64. [PubMed: 20388544]
- Bland ST, Beckley JT, Young S, Tsang V, Watkins LR, Maier SF, Bilbo SD. Enduring consequences of early-life infection on glial and neural cell genesis within cognitive regions of the brain. Brain, behavior, and immunity. 2010; 24:329–338.
- Carson MJ, Doose JM, Melchior B, Schmid CD, Ploix CC. CNS immune privilege: hiding in plain sight. Immunological reviews. 2006; 213:48–65. [PubMed: 16972896]
- Colton C. Immune Heterogeneity in Neuroinflammation- Dendritic cells in the brain. Journal of neuroimmune pharmacology : the official journal of the Society on NeuroImmune Pharmacology. 2012; 7
- Ji RR, Xu ZZ, Strichartz G, Serhan CN. Emerging roles of resolvins in the resolution of inflammation and pain. Trends in neurosciences. 2011; 34:599–609. [PubMed: 21963090]
- Kaur C, Ling EA. Study of the transformation of amoeboid microglial cells into microglia labelled with the isolectin Griffonia simplicifolia in postnatal rats. Acta anatomica. 1991; 142:118–125. [PubMed: 1781250]
- Kaur C, Ling EA, Wong WC. Development of the various glial cell types in the cerebral cortex of postnatal rats. Acta anatomica. 1989; 136:204–210. [PubMed: 2603632]
- Kaur C, Rathnasamy G, Ling EA. Roles of Activated Microglia in Hypoxia Induced Neuroinflammation in the Developing Brain and the Retina. Journal of neuroimmune pharmacology : the official journal of the Society on NeuroImmune Pharmacology. 2012
- Kettenmann H, Hanisch UK, Noda M, Verkhratsky A. Physiology of microglia. Physiological reviews. 2011; 91:461–553. [PubMed: 21527731]
- Li X, Rose SE, Montine KS, Keene CD, Montine TJ. Antagonism of Neuronal Prostaglandin E(2) Receptor Subtype 1 Mitigates Amyloid beta Neurotoxicity In Vitro. Journal of neuroimmune pharmacology : the official journal of the Society on NeuroImmune Pharmacology. 2012
- Ling EA, Kaur C, Wong WC. Expression of major histocompatibility complex and leukocyte common antigens in amoeboid microglia in postnatal rats. Journal of anatomy. 1991; 177:117–126. [PubMed: 1769886]
- Liu BS, Ferreira R, Lively S, Schlichter LC. Microglial SK3 and SK4 Currents and Activation State are Modulated by the Neuroprotective Drug, Riluzole. Journal of neuroimmune pharmacology : the official journal of the Society on NeuroImmune Pharmacology. 2012

- Madhusudan A, Vogel P, Knuesel I. Impact of Prenatal Immune System Disturbances on Brain Development. *Journal of neuroimmune pharmacology : the official journal of the Society on NeuroImmune Pharmacology*. 2012
- Mocchetti I, Campbell LA, Harry GJ, Avdoshina V. When Human Immunodeficiency Virus Meets Chemokines and Microglia: Neuroprotection or Neurodegeneration? *Journal of neuroimmune pharmacology : the official journal of the Society on NeuroImmune Pharmacology*. 2012
- Montine TJ, Morrow JD. Fatty acid oxidation in the pathogenesis of Alzheimer's disease. *The American journal of pathology*. 2005; 166:1283–1289. [PubMed: 15855630]
- Paul S, Ricour C, Sommereyns C, Sorgeloos F, Michiels T. Type I interferon response in the central nervous system. *Biochimie*. 2007; 89:770–778. [PubMed: 17408841]
- Ratnayake U, Quinn TA, Castillo-Melendez M, Dickinson H, Walker DW. Behaviour and hippocampus-specific changes in spiny mouse neonates after treatment of the mother with the viral-mimetic Poly I:C at mid-pregnancy. *Brain, behavior, and immunity*. 2012; 26:1288–1299.
- Sommer C, Birklein F. Fighting off pain with resolvins. *Nature medicine*. 2010; 16:518–520.
- Tarassishin L, Bauman A, Suh HS, Lee SC. Anti-Viral and Anti-Inflammatory Mechanisms of the Innate Immune Transcription Factor Interferon Regulatory Factor 3: Relevance to Human CNS Diseases. *Journal of neuroimmune pharmacology : the official journal of the Society on NeuroImmune Pharmacology*. 2012
- Xu ZZ, Berta T, Ji RR. Resolvin E1 Inhibits Neuropathic Pain and Spinal Cord Microglial Activation Following Peripheral Nerve Injury. *Journal of neuroimmune pharmacology : the official journal of the Society on NeuroImmune Pharmacology*. 2012

Biography