Editorial

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Microglia, the brain's double agent

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Conventional teaching has long dictated that the immune response following tissue injury exists as the organism's response to damaged cells. In relation to stroke, this response is initiated by activation of microglia, the brain's resident immune cell. Following this activation, peripheral immune cells from the circulation hone to the site of injury, and activate more brain microglia.[1] Through phagocytic and reparative properties, microglia have been viewed as the primary means by which cells that are no longer viable are contained and removed. By the 1990s, a new view became recognized that this immune response, while important to recovery and repair, could also worsen stroke outcome.[2] Through the ability of microglia to produce pro-inflammatory molecules and toxic mediators such as reactive oxygen species (ROS) and excitotoxins such as glutamate, worsened injury to ischemic cells and damage to adjacent, previously unaffected tissue was observed, and microglia could even impair recovery processes such as neurogenesis.[3] At the time, this new view was put to test with preclinical studies that showed robust immune responses beginning within hours of stroke onset[4,5] and functional studies showed that blocking inflammatory molecules and activation of microglia led to reduction in stroke size.[6] These early studies opened the way for what has become an explosion of papers examining the role of microglia in this immune response as a potential therapeutic target. In fact, in just the past 10 years, the number of papers published on the topic of microglia and stroke has increased by more than 10 fold. Studies in central nervous system trauma have also emerged in parallel, and as reviewed by Shields et al[7], indicate that there are many similarities in both conditions. This would suggest that therapeutics aimed at one condition may readily translate to the other.

Our collective knowledge on the topic of microglia continues to evolve. The 1990s-2000s focused on the notion that microglia exacerbate brain ischemia, yet, complete depletion of microglia has been shown to actually worsen inflammatory responses and neurological outcome.[8] More recent work has focused on the pleiotropic properties of this once overlooked cell. Advances in genomic and proteomic profiling and the increasing use of genetic mutant animal and bone marrow chimeric models has led to remarkable discoveries that indicate that while microglia can worsen stroke outcome, their role in its recovery cannot be neglected. How and what microglia are doing in the hours, days and weeks following stroke all depends on the many different phenotypes that these cells assume. In the acute stages of stroke, microglia are now thought to possess a largely pro-inflammatory, or 'M1' phenotype that leads to enlargement of the stroke size and worsened neurological outcome, since blocking microglial activation prevents this. However, it is now recognized that at some later time point, these cells take on the opposite phenotype where they begin to phagocytose non viable, necrotic tissue, and set the stage for reparative processes such as the restoration of synapses, angiogenesis, neurogenesis and gliogenesis. This latter microglial phenotype has since been described as a 'M2' or anti-inflammatory phenotype.

In this special issue of the journal, several studies are presented which once again, change and expand the way we view these cells. Through the use of gene profiling, a few papers harness the power of single cell RNA sequencing (RNA seq) to drill down on individual microglial phenotypes and their ability to change and assume different roles depending on the anatomic location, timing and even the underlying condition of the brain itself. Hu[9] in a commentary challenges the notion that microglia exist only in one of two phenotypes, and that the M1 vs M2 categorizations may be too simplistic. Recent work has shown that microglia exist in multiple phenotypical subtypes with varying degrees of pro- and anti-inflammatory markers which may even co-exist on the same cell. Further, this phenotype can be fluid depending on the external signals in its local environment. A few additional papers have

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built upon this theme showing that microglial responses may differ depending on a number of different factors. Deng et al[10] carried out a transcriptome analysis of isolated microglia after stroke using gene arrays. M1 and M2 patterns were found to be more complex than previously thought, and differential responses were observed depending on time after stroke and age of the subject, with more robust responses seen in younger brains. Focusing on microglia in the aged brain, Shi et al[11] used RNA seq to study differences in microglial activation in young vs old rodent brains following stroke and found that the inflammatory response is more chronic in aged brains and aged microglia tended to interact less with neurons. The study by Jiang et al[12] built upon this theme of aging and microglial functions. They showed that older microglia have decreased chemotactic capacity and reduced ability to stimulate repair and angiogenesis in the ischemic brain. Particularly since stroke tends to disproportionately affect the elderly, these observations may shed light on why older populations recover less well from stroke, and may be important in the development of potential therapies and interventions.

Microglia are also involved in regulating the neurovascular unit. Ronaldson and Davis[13] discuss the role of microglial phenotypes and their influence on the blood brain barrier (BBB). Like that of microglia elsewhere in the brain, perivascular microglia also conform to broad pro- or anti- inflammatory phenotypes that have the potential to disrupt and increase leakiness of or protect the BBB, respectively. Varga et al[14] describe previously under appreciated functions of microglia and their role in the electrical functions of neurons. Spreading depressions (SD) have been well described in experimental models where neurons are observed to depolarize in response to cortical application of potassium. A similar phenomenon has been described in stroke models where SDs have been linked to local changes in blood flow, and are thought to contribute to infarct expansion. In their work, not only was this phenomenon dysregulated in the absence of microglia, but this seemed to be dependent on the present of the P2Y12 purinergic receptor on microglial processes. SD has also been associated with migraines. Thus, these novel observations indicate that microglia are important to brain functions not previously recognized.

While microglia exist within the brain parenchyma itself, monocytes, their cousins in the peripheral circulation, also play complementary roles in recovery from stroke. Pedragosa et al[15] present new observations on the chemokine receptor CCR-2 which was previously reported to contribute to and exacerbate stroke outcome by increasing BBB leakiness. They show that CCR-2 on circulating monocytes, like brain microglia, possess heterogenous phenotypes, and that deletion of CCR-2 on these monocytes led to decreased angiogenesis and worsened neurological outcome.

New approaches to studying microglial reactions in live animals are described by Sillerud et al[16] who used nanoparticle-tagged Iba1 antibody to monitor microglial activation following experimental stroke using MRI. Consistent with prior histopathologic reports and validation studies presented by the authors, activated microglia were concentrated at the infarct margins and their numbers peaked at 7 days, then decreased thereafter. Such approaches have the potential for translation to the clinical level to validate experimental model findings and drive clinical trial design and even monitor response to treatments.

Microglia continue to be an area of great interest to scientists and clinicians studying stroke. They have been shown to participate in pro-inflammatory functions, but also in brain repair, BBB regulation and even neural functions. Yet, with each new discovery, more questions arise. The 1990s were declared the decade of the brain, but perhaps we have now arrived in the century of the microglia!

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References

1. Schroeter M, Jander S, Huitinga I, et al. Phagocytic response in photochemically induced infarction of rat cerebral cortex. The role of resident microglia. *Stroke* 1997; 28: 382–386.
2. Schwartz M. Macrophages and microglia in central nervous system injury: are they helpful or harmful? *J Cereb Blood Flow Metab* 2003; 23: 385–394.
3. Tobin MK, Bonds JA, Minshall RD, et al. Neurogenesis and inflammation after ischemic stroke: what is known and where we go from here. *J Cereb Blood Flow Metab* 2014; 34: 1573–1584.
4. Morioka T, Kalehua AN and Streit WJ. Characterization of microglial reaction after middle cerebral artery occlusion in rat brain. *J Comp Neurol* 1993; 327: 123–132.
5. Stoll G, Jander S and Schroeter M. Inflammation and glial responses in ischemic brain lesions. *Prog Neurobiol* 1998; 56: 149–171.

6. Dirnagl U, Iadecola C and Moskowitz MA. Pathobiology of ischaemic stroke: an integrated view. *Trends Neurosci* 1999; 22: 391–397.
7. Shields DC, Haque A, Banik NL. Neuroinflammatory responses of microglia in central nervous system trauma. *J Cereb Blood Flow Metab* 2020; 40(1S): S25–S33.
8. Jin WN, Shi SX, Li Z, et al. Depletion of microglia exacerbates postischemic inflammation and brain injury. *J Cereb Blood Flow Metab* 2017; 37: 2224–2236.
9. Hu X. Microglia/macrophage polarization: Fantasy or evidence of functional diversity? *J Cereb Blood Flow Metab* 2020; 40(1S): S134–S136.
10. Deng W, Mandeville E, Yasukazu Terasaki Y, et al. Transcriptomic characterization of microglia activation in a rat model of ischemic stroke. *J Cereb Blood Flow Metab* 2020; 40(1S): S34–S48.
11. Shi L, Rocha M ,Zhang W, et al. Genome-wide transcriptomic analysis of microglia reveals impaired responses in aged mice after cerebral ischemia. *J Cereb Blood Flow Metab* 2020; 40(1S): S49–S66.
12. Jiang L, Mu H, Xu F, et al. Transcriptomic and functional studies reveal undermined chemotactic and angiostimulatory properties of aged microglia during stroke recovery. *J Cereb Blood Flow Metab* 2020; 40 (1S): S81–S97.
13. Ronaldson PT, Davis TP. Regulation of blood–brain barrier integrity by microglia in health and disease: A therapeutic opportunity. *J Cereb Blood Flow Metab* 2020; 40(1S): S6–S24.
14. Varga DP, Menyhárt, Pósfai B, et al. Microglia alter the threshold of spreading depolarization and related potassium uptake in the mouse brain. *J Cereb Blood Flow Metab* 2020; 40(1S): S67–S80.
15. Pedragosa J, Francesc Miró-Mur F, Otxoa-de-Amezaga A, et al. CCR2 deficiency in monocytes impairs angiogenesis and functional recovery after ischemic stroke in mice. *J Cereb Blood Flow Metab* 2020; 40(1S): S98–S116.
16. Sillerud LO, Yang Y, Yang LY, et al. Longitudinal monitoring of microglial/macrophage activation in ischemic rat brain using Iba-1-specific nanoparticleenhanced magnetic resonance imaging. *J Cereb Blood Flow Metab* 2020; 40(1S): S117–S133.