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·**Editorial**·

Neuroinflammation

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The central nervous system (CNS), i.e. brain and spinal cord, is conventionally perceived as an immunologically-privileged site in that the tight junctions of endothelial cells, namely the blood brain barrier (BBB), shields the CNS from invasion by lymphocytes from the circulation. However, the integrity of the BBB is compromised in a number of pathological conditions such as traumatic brain injury, multiple sclerosis (MS), and stroke, which results in the infiltration of an array of lymphocytes from the periphery. Brain intrinsic microglia and astrocytes are highly proactive in interactions with the migrant lymphocytes. These interactions often lead to the release of inflammatory cytokines, *in situ* cell proliferation, and immune-mediated damage of myelin sheaths and secondary damage to axons and neurons in the case of MS. MS is an example of a group of classic neuroinflammatory diseases, in that inflammation and immune responses are the primary causes of CNS pathology. In this group of disorders, immune responses within the brain evolve in terms of intensity and antigen specificity. Such evolution often takes many years before causing overt pathology. In contrast, immune invasion and inflammation occur minutes to hours after traumatic brain injury, acute intracerebral hemorrhage (ICH), or acute ischemic stroke (AIS)[1]. In these circumstances, immune reactions, presumably from the innate arms of the immune system, contribute to the formation of peri-lesion inflammation and edema, causing mass effects and secondary ischemia, exert additional stress on already compromised neurons and other neural structures, and accelerate cell death[1]. In Alzheimer's disease (AD) and Parkinson's disease, focal immune responses and inflammation are elicited by the products of neuronal cell death. In AD, emerging evidence suggests that neuroinflammation is not a passive process, but contributes as much to pathogenesis as do the plaques and tangles themselves[2]. Nevertheless, the exact roles played by inflammation in neuronal damage and repair in these conditions are currently unclear.

Aided by an understanding of the mechanisms of neuroinflammation as well as by our increased ability to manipulate the immune system, the past two decades have witnessed a dramatic change in the management of MS. Currently, we have 12 disease-modifying therapies approved by the Food and Drug Administration (FDA). With these medications, the progression of the relapsing-remitting form of MS can be slowed, and in some cases, halted. A good proportion of these patients can live a productive life. In this issue of *Neuroscience Bulletin*, Huang[3] discusses extensively the efficacy and mechanisms of actions of disease-modifying medications in MS. These discussions can be instrumental in selecting the medications for individuals with MS whose response to a given therapy differs from others. Importantly, Huang also presents an exciting scenario of previous and ongoing randomized controlled trials that opened the way to FDA approval of these medications.

For MS and related demyelinating diseases of the CNS, a significant challenge remains the diagnosis and treatment of neuromyelitis optica spectrum diseases (NMOSDs) due to their similar clinical presentation to MS and lack of effective therapies. NMOSDs preferentially affect the optic nerve and spinal cord. Unlike MS, demyelination is secondary to an antibody response against aquaporin 4 (AQP4) in astrocytes and astrocyte damage in NMOSDs. NMOSDs are much less prevalent than MS in Caucasians. In part because of this, there is no approved

therapy to halt disease progression and there is no ongoing large therapeutic trial for this disease. However, NMOSDs are relatively prevalent in Asian populations. There might be opportunities to organize large coordinated efforts to reveal their clinical features and define therapies. Vigorous efforts are currently devoted to drug development in the preclinical and early clinical stages, i.e. eculizumab[4]. Drug development relies heavily on the availability of suitable models for NMOSDs, which are unfortunately lacking. In this issue, Li and Yan[5] introduce the most frequently-used models in NMOSD research and their potential advantages and limitations. AQP4-bearing astrocytes serve as a target for immune attack in NMOSDs. Astrocytes also serve as a bridge for communication between neurons and immigrant lymphocytes and influence the intensity of brain inflammation. This is well supported by evidence presented by Zhou *et al.* in a mouse model of neonatal sepsis[6].

Unlike the advancement of MS therapeutics, little progress has been made in the medical management of patients with AIS and ICH. Intravenous tissue plasminogen activator remains the only FDA-approved medication for AIS. Its accessibility is apparently limited by the narrow time window for effectiveness (4.5 h after onset) and high risk of hemorrhage. In ICH, although surgical decompression is accepted as potentially lifesaving for patients with large hematomas, no proven medical treatment exists. In an attempt to pinpoint the reasons for the failure of clinical trials in AIS, one could argue that the time window for AIS is too short for effective medical therapies. Namely, cell death through excitotoxicity, oxidative stress, and iron overload occurs minutes to hours after the cession of blood supply, when patients have not yet arrived at hospital[1].

Secondary brain damage in AIS and ICH is mostly due to inflammation and edema surrounding the ischemic core in AIS and hematoma in ICH, respectively. The emergence of inflammation is very swift after the onset of ischemia or ictus. However, the persistence of inflammation for several days to even weeks makes immune intervention possible[1]. Indeed, several proof-of-concept clinical studies have indicated that inhibition of lymphocyte homing to the brain within 72 h *via* 3-day oral fingolimod might reduce brain inflammation and improve the neurological outcomes in patients with AIS and ICH[7-9]. Fingolimod is a sphingosine-1-phosphate receptor (S1PR) modulator that prevents lymphocyte egress from lymphoid tissues and reduces lymphocyte infiltration into the CNS. It has been approved by the FDA for relapsing-remitting MS since 2010. Li *et al.*[10] followed up on the initial observation of rapid reduction of lymphocyte counts after fingolimod administration, and found that peripheral inflammatory mediators are also altered, supporting the notion that the S1PR modulation acts mainly on immune cells as well as inflammatory mediators, at least in the periphery.

There have been extensive discussions over the past few years regarding the suitability of animal models of stroke and to what extent these issues contribute to the failure of translating preclinical observations in animal studies to humans with stroke. Indeed, each model may represent only a fraction of the events that occur during stroke. We must understand this aspect together with the limitations of each model to improve the potential for clinical translation. Yan and Chen comprehensively cover these critical issues[11].

Collectively, I deem this Special Topic on Neuroinflammation is timely and focused. It illustrates the remarkable progress made in the management of classic CNS inflammatory diseases such as MS, and discusses emerging evidence that immune modulation could be promising in non-classic neuroinflammatory disorders such as stroke. It calls for more effort in deepening our understanding of the specificities of the immune response and inflammation within the CNS[12], in part by developing new animal models and rationally utilizing the existing ones. As we learn more about CNS immunology, i.e. the existence of lymphoid tissue in the brain[13], and immune-relevant evidence generated from randomized trials in MS, stroke (ACTION, NCT01955707), and AD[2], our ability to modulate immunity to attenuate tissue damage and promote neuronal repair in neurological diseases will be improved.

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