Editor’s Perspective

Novel Insights for Multiple Sclerosis and Demyelinating Disorders with Apoptosis, Autophagy, FoxO, and mTOR

Demyelinating disorders affect a large proportion of the world’s population. Multiple sclerosis (MS) is a severe demyelinating disease that may impact both the body’s immune system as well the function of myelin producing cells. MS is considered to be the most common demyelinating disorder that affects the immune system in conjunction with the central nervous system. Approximately 2.5 million individuals are affected by MS throughout the world. A continual increase in the prevalence of MS has occurred over the prior five decades. Furthermore, more women than men are affected by MS [1]. Since MS results in an array of impairments in the central nervous system that lead to blindness, motor function loss, cognitive impairment, sensory dysfunction, behavioral difficulties, and loss of coordination, it is hypothesized that multiple cellular mechanisms most likely account for the onset and progression of MS.

Interestingly, recent studies for MS point to the role of cell death and survival pathways that are overseen by apoptosis and autophagy [2, 3]. Apoptosis is initiated through a cascade of nuclease and protease activation that results in caspase activation [4-6]. There is both an early phase for apoptosis that consists of phosphatidylserine (PS) asymmetry loss on the plasma membrane [7-9] and a later phase that results in genomic deoxyribonucleic acid (DNA) degradation [10-12]. Apoptosis can occur at elevated levels during reactive oxygen species (ROS) generation, involve mitochondrial dysfunction during oxidative stress [13-19], and lead to demyelination and neuronal axon loss during MS [20]. Similar to apoptosis, autophagy also may be involved during oxidative stress and ROS generation [3, 15, 21-25] to lead changes in mitochondrial function [16, 26-29]. Yet, some studies also suggest that during immunosuppression, autophagy induction may lead to cellular protection during MS [30].

Apoptosis and autophagy play a critical role during MS and are closely linked to mechanisms tied to the novel pathways of mammalian forkhead transcription factors (FoxOs) [21, 26, 31] and the mechanistic target of rapamycin (mTOR) [30, 32-35]. In regard to FoxOs, the mammalian FOXO proteins of the O class have an important relationship to cell death pathways during neurodegenerative disorders [17, 26, 36-38]. FoxOs can lead to neuronal cell death through the activation of apoptosis. For example, increased FoxO3 activity may affect MS progression since it can result in pro-inflammatory cytokine activation and neuronal cell death [39]. In other work, nuclear retention of FoxO3a has been shown to correlate with brain DNA damage and apoptosis in individuals of advanced age [40]. Given these observations, focus has been directed to block FoxO activity by promoting inhibitory phosphorylation and retention of FoxOs in the cell cytoplasm to prevent DNA transcription. The targeting of FoxO activation has led to the induction of anti-aging pathways [41] and has increased cell survival during oxidative stress through the prevention of apoptosis [7, 19, 42-44]. Interestingly, the activity of FoxO1 transcription factors may play a role in the maturation of oligodendrocytes which can affect central nervous system myelination [45]. In addition, other work suggests that the progressive course of MS may be tied to epigenetic changes with DNA methylation and involve genetic variations of FoxO1 and FoxO3a [46]. In contrast to apoptosis, activation of autophagy in conjunction with FoxOs may lead to alternate observations. FoxO activation during autophagy has been shown to be beneficial to cell survival, indicating that a fine balance in FoxO activity may be required to promote cellular protection and survival in the nervous system. FoxOs through the activation of autophagy can lead to the clearance of toxic intracellular accumulations and promote neuronal survival [47, 48]. As an example of the potential protective nature of FoxOs during MS, prior studies have shown that osteopontin which is present in MS lesions can lead to clinical relapses by promoting the survival of activated T cells through the loss of FoxO3a activity [49].

As mentioned, demyelinating disease also can be influenced by mTOR pathways. mTOR is a 289-kDa serine/threonine protein kinase. The single gene FRAP1 encodes the protein for mTOR [50, 51]. mTOR also is known as the mammalian target of rapamycin and the FK506-binding protein 12-rapamycin complex-associated protein 1 [6, 52]. mTOR is a primary component of the protein complexes mTOR Complex 1 (mTORC1) and mTOR Complex 2 (mTORC2) [50, 53, 54]. In the nervous system, mTOR modulation can prevent oxidative stress injury in neurons [43, 55-57], alter the course of infectious processes [27, 58-63], and maintain metabolic homeostasis [64-67]. In relation to MS, mTOR has been associated with the progression of inflammation in the nervous system [33, 68]. Inhibition of mTOR activity may lead to myelin recovery and limit the progression of MS [30, 35]. It is important to recognize that mTOR activation prevents apoptotic cell death while decreased mTOR activity can reduce toxic intracellular accumulations with autophagy induction [23, 29, 65, 69-71], suggesting that complete inhibition of mTOR activity may be detrimental and a more balanced approach to controlling mTOR activity should be advocated for the treatment of MS.
Both FoxOs and mTOR represent novel pathways to address the detrimental effects of MS. Focus upon these pathways may identify novel treatment strategies for demyelinating disease with the understanding that balancing the influence of these pathways may be critical to achieve successful clinical outcomes. This issue of Current Neurovascular Research echoes such sentiments as we highlight a number of innovative mechanisms for several disorders that affect inflammation in the nervous system. New work examines the role of glibenclamide, a member of the sulfonylurea class of drugs and an oral hypoglycemic for the control of diabetes mellitus. During neuroinflammation following intracerebral hemorrhage, glibenclamide can increase the expression of brain-derived neurotrophic factors and limit the expression of pro-inflammatory factors. This work identifies a new potential for sulfonylurea receptor 1 regulatory agents to target secondary brain injury following cerebral hemorrhage as a result of inflammation in the brain. In regard to cerebral ischemic reperfusion injury, studies in this issue suggest that an inflammatory form of programmed cell death, namely pyroptosis, also may play a role during neuronal injury. The work demonstrates that inflammasomes consisting of the nucleotide-binding and oligomerization domain-like receptors (NLRs) can be inhibited during oxygen glucose deprivation injury and middle cerebral artery stroke to decrease injury and improve neuronal survival. In clinical studies with patients experiencing cerebral venous thrombosis presented in this issue of Current Neurovascular Research, patients with elevated neutrophil to lymphocyte ratios appear to have a long-term impaired prognosis as a result of subclinical inflammation in the brain. Additional companion work in this issue illustrates that increased neutrophil to lymphocyte ratios with elevated serum immunoglobulin G levels also results in an increased risk for relapse and a worse prognosis for patients with neuromyelitis optica spectrum disorder.

Studies in this issue of Current Neurovascular Research provide us with new perspectives on the role of inflammation in the nervous system. A number of mechanisms can contribute to neuroinflammation that ultimately impact the course of neurodegenerative disease. Building upon these innovative studies, additional work can provide new insights for novel pathways such as FoxOs and mTOR and examine how pathways of programmed cell death and pro-inflammatory factors can ultimately determine clinical outcomes for patients.

REFERENCES


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