Journal Club

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Protective Role of NF-κB in Inflammatory Demyelination

Xiaowei Shao
Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore 308232
Review of Stone et al.

One of the most exquisite adaptations in the vertebrate nervous system is myelination. Lipid-rich myelin sheaths greatly increase axonal conduction velocity by wrapping and insulating axons with a compact, multilayer membrane structure that increases resistance and reduces capacitance across the axonal membrane (Chang et al., 2016). In the CNS, myelination and remyelination after injury are accomplished by oligodendrocytes, a type of glial cell. Loss of myelin is associated with numerous pathologies, from autoimmune and congenital disorders to metabolic disturbances (Alizadeh et al., 2015). Multiple sclerosis (MS) is a common autoimmune disease that causes brain inflammation, demyelination, axonal degeneration, and neuronal and oligodendrocyte death. (Mc Guire et al., 2013; Traka et al., 2016). Although the precise etiology of MS remains unclear, it is believed that inflammatory effector cells, including peripheral immune cells and the CNS-resident microglia and astrocytes, damage oligodendrocytes and neurons. Moreover, interferon-γ (IFN-γ), a cytokine normally secreted by activated T cells and natural killer cells, has long been considered a key factor in the pathogenesis of MS and its animal model, experimental autoimmune encephalomyelitis (EAE) (Imitola et al., 2005). In the absence of other insults, transgenic mice overexpressing IFN-γ in the CNS recapitulate several pathological features of MS, such as chronic demyelination and reactive gliosis (Corbin et al., 1996; Renno et al., 1998).

One of the master regulators and effectors in immune and inflammatory responses is the nuclear factor-κB (NF-κB) family of transcription factors (Lawrence, 2009). NF-κB is a heteromeric protein that is sequestered in the cytoplasm under resting conditions by binding to NF-κB inhibitors (IκBs). Signals emanating from various immune receptors, such as Toll-like, interleukin-1, and tumor necrosis factor receptors, lead to phosphorylation of IκBs by the IκB kinase (IKK) complex. Phosphorylation of IκB promotes its degradation, freeing NF-κB to translocate to the nucleus, where it triggers the transcription of numerous genes, including proinflammatory cytokines, chemokines, and adhesion molecules (Mc Guire et al., 2013; Sun, 2017). In EAE, the inactivation of NF-κB typically alleviates disease pathologies by reducing inflammation exerted by the inflammatory effector cells (for review, see Mc Guire et al., 2013), indicating a proinflammatory effect of NF-κB. However, in cultured oligodendrocyte lineage cells, NF-κB has been shown to improve cell survival with or without inflammatory conditions (Nicholas et al., 2001; Hamanoue et al., 2004; Lin et al., 2012), suggesting a protective role of NF-κB.

In a study recently published in *The Journal of Neuroscience*, Stone et al. (2017) investigated how NF-κB affected oligodendrocyte survival and myelination under CNS inflammation *in vivo*. Stone et al. (2017) first generated mice that expressed IκBαΔN, which acts as a super-suppressor of NF-κB, selectively in oligodendrocytes and PNS Schwann cells. By itself, IκBαΔN expression altered neither the viability nor the myelinating function of oligodendrocytes, in agreement with an earlier study (Raasch et al., 2011). To determine whether NF-κB signaling was critical for oligodendrocytes in the context of inflammation, Stone et al. (2017) crossed IκBαΔN-expressing mice with mice that conditionally express IFN-γ in astrocytes. As Stone et al. (2017) expected based on a previous *in vitro* study (Lin et al., 2012), conditional expression of IFN-γ in the CNS led to activation of NF-κB in oligodendrocytes and other CNS cells in control mice, but not in oligodendrocytes expressing IκBαΔN.

Consistent with previous work, Stone et al. (2017) found that expression of the inflammatory mediator IFN-γ in the developing CNS reduced the number of oligodendrocytes, resulting in hypomyelination. Although IκBαΔN expression in oligodendrocytes did not in itself affect oligodendrocyte survival or myelination (as mentioned above), it exacerbated the effects of IFN-γ, even though levels of CNS inflammation were similar to those in mice expressing only wild-type IκB. These observations suggest that NF-κB protects myelin, enhances remyelination, and/or promotes oligodendrocyte survival in the presence of inflammation. They also suggest that the activation

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Correspondence should be addressed to Xiaowei Shao, Nanyang Technological University, Lee Kong Chian School of Medicine, 11 Mandalay Road, Clinical Sciences Building, Level 11, Singapore 308232. E-mail: shaoxw@ntu.edu.sg.
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of NF-κB in oligodendrocytes probably does not participate in IFN-γ-induced inflammation in the CNS.

Next, Stone et al. (2017) examined the influence of oligodendrocyte-specific NF-κB inactivation in two mouse models of MS. In the first model, the toxin cuprizone was administered to cause selective demyelination in the corpus callosum. This model is commonly used to study demyelination and remyelination processes in the CNS independent of peripheral immune responses (Ransohoff, 2012). Expressing IκBαΔN in oligodendrocytes had no obvious effect on demyelination or remyelination in this model. In contrast, inducing IFN-γ expression in astrocytes reduced the number of mature oligodendrocytes and the level of myelination that occurred during recovery from cuprizone treatment, and this effect was exacerbated when IκBαΔN was expressed in oligodendrocytes. The second MS model used was the EAE model, which shares many clinical and pathological characteristics with MS, including CNS inflammation. Stone et al. (2017) found that oligodendrocyte-specific expression of IκBαΔN increased the susceptibility of mice to EAE. Together, these results support the hypothesis that NF-κB activation is a positive modulator of oligodendrocytes and myelination during neuroinflammation.

Activation of NF-κB has different effects on different CNS cell types. Several studies have shown that in astrocytes, the activation of NF-κB is sufficient to initiate neuroinflammation and increase EAE pathogenesis (Raasch et al., 2011; Mc Guire et al., 2013; Lattke et al., 2017). Interestingly, recent work reported that NF-κB activation in astrocytes could be triggered by astrocytic phagocytosis of myelin debris after prominent myelin injury, and that this enhanced astroglial immune responses at the lesions of MS and other CNS demyelinating pathologies (Ponath et al., 2017). Another study (Gabel et al., 2016), however, revealed that inflammation-associated NF-κB activation led to a conversion of astrocytes into neural progenitor cells, suggesting a beneficial role for astrocytes in the regeneration of oligodendrocytes and neurons during inflammation. Limited data exist regarding the roles of oligodendroglial and neuronal NF-κB during inflammation. Although Stone et al. (2017) and their colleagues (Lin et al., 2012) proposed a protective role of NF-κB in oligodendrocytes both *in vivo* and *in vitro*, another investigation (Raasch et al., 2011) suggested that NF-κB activity in oligodendrocytes was dispensable for EAE pathogenesis. In addition, while there was a study showing that the activation of NF-κB through IKK2 protected neurons from EAE (Emmanouil et al., 2009), others reported that the neuronal NF-κB ablation did not alter the EAE pathology (Lee et al., 2012). Thus, more work needs to be done to reconcile these studies.

Dual roles of NF-κB in promoting both cell death and survival have been identified, depending on exact conditions. In the CNS, the detrimental effect of NF-κB on oligodendrocytes and neurons is probably indirect, resulting from enhanced inflammation caused by astrocytes and microglia upon activation of NF-κB. In fact, NF-κB is also known as a pivotal regulator of cell survival and proliferation. Gene products downstream of NF-κB, such as cIAPs, BCL2s, TRAF1/TRAF2, and superoxide dismutase, are important anti-apoptotic and pro-survival proteins (Mattson and Meffert, 2006). Likewise, NF-κB activates the expression of cyclins, c-myc, and growth factors that accelerate cell proliferation. Further investigations are required to elucidate the specific molecular mechanisms that protect oligodendrocytes from inflammation downstream of NF-κB activation. In summary, the study by Stone et al. (2017) offers an interesting avenue, which may ultimately provide novel targets for therapeutic intervention in inflammatory demyelinating disorders.

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