LSU Health Sciences Center

Neuroscience Center of Excellence

FACULTY CANDIDATE

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Presenting
"Endoplasmic reticulum stress modulates the response of oligodendrocytes to interferon-gamma"

Multiple sclerosis (MS) is an autoimmune demyelinating disease of the central nervous system (CNS). The T-cell derived IFN-γ is regarded as a major pro-inflammatory cytokine involved in myelin damage and repair in MS and experimental autoimmune encephalomyelitis (EAE), an animal model of MS, however, the data concerning its roles in these disorders are at times contradictory. Using transgenic mice that allow for temporally regulated delivery of IFN-γ to the CNS using a tetracycline controllable system, we found that the beneficial or detrimental effects of IFN-γ on the development of EAE were dependent on the timing of its presence. CNS delivery of IFN-γ at the recovery stage of EAE impaired the disease recovery and suppressed remyelination and oligodendrocyte regeneration in demyelinated lesions. Surprisingly, CNS delivery of IFN-γ before EAE onset ameliorated the disease course and prevented demyelination, axonal damage, and oligodendrocyte loss. Moreover, we demonstrated endoplasmic reticulum (ER) stress-induced by IFN-γ in oligodendrocytes contributed to the paradoxical effects of this cytokine in the pathogenesis of MS/EAE. Pancreatic ER kinase (PERK), an ER localized kinase, is activated by ER stress and initiates an adaptive program that balances protein biosynthesis with ER-folding capacity and contributes to the activation of most genes in the ER stress response. Using PERK knockout mice, we found that PERK deficiency significantly exacerbated remyelination failure induced by IFN-γ in demyelinated lesions. Interestingly, I also found PERK was essential for the protective effects of IFN-γ in EAE. Importantly, our data indicate therapeutic strategies that enhance PERK-mediated adaptive response, without causing ER stress, could promote oligodendrocyte survival in immune-mediated demyelination diseases.

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LSU Lion's Building, 2020 Gravier Street
New Orleans