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Ifit2 Protect Mice from Murine-β-Coronavirus Induced Neuroinflammatory Demyelination

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Abstract

Ifit2, an interferon-induced protein with tetratricopeptide repeats 2, is critical in restricting neurotropic murine β-coronavirus RSA59 infection. While the protective role of Ifit2 is established for acute viral encephalitis, less is known about its influence on demyelination during the chronic phase of RSA59 infection. This commentary highlights key aspects of the study by Sharma et al., which demonstrated that Ifit2 deficiency causes extensive RSA59 viral spread in the spinal cord associated with impaired T-cell infiltration. Infected Ifit2-/- mice showed reduced T-cell activation in the cervical lymph nodes and preserved blood-brain-barrier integrity. Also, RSA59-infected Ifit2-/- mice showed severe demyelination and persistent viral load in the chronic phase of the disease. Thus, Ifit2 provides antiviral functions by promoting acute Neuroinflammation, aiding virus control, and limiting severe demyelination.

Keywords: Interferon; Neuro inflammatory; Corona virus

Description

Interferons exert their biological effect by inducing and activating certain sets of genes collectively known as Interferon Stimulated Genes (ISGs) [1]. Interferon Induced Protein with Tetratricopeptide repeats 2 (Ifit2) is one such ISG shown to have antiviral effects against various RNA viruses like West Nile virus, Sendai virus, vascular stomatitis Virus, and Mouse Hepatitis Virus (MHV) [2]. Infection of a dual hepatotropic and neurotropic strain of Mouse Hepatitis Virus (vMHV-A59) in Ifit2 deficient mice caused enhanced viral spread with impaired IFNα/β upregulation in the Central Nervous System (CNS) [3]. Ifit2 deficient (-/-) mice infected with MHV-RSA59 showed impaired acute microglial activation, associated with reduced *CX3CR1* expression, which consecutively limits migration of peripheral lymphocytes into the brain, leading to insufficient virus control followed by severe morbidity and mortality [4]. The functional role of Ifit2 during acute Neuroinflammation in constraining viral infection is well established. Sharma et al., have reported its protective role during the chronic progressive neuroinflammatory demyelination phase [5].

Sharma et al., have compared the neuropathological features induced upon intracranial inoculation of Wild-Type (WT) and Ifit2-/- C57Bl/6 mice with a demyelinating strain of MHV, RSA59 [5]. Histopathologically, the spinal cord of RSA59 infected Ifit2-/- mice showed enhanced viral replication and spread throughout the grey and white matter region at day 5 p.i., along with impaired microglia/macrophage activation marked by Ionized calcium-binding adaptor molecule 1 (Iba1) expression. Glial Fibrillary Acidic Protein (GFAP) expression, which determines the Astrocytic activation, remained unaltered between WT and Ifit2-/- mice at day 5 p.i. [5]. Moreover, peripheral immune cell infiltration of $CD4^+$ and $CD8^+$ T cells reduced significantly at day 7 p.i. in the spinal cord of Ifit2-/- mice [5] similar to those previously reported in the brain [4]. Sharma et al., have elucidated the cause of diminished lymphocytic population in the CNS of Ifit2-/- mice upon RSA59 infection by analyzing the Cervical-Lymph-Node (CLN) and Blood-Brain-Barrier (BBB) [5].

CLNs are secondary lymphoid organs primarily known for their role in the immune response against various neurotropic viruses. mRNA analysis of CLNs of RSA59 infected Ifit2-/- mice showed heightened viral load, impaired IFNγ, CD40, CXCL9, CSF2, CD4, and CD8 expression, indicating the inability of viral clearance in CLN [5]. Flow cytometric analysis of CLN of RSA59 infected Ifit2-/- mice showed a diminished population of $CD4^+$ T cells along with impaired IFNγ production. A reduced population of effector and Effector/Memory (E/EM) T cells ($CD44^+CD62L^-$) and an increased Naïve T cell population ($CD44^-CD62L^+$) showed the inability of CLN to induce a viral-specific immune response, which resulted in enhanced viral load in Ifit2-/- mice. Apart from CLN, Sharma et al., reported that RSA59 infected Ifit2-/- mice showed relatively intact BBB, as indicated by decreased Texas Red Dextran dye uptake and increased expression-colocalization of claudin-5 and ZO-1. Sharma et al., highlighted the pivotal functional role of Ifit2 in maintaining BBB integrity upon RSA59 infection despite largely unaltered BBB destabilizing cytokine chemokines expression in the CNS [3,5]. The precise regulatory mechanism of Ifit2-dependent BBB integrity is yet to be fully understood. Overall, Sharma et al., highlighted that Ifit2 restricts viral replication by inducing acute Neuroinflammation in the CNS by enhancing microglial activation, Effector/Effector-Memory (E/EM) T cell activation in CLN, and Blood-brain barrier permeability.

To analyze the chronic phase (day 30) of the disease, Sharma et al., 2023 lowered the RSA59 inoculum to 1/40th of LD50 in Ifit2-/- mice, considering high mortality even in 1/10th of the LD50 beyond day 7 p.i. The spinal cord of RSA59-infected Ifit2-/- mice showed viral persistence in white matter regions indicated by Myelin Basic Protein (MBP) and myelin Proteolipid Protein (PLP) positive areas as opposed to the occasional presence of viral antigen in WT mice. The spinal cord of Ifit2-/- mice showed inflammatory lesions and severe myelin loss accompanied by the presence of amoeboid-shaped phagocytic CD11b^{+} Microglia/macrophages in grey and white matter regions. Furthermore, Sharma demonstrated Iba1^{+} Microglia/Macrophages engulfing white matter protein MBP and PLP in WT and Ifit2-/- mice. However, myelin loss and phagocytic microglia/macrophages were significantly more in Ifit2-/- mice, indicating an intricate role of Ifit2 in modulating microglia/monocyte/Macrophage activity [5]. Notably, microglia/monocyte/Macrophage activation was substantially impaired in the acute phase of Neuroinflammation in RSA59-infected Ifit2-/- mice, accompanied by low expression of *CX3CR1* [4]. Conversely, in the chronic phase, these cell populations turned into more aggressively myelin-engulfing phagocytic cells, leading to augmented demyelination manifested clinically as partial to complete hind limb paralysis, causing a moribund state and death of the mice, indicating the need for Conditional deletion of Ifit2 in selected cell types to dissect the contribution of Ifit2 in this demyelinating disease model [6].

Overall, Sharma et al., highlighted that Ifit2 promotes Neuroinflammation by orchestrating the activation of microglia/macrophages in the central nervous system, stimulating T cells in the CLN, and enhancing BBB integrity, leading to viral clearance in the acute phase of infection, thereby protecting mice from developing severe chronic neuroinflammatory demyelination [5].

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