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Inflammasome dependency key for treating EAE

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Interferon- β (IFN β) can be used to treat patients with multiple sclerosis but, for unclear reasons, one-third of patients do not respond to this therapy. Now, a study by Inoue *et al.* suggests that the success of IFN β therapy may be linked to inflammasome involvement in disease. They report that in mice with experimental autoimmune encephalomyelitis (EAE), IFN β therapy is only effective when disease development is dependent on the NOD-, LRR- and pyrin domain-containing 3 (NLRP3) inflammasome.

Previous studies had shown that IFN β can ameliorate EAE disease by inhibiting the pro-inflammatory functions of macrophages and dendritic cells, but the mechanisms involved were not understood. Inoue *et al.* found that macrophages treated with type I IFNs produced lower levels of interleukin-1 β (IL-1 β) and IL-18 in response to stimuli that activate the NLRP3 inflammasome. They showed that IFN-mediated signalling in macrophages upregulates the expression of suppressor of cytokine signalling 1 (SOCS1), leading to inhibition of the RHO family GTPase RAC1. This inhibition of RAC1 was found to suppress the generation of reactive oxygen species (ROS) by mitochondria, a process that is known to trigger the NLRP3 inflammasome. Therefore, IFN-mediated signalling appears to suppress the production of IL-1 β and IL-18 by inhibiting ROS-driven NLRP3 inflammasome activation.

The authors next explored how IFN-dependent suppression of inflammasome activation affects disease development in EAE. For these studies, they used two distinct protocols to induce EAE. The first was a standard protocol, in which mice were immunized with a myelin peptide in complete Freund's adjuvant (CFA), and the second was a more aggressive protocol, in which the CFA used for immunization contained a higher dose of heat-killed mycobacteria. By using mice deficient in NLRP3 or in the adaptor protein ASC, the authors showed that the development of EAE in mice subjected to the standard protocol was dependent on a functional NLRP3 inflammasome. However, in mice immunized using the aggressive EAE protocol, activation of the NLRP3 inflammasome was not required for disease development. Interestingly, mice immunized using the standard EAE protocol could be protected from disease if they were treated with IFN β . By contrast, IFN β treatment did not protect mice that were subjected to the aggressive EAE protocol.

Finally, the authors used a third distinct model of EAE, in which disease was induced by transferring activated myelin-specific CD4 $^+$ T cells into immunodeficient hosts. Notably, this model of disease was also found to be dependent on the NLRP3 inflammasome and treatable with IFN β . Taken together, the data suggest that a better understanding of the roles of inflammasome activation in multiple sclerosis might one day be useful for determining optimal treatment regimens.

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ORIGINAL RESEARCH PAPER Inoue, M. *et al.* Interferon- β therapy against EAE is effective only when development of the disease depends on the NLRP3 inflammasome. *Sci. Signal.* **5**, ra38 (2012)