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The early protective innate immune response against West Nile virus

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The type I interferon (IFN)- α/β response plays an essential role in controlling West Nile virus (WNV) tropism, replication and spread to the central nervous system (CNS) in mice. Induction of IFN- α/β relies on the detection of viruses by specific host factors known as pattern-recognition receptors. Central to this signaling pathway are the transcription factors interferon regulatory factors (IRF)-3 and IRF-7, which induce IFN- α/β gene expression. We used IRF-3^{-/-}, IRF-7^{-/-} and IRF-3^{-/-} × IRF-7^{-/-} mice to define how a deficiency of master innate immune response transcriptional factors impacts WNV pathogenesis and IFN signaling responses. Whereas WNV-infected wild type mice exhibited 35% mortality, mice lacking IRF-3 and/or IRF-7 had 100% mortality with enhanced viral burdens in peripheral and CNS organs, with altered tissue and cellular tropism. A deficiency in IRF-3 did not alter the systemic IFN response in vivo or IFN- α/β production ex vivo in immune cells. However, IRF-3 restricted WNV replication in macrophages by regulating basal expression of host defense molecules. Moreover, IRF-3 regulated WNV replication through IFN-dependent mechanisms in neurons. In contrast, an absence of IRF-7 abolished the systemic IFN production in mice and abrogated IFN- α responses in primary cells with little effect on IFN- β induction. Notably, a combined deficiency of IRF-3 and IRF-7 sustained enhanced WNV replication in vivo and in primary cells but did not completely abolish the IFN- β responses. These data show an essential role of IRF-3 and IRF-7 in the early control of WNV infection by regulating

not only IFN responses but also antiviral programs in a cell/tissue-specific manner.