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ANTIVIRAL IMMUNITY

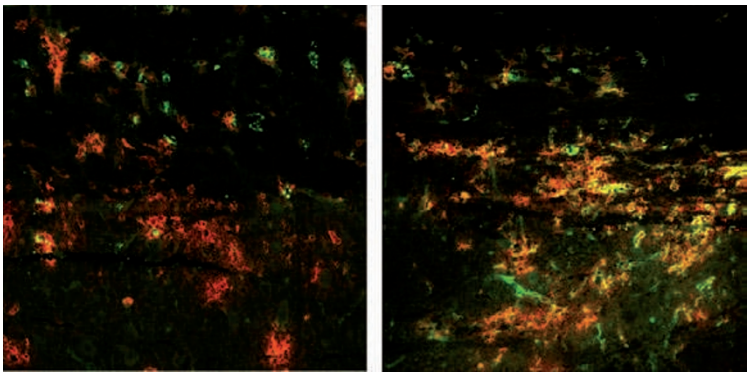
A new role for RNase L

RNase L plays an integral part in antiviral immunity by cleaving viral RNA and thereby activating the type I interferon (IFN) response. A study recently published in *PLoS Pathogens* now shows that RNase L also protects from virus-induced demyelination of the central nervous system (CNS).

To examine the role of RNAse L during viral encephalitis, Ireland *et al.* infected RNase L-deficient (*Rnasel*$^{-/-}$) mice with the JHM strain of murine hepatitis virus (MHV-JHM), which replicates exclusively in the CNS. Infected *Rnasel*$^{-/-}$ mice showed similar disease progression to wild-type mice but had increased disease severity and higher mortality rates. This was not due to increased viral replication rates, decreased type I IFN responses or increased CNS inflammation, although infection of the brainstem was sustained. Instead, *Rnasel*$^{-/-}$ mice had accelerated and increased demyelination in the brainstem and spinal cord, which coincided with high levels of axonal damage.

> RNase L … protects from virus-induced demyelination of the central nervous system

Demyelination in infected *Rnasel*$^{-/-}$ mice correlated with the increased presence of apoptotic cells, which could be found in both the spinal cord white matter (made up of axons) and grey matter (made up of cell bodies) of *Rnasel*$^{-/-}$ mice by 10 days after infection. By contrast, in wild-type mice the appearance of apoptotic cells was delayed and was limited to the white matter. Although it was unclear whether the apoptotic cells were neurons, microglia (CNS macrophages) or infiltrating leukocytes, this finding indicates that RNase L protects from apoptosis in white and grey matter. Demyelination and damage in the spinal cords of *Rnasel*$^{-/-}$ mice also correlated with the presence of virus-infected cells in the grey matter, which were absent in wild-type mice; no difference was observed in the white matter. The infected cells were identified as microglia and found to carry high levels of viral mRNA.



Co-localization of viral antigens (labelled green) and microglia (labelled red) in the spinal cords of wild-type (left) and *Rnasel*$^{-/-}$ (right) mice. Image courtesy of Derek Ireland, Cleveland Clinic, Ohio, USA.

The authors speculate that, in the absence of RNase L, focal infection of microglia in grey matter could impair their neuroprotective function and, consequently, result in severe CNS pathology.

Together, these findings indicate a new role for RNase L in protecting microglia from viral infection, which in turn protects the CNS from demyelination. Further studies will be required to deduce the molecular mechanism of this new function.

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ORIGINAL RESEARCH PAPER Ireland, D. D. *et al.* RNase L mediated protection from virus induced demyelination. *PLoS Pathog.* **5**, e1000602 (2009)