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VIRAL PATHOGENESIS

Neural receptor for reovirus revealed

> reovirus uses NgR1 for neuronal attachment and infection of the CNS

The neurotropic virus mammalian reovirus causes systemic disease by spreading from an initial site of replication in the intestine to the central nervous system (CNS); however, the neural receptor has been unknown. Konopka-Anstadt *et al.* now show that reovirus uses the protein receptor NgR1 for entry into neurons.

The initial tethering of reovirus to mammalian cells is mediated by low-affinity attachment to sialylated glycans, followed by high-affinity binding to protein receptors. In mice, reovirus uses junctional adhesion molecule A (JAM-A) for bloodstream dissemination from the intestine to sites of secondary infection. Although JAM-A is the only known protein receptor for reovirus, it is not required for entry into, and replication in, the CNS; furthermore, following intracranial inoculation, reovirus can cause neurological disease in mice that lack JAM-A, which indicates that an alternative receptor is used.

Using a whole-genome small interfering RNA (siRNA) screen, the glycosyl phosphatidylinositol-anchored, leucine-rich repeat protein NgR1 was identified as a candidate protein required for reovirus infection of HeLa cells. Although NgR1 is expressed on cervical epithelial cells, its expression is more prominent on CNS neurons, which indicates that NgR1 might function as a neural receptor. To test this hypothesis, the authors examined reovirus infection of Chinese hamster ovary cells that were transfected with plasmids encoding NgR1, JAM-A (as a positive control) or the coxsackievirus and adenovirus receptor (CAR; as a negative control). In contrast to CAR, both JAM-A and NgR1 enabled reovirus infection, and pretreatment of cells with NgR1-specific antibodies blocked infection, which suggested that NgR1 functions in viral attachment. Flow cytometry experiments confirmed that NgR1 does indeed enable viral attachment, and removal of NgR1 from the cell surface or pretreatment of the virus with soluble NgR1 abolished virus infection. Moreover, the authors found that, although wild-type neurons were efficiently infected by the virus, infection of *NgR1*-null neurons was severely diminished. These data provide direct evidence that reovirus uses NgR1 for neuronal attachment and infection of the CNS. Further experiments showed that reovirus uses distinct capsid proteins to attach to JAM-A and NgR1, but more work is needed to determine the binding partner for NgR1.

Although there is much to learn about the mechanism of reovirus infection of the CNS via NgR1, this study defines NgR1 as the first neural receptor for this virus and highlights the importance of distinct cellular receptors for determining viral tropism.

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ORIGINAL RESEARCH PAPER
Konopka-Anstadt, J. L. *et al.* The Nogo receptor NgR1 mediates infection by mammalian reovirus. *Cell Host Microbe* **15**, 681–691 (2014)