VIRAL PATHOGENESIS

IRES knocks out rabies

Non-segmented negative-strand RNA viruses that can infect neurons in the central nervous system include measles virus, mumps virus, Borna virus, the emerging deadly Nipah and Hendra viruses and rabies virus. Until now there has been no method available to control the expression of individual genes of these viruses. According to a report published in the *Journal of Virology*, replacing the transcription signals of the rabies virus phosphoprotein gene with internal ribosome entry sites (IRESs) from poliovirus or human rhinovirus type 2 (HRV2) enables downregulation of phosphoprotein expression at the level of translation and can render rabies virus avirulent.


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Although rabies and other non-segmented negative-strand RNA viruses can replicate in all cell types, positive-strand RNA viruses, such as poliovirus and HRV2, have a restricted host range. There is evidence that IRESs in the 5′-untranslated regions of positive-strand RNA viruses are subject to cell-type inhibition and can mediate cell-type specificity. To test whether IRESs can affect gene expression of non-segmented negative-strand RNA viruses, Marschalek *et al.* replaced the transcription signals of the rabies phosphoprotein gene with IRESs from poliovirus and HRV2.

Using a dual reporter system that inserts different luciferase reporters upstream and downstream of the IRES they were able to monitor the translation initiation of the IRES elements in different cells. Unexpectedly, they found that the HRV2 IRES was active in all cell types, including neurons. Previous reports had indicated that HRV2 could not replicate in neurons, unlike the neurotropic poliovirus. In spite of this, both types of recombinant virus that expressed the phosphoprotein under the control of the IRES were avirulent in neonatal mice, whereas wild-type rabies virus was 100% lethal.

Infection of neurons with RNA viruses is initially controlled by interferon-□ (IFN□) and subsequently by virus-specific antibodies and T-cell derived IFN□. The rabies virus phosphoprotein, which is an essential cofactor of the viral polymerase and also has a role in encapsidation of replicated genomes, functions to dampen the host response by counteracting the production of IFN. The most striking finding from this study is that translational attenuation of phosphoprotein through insertion of IRESs from poliovirus or HRV2 limited the ability of recombinant rabies viruses to counteract the production of IFN, as shown by the failure of recombinant viruses to prevent transcription of the host *Ifnβ* gene. The authors propose that the phosphoprotein has a vital role in controlling the host innate immune response.

Although there are several post-exposure vaccines for rabies, infection is almost always fatal if the virus reaches the brain. These studies reveal that translational control of individual genes is a promising strategy to attenuate replication and virulence of live non-segmented negative-strand RNA viruses and might provide a basis for a new vaccine formulation.

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ORIGINAL RESEARCH PAPER Marschalek, A. *et al.* Attenuation of rabies virus virulence and replication by picornavirus IRES elements. *J. Virol.* 10 Dec 2008 (doi:10.1128/JVI.02055-08)