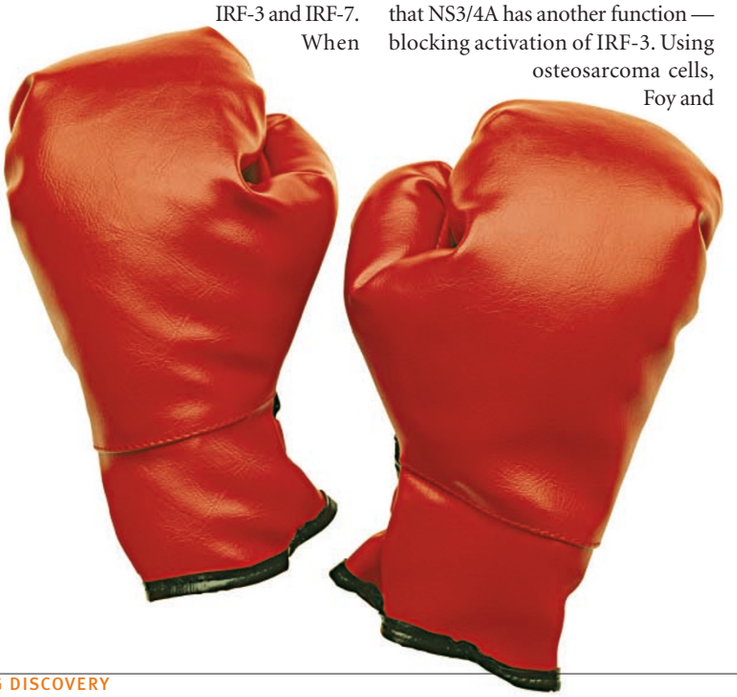
VIRAL INFECTIONS

A double whammy for hep C

Persistent hepatitis C virus (HCV) infections — the main cause of liver disease worldwide — are a function of the ability of HCV to block its host's innate immune response. Expression of interferon (IFN), a key component of this defence, is induced by IFN regulatory factors (IRFs) after viral challenge. But what switches on the IRFs, and how does the virus interfere with this process to circumvent the immune response? Two studies published online in *Science* provide answers to these long-standing questions and highlight a promising target for drug development.

In the first study, Sharma and colleagues identified two IκB kinase (IKK)-related kinases that activate IRF-3 and IRF-7. When expressed in HEK293 cells, IKKε and TANK-binding kinase 1 (TBK1) activated the IRFs by phosphorylating the serine residue at position 396. Co-expression of IKKε or TBK1 with IRFs stimulated a variety of IFN promoters by up to 2,000-fold and inhibited virus replication in a *de novo* infection model, demonstrating the central function that IKKε and TBK1 have in activating host defences.

But these defences can be breached, and Foy *et al.* have shown that an HCV enzyme called NS3/4A does just that. NS3/4A is a protease complex that plays a crucial part in viral replication by catalysing the post-translational processing of non-structural HCV proteins. But it seems that NS3/4A has another function — blocking activation of IRF-3. Using osteosarcoma cells, Foy and colleagues showed that NS3/4A blocks the accumulation of activated IRF-3. In turn, induction of the IRF-3-responsive promoters of several IFN-stimulated genes is strongly inhibited in hepatoma cells. The authors suggest that NS3/4A inhibits IRF-3 activation by perturbing the enzymes that catalyse its phosphorylation — the newly identified IKK-related kinases, IKKε and TBK1.



As if it's not enough that NS3/4A-mediated inhibition of IRF-3 activation promotes the persistence of HCV infections by compromising the host's innate immune response, it probably also reduces the effectiveness of IFN-based therapies — the current standard treatment — as many IFN-responsive genes contain IRF-3 target sites within their promoters. So, antivirals that target NS3/4A might be doubly efficacious, restoring the capacity of the host to fight back, while weakening the virus by interfering with the protein processing that is essential to its replication.

Suzanne Farley

References and links

ORIGINAL RESEARCH PAPERS Foy, E. *et al.* Regulation of interferon regulatory factor-3 by the hepatitis C virus serine protease. *Science* 17 April 2003 (doi: 10.1126/science.1082604) | Sharma, S. *et al.* Triggering the interferon antiviral response through an IKK-related pathway. *Science* 17 April 2003 (doi: 10.1126/science.1081315)

FURTHER READING Tan, S.-T. *et al.* Hepatitis C therapeutics: current status and emerging therapies. *Nature Rev. Drug Discov.* **1**, 867–881 (2002)

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Encyclopedia of Life Sciences:
http://www.els.net/
Hepatitis C virus | interferons