INNATE IMMUNITY

Unfolding antiviral defences

The innate immune system plays a key part in host defence against viruses. In a study published in *Cell Host & Microbe*, Liu and colleagues show that the unfolded protein response (UPR) triggered by viral infection results in the ubiquitination and degradation of the type I interferon (IFN) receptor subunit IFNAR1.

After being produced in response to viral infection, IFNs bind to their cognate receptors and activate Janus kinases (JAKs). In turn, JAKs initiate a signalling cascade that not only results in activation of antiviral defence pathways but also stimulates degradation of IFNAR1. Degradation is triggered by serine phosphorylation of IFNAR1 within its destruction motif by an unidentified kinase that functions downstream of JAK. However, when overexpressed, IFNAR1 is degraded by a second pathway, independently of IFN binding and JAK activity, which, Liu and colleagues proposed, may depend on the UPR.

The authors found that either overexpression of IFNAR1 or treatment with known UPR inducers promoted IFNAR1 ubiquitination and accelerated the degradation of this receptor. Degradation depended on phosphorylation of the IFNAR1 destruction motif and on the activity of one particular UPR sensor, the PKR-like ER kinase (PERK). PERK did not phosphorylate IFNAR1 directly, suggesting that it is the PERK-dependent downstream signalling induced by the UPR that is responsible for JAK and ligand-independent IFNAR1 turnover.

Liu and colleagues also found that some viruses, such as vesicular stomatitis virus or hepatitis C virus, exploit this mechanism for rapid downregulation of IFNAR1, which leads to the inhibition of IFN signalling and anti-viral resistance. Virally triggered degradation of IFNAR1 may enable viruses to render the already infected host cell insensitive to IFN, thereby avoiding innate immune defences and allowing completion of the viral lytic cycle.

These studies demonstrate that, through activation of the UPR and downregulation of IFNAR1, viruses are able to attenuate host cell defences. The precise mechanisms involved, including the kinase (or kinases) responsible for PERK-dependent phosphorylation of IFNAR1, remain to be determined.

Andrew Jermy

> “Virally triggered degradation of IFNAR1 may enable viruses to render the already infected host cell insensitive to IFN…”

ORIGINAL RESEARCH PAPER Liu, J. *et al.* Virus-induced unfolded protein response attenuates antiviral defenses via phosphorylation-dependent degradation of the type-I interferon receptor. *Cell Host Microbe* **5**, 72–83 (2009)