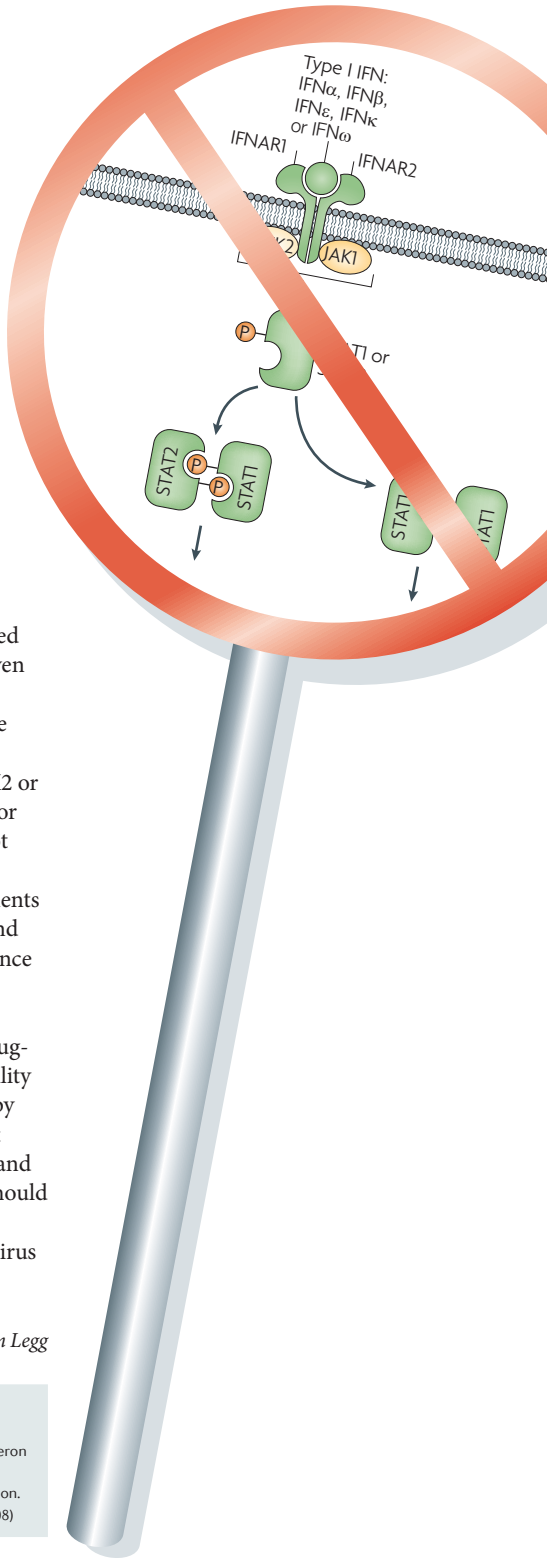
VIRAL IMMUNE EVASION

Interferon interference



Interferon (IFN) signalling constitutes an important aspect of innate immunity, and must be overcome early on for successful viral infection. In the *Journal of Virology*, Bisson *et al.* report on the inhibition of IFN-mediated signalling by Kaposi's sarcoma-associated herpesvirus (KSHV).

The authors compared the response to IFN of cells lytically infected with KSHV with that of uninfected cells. The infected cells showed markedly less phosphorylation of the downstream signalling components signal transducer and activator of transcription 1 (STAT1) and STAT2, indicating that the IFN response was inhibited. When the authors screened 80 KSHV open-reading frames for their ability to suppress IFN-mediated reporter activity, they identified two factors, one of which they named regulator of IFN function (RIF).

Transient transfection of RIF resulted in decreased phosphorylation of endogenous STAT1, STAT2 and two other upstream components of the IFN pathway, Janus kinase 1 (JAK1) and leukocyte tyrosine kinase receptor (LTK; also known as TYK1), in response to IFN. Consequently, STAT proteins showed impaired nuclear translocation, and transcript levels of the IFN-inducible gene *ISG15* decreased.

Transiently expressed RIF coimmunoprecipitated with transiently expressed JAK1 and STAT2, and to a lesser extend with TYK2; this interaction prevented the activation of JAK1 and TYK2, implying that RIF affects IFN signalling at a membrane-proximal stage. So, Bisson *et al.* investigated whether RIF could interact with the IFN receptor subunits, IFNAR1 and IFNAR2. Transiently transfected RIF indeed interacted with both subunits, even in the absence of IFN. This association did not, however, displace STAT2 (or STAT1) from the IFN receptor, nor did it displace TYK2 or JAK1 from the tails of the receptor subunits. Therefore, RIF does not seem to block IFN signalling by preventing downstream components that interact with the receptor, and the mechanisms of IFN interference by RIF remain unclear. RIF can also promote a STAT2–IFNAR1 association, which Bisson *et al.* suggest might further reduce the ability of STAT2 to be phosphorylated by JAK1. The authors conclude that "[d]etermination of RIF's direct and indirect interaction partners…should enrich our understanding of the mechanisms controlling herpesvirus replication and pathogenesis."

Katrin Legg

> "Transient transfection of RIF resulted in decreased phosphorylation of endogenous STAT1, STAT2 and two other upstream components of the IFN pathway…"

ORIGINAL RESEARCH PAPER Bisson, S. A., Page, A. -L. & Ganem, D. A KSHV protein that forms inhibitory complexes with type I interferon receptor subunits, Jak and STAT proteins and blocks interferon-mediated signal transduction. *J. Virol.* 11 Mar 2009 (doi: 10.1128/jvi.02516-08)