MACMILLAN \ David Tolley/Rob Judges

VIRAL IMMUNE EVASION

NLR identity theft

Kaposi's sarcoma-associated herpesvirus (KSHV) can cause lifelong latent infection in humans and, eventually, give rise to certain cancers. Gregory and colleagues now report that a previously uncharacterized KSHV protein inhibits inflammation and cell death by blocking formation of the inflammasome.

When a pathogen enters the host cytosol, it can trigger the activation of certain NOD-like receptors (NLRs), and these then trigger the formation of inflammasomes, which are large oligomeric complexes that contain a specific NLR, an adaptor protein and pro-caspase 1. Inflammasome formation results in the successive activation of caspase 1 and the interleukins IL-1β and IL-18, leading to inflammation and, eventually, cell death. Gregory *et al.* found that KSHV Orf63 showed sequence similarity to NLRP1 (NOD-, LRR- and pyrin domain-containing 1), one of the human NLRs. Orf63 contains a leucine-rich repeat (LRR) and a nucleotide-binding domain (NBD), two domains that are required in NLRP1 for oligomerization, but lacks other domains needed in NLRP1 for caspase activation. To investigate whether Orf63 might act as an NLRP1 inhibitor, the authors expressed Orf63 in various cell lines. After inducing inflammasome formation by adding a bacterial cell component (muramyldipeptide), they observed that Orf63-expressing cells had lower production of IL-1β, decreased caspase 1 activity and a lower rate of NLRP1-dependent cell death. Co-immunoprecipitation experiments using Orf63, NLRP1 and partially deleted versions of the two proteins showed that Orf63 inhibits the self-association of NLRP1 and the interaction between NLRP1 and pro-caspase 1 by a direct interaction with the NLRP1 oligomerization domains. Orf63 also interacted with two other NLRs (namely, NOD2 and NLRP3). Finally, the inhibition of Orf63 synthesis by expression of a small interfering RNA in several cell lines demonstrated that Orf63 is required for expression and replication of the viral genome during both primary infection and reactivation from latency.

> “this KSHV protein is the first NLR homologue to be found in a pathogen”

Thus, Orf63 inhibits IL-1β secretion through direct interaction with a NLR component of the inflammasome. Moreover, this KSHV protein is the first NLR homologue to be found in a pathogen. It remains to be seen whether the subversion of cellular NLRs is a survival strategy used by other viral or bacterial pathogens.

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ORIGINAL RESEARCH PAPER Gregory, S. M. *et al.* Discovery of a viral NLR homolog that inhibits the inflammasome. *Science* **331**, 330–334 (2011)
FURTHER READING Bergsbaken, T., Fink, S. L. & Cookson, B. T. Pyroptosis: host cell death and inflammation. *Nature Rev. Microbiol.* **7**, 99–109 (2009)