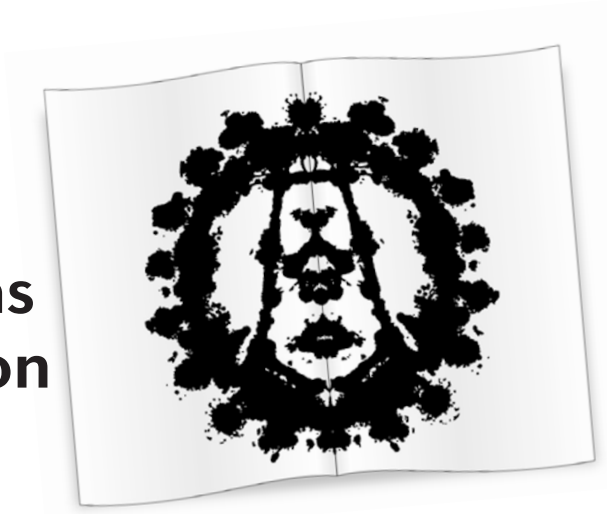

ANTIVIRAL IMMUNITY

TRIM5 moonlights as a pattern recognition receptor

TRIM5 is a RING domain E3 ubiquitin ligase that restricts infection of HIV-1 and other retroviruses on entry into the cell by engaging the viral capsid and inducing premature uncoating. Writing in *Nature*, Pertel *et al.* now show that, in addition to restricting retroviruses, TRIM5 has a general role in cellular immunity through the activation of innate immune signalling pathways.

Several recent studies had suggested that TRIM5 has a role in signal transduction processes. When Pertel *et al.* knocked down the expression of endogenous human TRIM5 using RNA interference, they detected a significant decrease in the expression of AP1-responsive and nuclear factor-κB (NF-κB)-responsive inflammatory mediators. Conversely, ectopic expression of TRIM5 in HEK-293 cells stimulated both the AP1 and NF-κB signalling pathways, which in turn stimulated the expression of genes in a pattern that was reminiscent of the response to lipopolysaccharide (LPS) detection by the pattern recognition receptor Toll-like receptor 4 (TLR4)–MD2 (also known as LY96). Interestingly, knockdown of TRIM5 attenuated cellular responses to LPS in a range of cell types.

> “acting as a pattern recognition receptor that activates innate immune signalling pathways was probably the original function of TRIM5”

To determine the mechanism by which TRIM5 activates the AP1 and NF-κB signalling pathways, the authors looked for interactions between TRIM5 and 20 proteins from the signalling pathways that are known to be induced by LPS. TRIM5 was found to interact with TAB2, TAB3 and TAK1 (also known as NR2C2), which are components of the TAK1 kinase complex, as well as with the E2 ubiquitin conjugation enzymes UBC13 (also known as UBE2N) and UEV1A (also known as UEV1). Knockdown of TRIM5 expression blocked LPS-induced TAK1 activation, whereas knockdown of TAK1 expression blocked TRIM5-dependent activation of AP1 signalling. Furthermore, in a cellular model of TRIM5-mediated restriction of retroviral infection, knockdown of TAK1 allowed productive HIV-1 infection. UBC13 and UEV1A can promote the crosslinking of ubiquitin monomers via K63, producing substrate-free ubiquitin chains that can activate the TAK1 complex. Accordingly, incubation of TRIM5 with ubiquitin, E1 enzyme, UBC13 and UEV1A *in vitro* led to the production of K63-linked ubiquitin chains. Furthermore, the addition of a reconstituted HIV-1 capsid lattice to these assays greatly stimulated the production of K63-linked ubiquitin chains.

The authors suggest that acting as a pattern recognition receptor that activates innate immune signalling pathways was probably the original function of TRIM5 and that the capsid recognition and restriction activities of TRIM5 are likely to have evolved later.

Andrew Jermy

ORIGINAL RESEARCH PAPER Pertel, T. *et al.* TRIM5 is an innate immune sensor for the retrovirus capsid lattice. *Nature* **472**, 361–365 (2011)
FURTHER READING Ozato, K. *et al.* TRIM family proteins and their emerging roles in innate immunity. *Nature Rev. Immunol.* **8**, 849–860 (2008)