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Previews

Trim5 TAKes on Pattern Recognition

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Retroviral capsids can be recognized and degraded by a host protein, Trim5α. A recent study in *Nature* (Pertel et al., 2011) shows that, upon sensing of the retrovirus capsid lattice, Trim5α generates free ubiquitin chains that activate the TAK1 kinase and downstream innate immune response genes.

The cytoplasmic protein Trim5α, encoded by the *Trim5* gene, was discovered in rhesus macaques as a factor that blocks HIV-1. However, the human homolog of this gene does not block HIV-1 effectively. Since its discovery, *Trim5* is found to be present in most mammals and can block many retroviruses (and only retroviruses, thus far), but each species has a unique specificity toward viral capsids from different retroviruses. Moreover, Trim5α exerts a selective pressure on retroviruses to escape by evolving mutations in their capsid (Kirmaier et al., 2010). Because *Trim5* has undergone episodes of adaptive evolution in primates in regions of the protein that recognize the viral capsid, the evolutionary arms race between primates and pathogenic retroviruses is likely an ancient one. The interaction between Trim5α and the retroviral capsid was initially thought to be a simple recognition event followed by disruption of the viral capsid. However, recent work by the Luban group (Pertel et al., 2011) now shows that Trim5α sensing of the retroviral capsid lattice serves an additional and important role in activating a signal transduction pathway leading to the production of inflammatory cytokines and the establishment of a generalized antiviral state.

Pathogens are recognized as non-self by intracellular sensors that in turn trigger an amplification cascade of host defense responses against them. Innate immunity sensors are germline-encoded "receptors" called pattern recognition receptors (PRRs) that recognize microbial signatures, or "patterns," which, in a pathogenic context, are referred to as pathogen-associated molecular patterns (PAMPs). Upon sensing PAMPs, PRRs signal posttranslational activation of kinases (such as TAK1) and transcriptional

activation of key downstream regulators such as IFN (interferon) and nuclear factor kappa B (NF-κB). While PRRs that sense bacteria mostly recognize chemical and/or structural features (such as lipopolysaccharide, LPS), PRRs that recognize viral infections most often do so by recognizing nucleic acids that are either in appropriate intracellular compartments or have modifications that distinguish them from host nucleic acids. Recently, however, Trim21 has been shown to be a protein sensor of a viral infection by recognizing antibody-bound virus in the cytoplasm (Mallery et al., 2010). Also, a recent publication has shown that Trim5α recognizes a "pattern" on retroviral capsids by assembling hexagonally on the capsid lattice (Ganser-Pornillos et al., 2011).

One of the pathways that is activated after PRR-PAMP interactions is the TAK1 kinase complex involving ubiquitination. Ubiquitination of substrates requires activation of ubiquitin (Ub) by a Ub-activating enzyme (E1), followed by transfer of Ub to a Ub-conjugating enzyme (E2), followed by transfer of Ub onto the final substrate via a Ub-protein ligase (E3). When cell surface PRRs are stimulated, factors such as TNF receptor-associated factor 6 (TRAF6) are recruited to the receptor. TRAF6 is a RING domain-containing E3 Ub-ligase, which, together with E2 Ub-conjugating dimers UBC13/UEV1A, catalyzes the synthesis of K63-linked polyubiquitin chains (Figure 1). These chains function as a scaffold to recruit the TAK1 kinase and regulatory subunits TAB1, TAB2, and TAB3. Formation of this kinase complex results in activation of TAK1 and a subsequent signal cascade. Trim5α is also a RING domain-containing E3 ubiquitin ligase, but the role of the RING domain in Trim5

inhibition of retroviruses has been controversial. Through a series of elegant cell culture and in vitro experiments using purified proteins, Pertel et al. (2011) provide evidence for a model whereby Trim5α, upon recognition of retroviral capsids, engages E2 Ub-conjugating enzymes UBC13 and UEV1A to generate free K63-linked polyubiquitin chains which subsequently activate TAK1. Activation of TAK1 occurs through direct interactions of Trim5α with the TAK1 complex consisting of TAK1, UBC13/UEV1A, and adaptor proteins TAB2 and TAB3. These events lead to downstream activation of transcriptional and posttranslational innate immune responses (Figure 1). Thus, by linking capsid recognition events to a direct mechanism for activation of innate immune response genes, Pertel et al. show that Trim5α acts as a bona fide protein-sensing PRR.

In some species, such as cows and rodents, expansions have occurred in the *Trim5* locus resulting in up to eight homologs in mice (Tareen et al., 2009). Interestingly, one of these mouse *Trim5* homologs, confusingly known as *Trim30*, was shown to also be involved in TAK1 signaling, however by degrading TAB2 and TAB3, therefore resulting in an opposite effect (Shi et al., 2008) as that described for human Trim5α. These results may complicate the use of mice as models for testing the in vivo relevance of this locus in innate immunity to pathogenic infections.

Curiously, Trim5α also has a role in signaling resulting in antiviral consequences that are independent of retroviral capsid recognition. Knockdown of Trim5α in myeloid cells blunted the transcriptional responses of these cells to LPS, a PAMP derived from gram-negative bacteria.

Moreover, treatment of cells with LPS leads to a generalized antiviral state, and knockdown of Trim5α partially relieves this block to a range of viruses that are not directly recognized by Trim5α (Pertel et al., 2011). Another study had also shown that overexpression of Trim5α activates NF-κB in the absence of retroviral capsid recognition (Tareen and Emerman, 2011). These results put Trim5α as a central player in generalized innate immune responses. Indeed, although HIV-1 is poorly recognized by human Trim5α, this protein could nonetheless be important in HIV-1 progression, since low levels of LPS are associated with chronic immune activation in AIDS patients (Brenchley et al., 2010). Moreover, there are human polymorphisms in *Trim5*, and one in particular, a mutation in the RING domain (H43Y), that has been associated with HIV progression in some studies (van Manen et al., 2008). It will be important to look at the role of human polymorphisms in *Trim5* that might have subtle differences in signaling cascades in the clearance of pathogens in chronic and acute infections. Furthermore, as *Trim5*
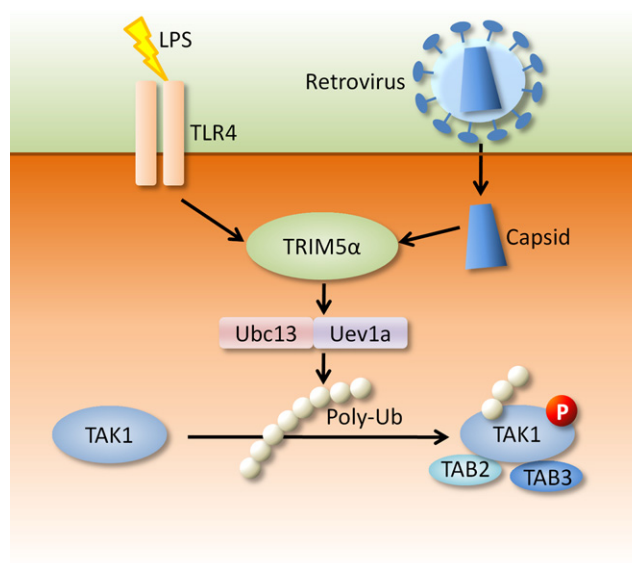

Figure 1. Trim5α Functions as a PRR to Activate Innate Immunity Signaling
Upon sensing viral capsid, Trim5α, together with E2-conjugating enzymes UBC13/UEV1A, catalyzes the synthesis of K63-linked polyubiquitin (poly-Ub) chains. These chains serve as a scaffold to recruit the TAK1 kinase complex consisting of TAK1 and the regulatory proteins TAB2 and TAB3. These events result in activation of TAK1 via its autophosphorylation on Thr187, subsequently activating transcriptional regulators such as NF-κB. Trim5 also plays a role in LPS signaling via the Toll-like receptor 4.

polymorphisms have also been associated with the degree of responsiveness to Rubella vaccination (Ovsyannikova et al., 2010), it is possible that finding ways to artificially engage Trim5α might prove to be a useful strategy to induce responses in the context of candidate HIV vaccines.

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