

Figure 1 | The design of Qi and colleagues' energy-harvesting devices¹. The stretchable devices consist of wavy ribbons made of piezoelectric material (lead zirconate titanate; PZT) on silicone rubber. They can withstand greater applied mechanical strain without cracking than can equivalent materials made into flat ribbons.

strain without fracturing. Qi *et al.*¹ have now extended this concept for the fabrication of stretchable, energy-harvesting devices using the technique of epitaxial layer transfer (ELT).

ELT involves the selective etch, lift-off and transfer of a single-crystalline thin film from a primary substrate, on which the film has been grown, to a secondary, receiver substrate. The technique allows the placement of a user-defined semiconductor 'X' on a substrate 'Y' (termed X-on-Y, or XoY) and has proved useful in a broad spectrum of electronic and photonic applications. ELT was used^{3,4} as early as 1975, when micrometre-scale gallium arsenide/aluminium gallium arsenide (GaAs/AlGaAs) films were transferred from bulk GaAs wafers to glass substrates to enable the production of GaAs night-vision goggles and solar cells. In the late 1980s, a similar process was used⁵ to fabricate thin-film GaAs diode lasers and other optoelectronic devices on glass substrates. And in the mid-to-late 2000s, researchers demonstrated^{2,6} the ability to extend the ELT technique to substrates that are mechanically flexible and stretchable. This then led to the development of electronic devices that can conform to cover irregular and curvy surfaces.

Recently, the utility of ELT was further expanded⁷ to allow the transfer of ultrathin films of type III–V semiconductors — down to a few nanometres in thickness — to silicon/silicon oxide (Si/SiO₂) substrates. This advance⁷ offers the advantage of combining III–V semiconductors, which have high electron mobility, with well-established silicon technology for the exploration of energy-efficient electronics. Qi and colleagues' work¹ demonstrates yet another application of the ELT process: the production of buckled PZT strips on a rubber substrate for use as piezoelectric energy-harvesting devices.

More specifically, their approach is as follows. First, they pre-stretched a slab of silicone

rubber. Second, they transferred, by means of ELT, PZT ribbons that had been patterned on a magnesium oxide substrate to the pre-stretched silicone substrate. After releasing the rubber substrate, the initially flat ribbons buckled, forming wavy geometries of amplitude and wavelength that depended on, among other factors, the thickness of the ribbons and their interaction with the rubber.

Next, the authors measured the piezoelectric response of the wavy PZT ribbons (Fig. 1), as well as that of flat PZT ribbons, to applied mechanical strain. In comparison to flat PZT ribbons, which exhibited failure under less than 1% strain, wavy ribbons withstood up to about 8% strain without cracking. Interestingly, wavy PZT ribbons also displayed an enhancement of up to 70% in piezoelectric response compared with flat ribbons, which the authors attribute to the large location-dependent strain gradient of the wavy structures.

Qi and colleagues' stretchable, piezoelectric energy-harvesting materials are an important advance in the rapidly growing field of conformal electronics and sensors. But as they

themselves note¹, as far as the actual manufacturing of devices is concerned, a number of engineering challenges remain. Specifically, low-cost generation of wavy piezoelectric strips on large areas of substrate — ranging from cubic centimetres to metres of surface coverage — has yet to be demonstrated, and requires further research. In addition, more work is needed to determine the maximum density of electrical energy that can be generated by the devices, which will effectively establish their potential niche applications. ■

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IMMUNOLOGY

TRIM5 does double duty

TRIM5 proteins limit retroviral infection by targeting the viral coat. It now seems that these proteins can also serve as pattern-recognition receptors, which initiate cellular innate immune responses. SEE LETTER P.361

CHRISTOPHER AIKEN & SEBASTIAN JOYCE

Mammalian proteins use various mechanisms to restrict retroviral infection¹. One such protein, TRIM5, blocks HIV-1 infection in some primate species: when the virus enters a cell, TRIM5 engages with the viral coat, or capsid, inducing premature uncoating². On page 361 of this issue, Pertel and co-workers³ report that this protein has another function: TRIM5 is involved in activating cellular innate immune responses.

Cells sense infection with viruses and bacteria by detecting pathogen-specific molecules, including double-stranded RNA, lipids and carbohydrates. These molecules often form repeating structures — referred to as pathogen-associated molecular patterns — that bind to pattern-recognition receptors and activate signalling pathways that result in inflammation and cellular resistance to infection.

Pertel *et al.* show that increased expression of TRIM5 promotes the expression of specific genes by activating immune signalling pathways that are mediated by the transcription

factors AP-1 and NF- κ B. Accordingly, the removal of TRIM5 from cells not only reduces the expression of specific genes involved in innate cellular responses, but also allows HIV-1 to infect cells exposed to LPS. (LPS is a bacterial membrane component that binds the pattern-recognition receptor TLR4 and prevents HIV-1 infection by inducing a cellular antiviral state.) TRIM5's contribution to LPS-induced resistance to HIV-1 is probably independent of viral recognition: the cells Pertel and colleagues studied contain human TRIM5 α , which does not bind the HIV-1 capsid efficiently. Nonetheless, their data indicate that TRIM5 contributes to innate immune responses triggered by a specific pattern-recognition receptor.

In addition to binding to and restricting retroviral capsids, TRIM5 is an E3 ligase enzyme that catalyses the attachment of the small modifier protein ubiquitin to itself and, potentially, to other proteins⁴. Whether the ubiquitin-ligase activity of TRIM5 plays a part in its retrovirus-restriction activity had remained unclear.

The attachment of multiple ubiquitin molecules to a target protein often leads to

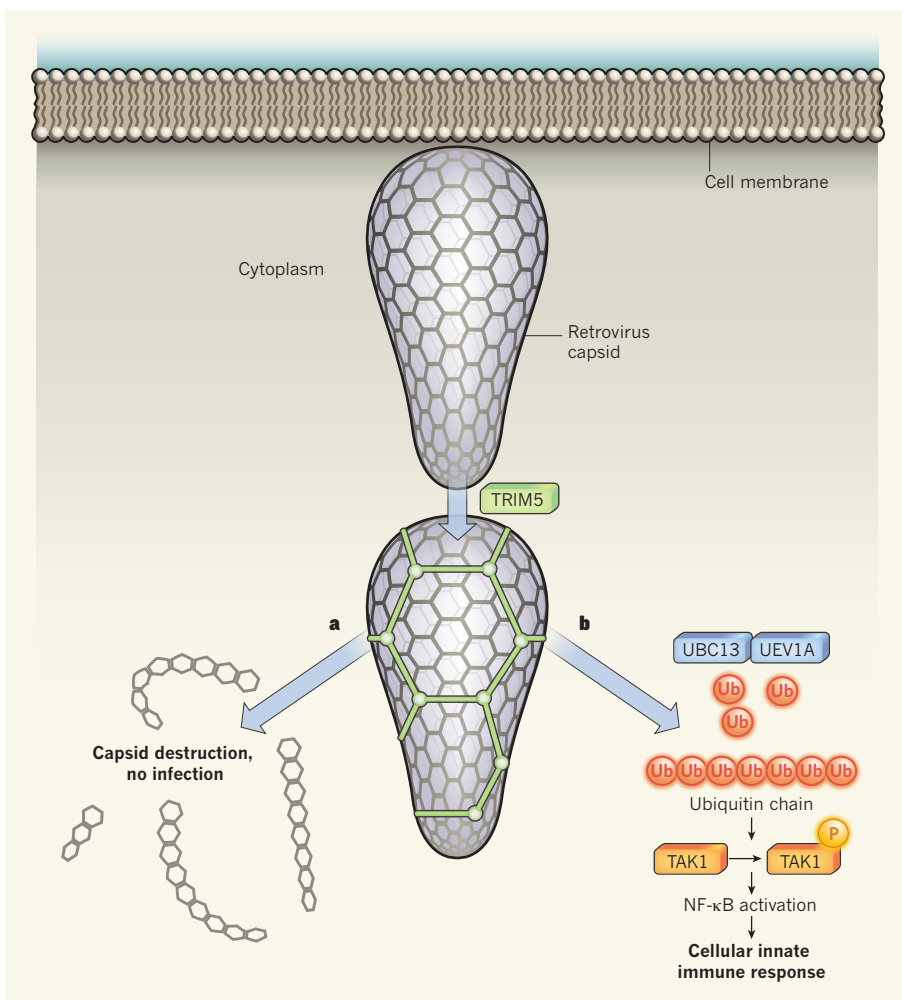


Figure 1 | TRIM5 strikes twice. When a retrovirus enters the host cell cytoplasm, TRIM5 proteins bind to the viral capsid, causing structural alterations that lead to capsid fragmentation (a). Pertel *et al.*³ show that TRIM5 binding to the viral capsid also activates the protein's ubiquitin ligase activity, which, together with the UBC13–UEV1A enzyme complex, results in the synthesis of ubiquitin (Ub) chains. The chains stimulate TAK1 phosphorylation and the expression of NF- κ B-dependent genes (b). This may induce an antiviral state, further protecting the host from infection.

its destruction. But ubiquitin also has other cellular roles. For instance, unattached ubiquitin chains, which form through the binding of one ubiquitin molecule to the lysine 63 (K63) amino-acid residue of another ubiquitin, can directly activate protein kinase enzymes⁵ such as TAK1, which mediates innate immune signalling by activating AP-1 and NF- κ B. In a survey of candidate host proteins through which TRIM5 might signal, Pertel *et al.*³ found that this protein associates with TAK1 and with TAB2 and TAB3 — adaptor proteins that facilitate TAK1 activation. The ubiquitin-conjugating enzyme complex UBC13–UEV1A also associates with TRIM5 (Fig. 1).

To analyse the catalytic activity of TRIM5 *in vitro*, the authors produced TRIM5–CypA, a fusion protein, from owl monkey cells. This is a noteworthy technical achievement, because TRIM5 proteins are notorious for their insolubility and so are difficult to manipulate. Using this construct, Pertel *et al.* demonstrated that

TRIM5 catalyses the formation of K63-linked ubiquitin chains *in vitro*, activating TAK1. TRIM5 extracted from human cells also made K63-linked ubiquitin chains, suggesting that this activity is common to TRIM5 proteins of different species. In this respect, TRIM5 proteins thus resemble TRAF6, another ubiquitin ligase that catalyses the formation of K63-linked ubiquitin chains and activates NF- κ B signalling⁶.

What is the link between TRIM5 binding to a retroviral capsid and its ubiquitin-ligase activity, which induces cellular innate immunity? TRIM5 α assembles into a large hexameric lattice on the viral capsid surface⁷, but whether capsid engagement influences its catalytic activity was unknown. In an experimentally well-controlled biochemical study, Pertel *et al.* show that TRIM5–CypA binding to artificial capsid-like structures markedly activates the synthesis of K63-linked ubiquitin chains *in vitro*. So it seems that sensing of the viral capsid induces TRIM5's ubiquitin ligase

activity, which, in turn, promotes innate immunity.

The researchers did not directly investigate whether this is also the case in cells. They show, however, that exposure of the cells to a restriction-sensitive retrovirus results in the activation of several genes involved in innate immunity. For at least one of the genes, TRIM5 depletion prevented its activation. Thus, engagement of the viral capsid by TRIM5 correlates with innate immune signalling, leading the authors to conclude that this protein is a bona fide pattern-recognition receptor for retroviral capsids.

If viral engagement by the restrictive TRIM5 proteins is enough to prevent infection, what is the point of an innate antiviral response on top of this? Perhaps it is that, because TRIM5 restriction can be overcome at high viral doses, the innate response protects neighbouring cells, thereby preventing viral spread within the host. Moreover, restriction may be coupled to the signalling activity of TRIM5: Pertel *et al.*³ report that depletion of cellular UBC13 and TAK1 enhances the retroviral infection of cells that express a restrictive TRIM5 protein. This observation is unexpected, because it has been reported that TRIM5 inflicts direct structural damage on the viral capsid^{8,9} and that ubiquitination is not necessary for the restriction of viral infection¹⁰.

It is possible that the ubiquitin ligase activity of TRIM5 is important for both restriction and cell signalling, but that the two effects are independent. Furthermore, UBC13 and TAK1 may act in other ways to enhance the restriction activity of TRIM5 — for instance, by modulating its stability, activity or intracellular localization. Whether the human TRIM5 α protein, which unfortunately does not prevent HIV-1 infection, alerts the host to the presence of the virus remains to be seen.

Pertel *et al.*³ uncover a surprising facet of TRIM5 biology and a new mechanism for cellular sensing of viruses. Their paper is sure to stimulate the interest of virologists and immunologists alike. ■

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