Retroviral TRIMming

In February of this year, Joseph Sodroski and colleagues identified a cytoplasmic protein known as TRIM5 α (tripartite motif protein 5 α) as restricting HIV-1 infection in Old World monkeys (see Further reading). Now, three new papers show that TRIM5 α can account for other previously recognized retroviral-restriction activities in monkeys and in humans, indicating that the TRIM family might have a widespread, evolutionarily conserved role in innate immunity to retroviral infection.

The mouse retroviral-restriction factor Fv1 (Friend-virus-susceptibility factor 1) protects against infection with murine leukaemia virus (MLV), with the two main alleles, *Fv1^I* and *Fv1^b*, conferring resistance to different strains of MLV (B-MLV and N-MLV, respectively). Although the mechanism of action of Fv1 is unknown, it seems to involve an effect on viral capsid (CA) proteins, because polymorphism at position 110 of MLV CA determines the B- or N-tropism. Since the description of Fv1 more than 30 years ago, it has been shown that cells from other mammals can also restrict N-MLV, but not B-MLV, infection in a CA110-dependent manner; the corresponding human activity is known as Ref1 (restriction factor 1) and the simian activity is known as Lv1 (lentiviral-susceptibility factor 1). However, until now, the proteins responsible for Ref1 and Lv1 activity have not been directly determined.

All three groups showed that introduction of human TRIM5 α into a variety of cells from different species reproduced human Ref1 activity, in that it significantly blocked N-MLV infectivity but did not affect B-MLV infectivity. Reduction of TRIM5 α expression with small interfering RNA (siRNA) rescued permissivity to restricted N-MLV without affecting the unrestricted infectivity of B-MLV. Similarly, TRIM5 α from rhesus and African green monkeys reproduced the known restriction pattern of Lv1.

Mouse Fv1 is derived from an endogenous retroviral Gag protein, but this identification of Ref1 and Lv1 as TRIM5 α shows that they are not related to Fv1 or any Gag protein, despite the similar restriction patterns and specificity for position 110 of MLV CA. To explain this, Towers and colleagues propose a model in which Fv1 lies upstream of and depends on TRIM5 α for its activity. In support of this, using a human cell line that expresses mouse Fv1-N and can therefore restrict both N-MLV through endogenous human TRIM5 α and B-MLV through exogenous mouse Fv1-N, they showed that downregulation of TRIM5 α expression by siRNA rescues both N-MLV and B-MLV permissivity.

In addition to MLV, TRIM5 α can also restrict infection with other retroviruses, depending on

the species. For example, TRIM5 α from African green monkeys, but less so from humans, could restrict HIV-1 (as shown by Stoye and colleagues, and Bieniasz and colleagues). Also, TRIM5 α from African green monkeys could restrict infection with a strain of simian immunodeficiency virus (SIV) from macaques but not an SIV strain from African green monkeys. Therefore, Bieniasz and colleagues suggest that TRIM5 α might have evolved to prevent cross-species retroviral transmission and that for a particular retrovirus to colonize a new species requires adaptation to avoid species-specific TRIM5 α -mediated restriction — probably by mutations in the CA protein.

Given that the TRIM motif is shared by proteins encoded by more than 30 genes in the human genome, this interest in TRIM5 α might lead to the discovery of a family of TRIM factors that restrict different viruses. Indeed, Stoye and colleagues showed that TRIM1 from African green monkeys, humans and owl monkey kidney cells could restrict N-MLV.

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References and links

ORIGINAL RESEARCH PAPERS Hatzioannou, T., Perez-Caballero, D., Yang, A., Cowan, S. & Bieniasz, P. D. Retrovirus resistance factors Ref1 and Lv1 are species-specific variants of TRIM5 α . *Proc. Natl Acad. Sci. USA* **101**, 10774–10779 (2004) | Keckesova, Z., Ylinen, L. M. J. & Towers, G. J. The human and African green monkey TRIM5 α genes encode Ref1 and Lv1 retroviral restriction factor activities. *Proc. Natl Acad. Sci. USA* **101**, 10780–10785 (2004) | Yap, M. W., Nisole, S., Lynch, C. & Stoye, J. P. Trim5 α protein restricts both HIV-1 and murine leukemia virus. *Proc. Natl Acad. Sci. USA* **101**, 10786–10791 (2004).

FURTHER READING Stremlau, M. *et al.* The cytoplasmic body component TRIM5 α restricts HIV-1 infection in Old World monkeys. *Nature* **427**, 848–853 (2004).

IN THE NEWS

UK 5-in-1 baby vaccine

The UK government has announced that, from September, a new 5-in-1 vaccine against diphtheria, tetanus, pertussis (whooping cough), Hib (*Haemophilus influenzae* type b) and polio will be given to babies of more than two months of age.

Specifically, there are three main changes to the current protocol. In response to the success of the worldwide polio-eradication programme, the separate oral administration of live attenuated polio virus — which provides better protection at the population level but carries a risk of paralytic disease — is being replaced by injection of dead virus. The pertussis component is being switched from a whole-cell vaccine to an acellular component vaccine, to reduce side-effects. The mercury-containing preservative thiomersal is also being removed. Health Minister John Hutton explained that “The changes set out today will further improve the [vaccination] programme and benefit children.”

However, although parent groups have welcomed the removal of mercury, which some studies have linked to autism-like symptoms, they are concerned that the combination of vaccines into a single injection will ‘overload’ a baby’s immune system. As Jacki Fletcher, founder of Jabs (Justice, Awareness and Basic Support), said “How did they find out it was safe to do it in this combination?”

These doubts come despite the fact that the 5-in-1 vaccine has been given to 3.5 million children in Canada during the past 7 years. Elizabeth Miller of the UK’s Health Protection agency also explained that because the purified acellular form of pertussis only contains four antigens compared with hundreds in the whole-cell form, this will actually “reduce the amount of immune stimulation” (*New Scientist*).

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