

## Immune cells take in unknown enemies

MHC class I molecules normally present endogenously synthesized antigens and thus activate cytotoxic T lymphocytes (CTLs). In antigen-presenting cells (APCs), however, some seemingly extracellular antigens are cross-presented: they are loaded onto the class I pathway in addition to their usual presentation by MHC class II. For example, APCs in mice were recently shown to activate antipoliovirus CTLs, despite lacking a receptor for the virus, presumably by cross-presenting poliovirus antigens on class I. But now Stefan Freigang, Rolf Zinkernagel, and colleagues (University of Zurich, Zurich, Switzerland) show that the missing receptor does not stop viral uptake in APCs, suggesting that cross-presentation

is not needed as an explanation.

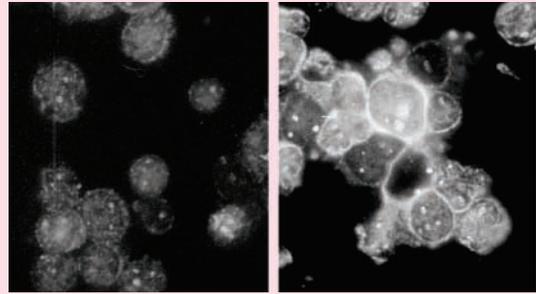
“Even in a situation where everybody would suspect that cross-presentation is going on, we see that APCs are taking in the virus,” says Freigang. His group finds viral RNA in APCs of the receptorless mice. Further, the RNA had to be translated to elicit CTL

responses. Thus, even if cross-presentation—which does not require translation—might occur, it is too inefficient under physiological infection conditions to cause an immune response.

Not all cells are susceptible to viral infection, since only transgenic mice expressing the poliovirus receptor

develop disease symptoms. So what is special about APCs is not clear. “We can only speculate on how the virus gets into the cell,” says Freigang. Perhaps a subset of APCs has the ability to take in a variety of pathogens with a nonspecific receptor. ■

Reference: Freigang, S., et al. 2003. *Proc. Natl. Acad. Sci. USA.* 10.1073/pnas.1835685100.

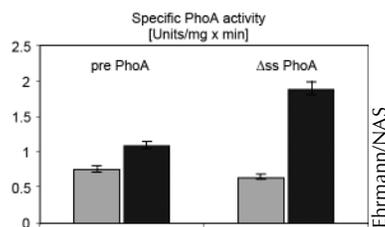


Poliovirus RNA (white) still gets into APCs that lack the right receptor.

Freigang/NAS

## Fold me or leave me

New results from Markus Eser and Michael Ehrmann (Cardiff University, Cardiff, UK) indicate that the protein that sends secreted proteins through the translocon also prevents cytoplasmic proteins from meeting the same fate.



**SecA helps proteins fold (right), unless they have a signal sequence (left).**

Secreted bacterial proteins are targeted to and pushed through the translocon by the protein SecA. Because proteins must be threaded through the translocon in an unfolded state, the authors guessed that SecA might prevent folding of signal sequence-containing, and therefore secreted, proteins. Instead, they found just the reverse—SecA promotes the folding of proteins that lack export signals.

SecA bound to unfolded proteins even if they did not contain signal sequences. For proteins lacking an export signal, SecA promoted their folding to an active state. Once folded, SecA no longer binds, so secretion is thwarted. SecA did not have chaperone activity with signal sequence-containing proteins. What accounts for this difference is not yet known, but perhaps strong binding of SecA to the signal sequence disrupts its ability to promote folding. Yeast and human cells do not have a SecA homologue, but a different translocon-associated chaperone may perform an analogous function. ■

Reference: Eser, M., and M. Ehrmann. 2003. *Proc. Natl. Acad. Sci. USA.* 10.1073/pnas.2234410100.

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Ehrmann/NAS

## Fusion gets in the groove

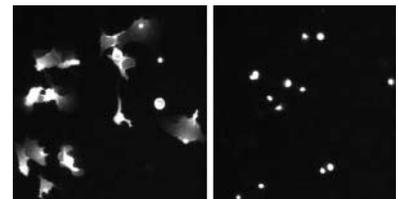
The only confirmed mechanism for protein-mediated membrane fusion involves the formation of helix bundles, in which helices attached to two membranes pack against one another to draw together the membranes. In the final fused state, six-helix bundles are formed by HIV Env and paramyxovirus F proteins, members of the class I group of viral fusion proteins. Although the class I founding member, influenza HA, also forms a six-helix bundle, Heather Park, Jennifer Gruenke, and Judith White (University of Virginia, Charlottesville, VA) now show that this bundle is not sufficient for fusion.

For HA, interactions between a nonhelical region and a trimer of helices cause fusion. Using mutational analyses, the group shows that fusion requires contacts between a long chain, which they call the leash, near the viral membrane with the helices near the target membrane (usually a host endosome as the virus escapes into the cytoplasm). They suggest that packing of the leash into the

grooves of the helices condenses HA, thus bringing together viral and host membranes. “There’s nothing holy about helix-helix interactions as a means to pull membranes together,” says White.

“You can do it with other types of interactions.” This may help explain why class II viral fusion proteins work although they do not have a lot of helical structure. ■

Reference: Park, H.E., et al. 2003. *Nat. Struct. Biol.* 10.1038/nsb1012.



Membrane fusion is blocked by mutations in the HA leash region (right).

White/Macmillan