Antiviral walls

The innate immune system has the tricky task of foiling all invaders rather than targeting a specific few. Eugenia Leikina, Leonid Chernomordik (NIHHD, Bethesda, MD), and colleagues report that defensin antimicrobial peptides use a unique nonspecific method: they cross-link surface glycoproteins and thus freeze them in place. The resulting web of proteins obstructs the fusion of viral and cell membranes.

Defensins caught Chernomordik’s eye because he works on membrane fusion and the defensins have broad specificity. He thought they might interfere with membrane properties, but was disappointed when they accelerated rather than inhibited fusion between protein-free liposomes.

With virus-infected cells, however, things got more interesting. Defensins did not block virus binding or endocytic uptake but did block membrane fusion. Membrane glycoproteins no longer diffused over the membrane surface.

The lack of diffusion may be the key. When a virus binds to a cell there is still a gap of ~10 nm between the membranes, which can be closed only when proteins in a tiny patch happen, via random diffusion, to get out of the way. With defensins bound, suggests Chernomordik, “the proteins would not move away.”

“This might be the first natural antiviral agent targeting fusion,” says Chernomordik. “The fusion stage targeted is elusive, because if proteins are mobile it is not rate limiting.” He also notes a tantalizing analogy to prokaryotes, which use covalently cross-linked proteoglycans as a barrier, forcing bacteriophages to use injection rather than fusion mechanisms. “For a short time,” he says, “our cells become prokaryotic by erecting these walls.” JCB

Repairing for death

The targets of cytotoxic T lymphocytes (CTLs) determine their own mode of death, say Dennis Keefe, Judy Lieberman, and colleagues (Harvard Medical School, Boston, MA). The dying cells patch themselves up so that rapid and messy necrosis is avoided in favor of a more lengthy and controlled apoptosis.

The CTLs deliver their insult in the form of perforin, a pore-forming protein that helps get proteases called granzymes into the target cell. The Boston group showed that perforin addition to a target cell induced a Ca2+ transient and a massive plasma membrane repair response. Similar Ca2+-induced responses, in which lysosomal and other membranes are recruited to patch up plasma membrane holes, are known to be induced by mechanical damage to cell membranes.

Blocking the rise in Ca2+ and thus the repair response resulted in far more necrosis. This is presumably a consequence of breaching the plasma membrane barrier. Necrosis is induced before there is time to induce the slower process of apoptosis, which tends to sequester intracellular proteins and thus avoid unwanted autoimmune responses.

If the plasma membrane is being repaired, perforin is probably acting within endosomes to release granzymes into the cytoplasm. The Boston group gathered more evidence for this theory, but they still want to find out how perforin induces higher levels of endocytosis, and what changes within the endosome turn on perforin’s pore-forming activity. JCB

Mito immunity

Mitochondria may serve as a surveillance site where innate immune responses and apoptosis are coordinated, say Rashu Seth, Zhijian Chen, and colleagues (UTSW, Dallas, Texas). They base this idea on their discovery of an antiviral protein that hangs out on mitochondria.

The protein was discovered by three groups and named MAVS, VISA, and IPS-1. Overexpression of MAVS (named for its mitochondrial antiviral signaling) induces interferon expression and thus increased antiviral defenses. It operates downstream of RIG-I, which detects viral double-stranded RNA, but upstream of the NF-kB and IRF3 families of transcription factors. RNAi of MAVS abolishes viral activation of NF-kB and IRF3 and thus knocks out the antiviral response.

MAVS function requires its transmembrane domain, which resembles that of the apoptosis protein Bcl-2. Both proteins are found on mitochondria. This puts MAVS closer to some viruses, which replicate using membranes such as the ER and perhaps mitochondria. It may also allow the coordination of decisions by the innate immune system and the apoptosis machinery; some members of the latter have already been implicated in innate immunity. Chen suggests that innate immunity may be just one more service that mitochondria provide for the cell. JCB

References:
Kawai, T., et al. 2005. Nat. Immunol. doi:10.1038/ni1243.
Seth, R.B., et al. 2005. Cell. 122:669–682.
Xu, L.-G., et al. 2005. Mol. Cell. 19:727–740.