

Research Roundup

When is a virus an exosome?

A bold new theory suggests that retroviruses have hijacked an intercellular communication system for both their biogenesis and spread. The concept, outlined by Stephen Gould, Amy Booth, and James Hildreth (Johns Hopkins University, Baltimore, MD) has implications for HIV treatment and immunization strategies, and may explain why tissue rejection occurs in humans.

Hildreth was looking at human proteins that HIV acquires during its biogenesis, and noticed that lysosomal proteins were in the mix. This ties in with recent findings in this and other journals that HIV is packaged in late endosomes (for review see Amara and Littman, 2003).

In uninfected cells, this endosomal compartment invaginates to form small, internal vesicles. The bag of vesicles, or multivesicular body, can fuse with the plasma membrane to disgorge these vesicles, named exosomes, which then travel to other cells to transmit messages. In the immune system, exosomes transfer peptide-laden MHC proteins to noninfected cells, and also act as miniature versions of antigen-presenting cells.

Hildreth now proposes that “the virus

is fully an exosome in every sense of the word.” Others have found that HIV particles contain MHC, but by the exosome hypothesis they may also contain proteins that exosomes use to fuse with target cells and to avoid attack by complement. As Gould points out, an exosome makes a perfect vector for HIV, because an exosome “is not just proteins in a vesicle, it’s something that is meant to traffic.”

The idea may explain how HIV both infects cells that lack receptors for its surface gp120 protein, and avoids robust, virus-directed immune responses. “Even if one completely blocks the gp120-related pathway of entry, HIV will have this second, albeit less efficient, means of getting into cells,” says Hildreth.

To block all entry, suggests Hildreth, perhaps the MHC should be the target. Alloimmunization—immunization with a wide range of MHC and other protein variants (e.g., by injecting killed leukocytes)—might allow a newly infected individual to mount a quick attack on the incoming HIV, which is packed with foreign MHC. Gould even suggests, “this is why we have tissue rejection responses—[they evolved] to protect us from retroviruses.” He points out that alloimmunity predates and thus could not have arisen from adaptive immunity.

The more extreme idea of xenoimmunization does work in monkeys, which can reject SIV grown in human cells. And for Thomas Lehner (Guy’s Hospital, London, UK), who has been pushing the idea for several years, alloimmunization “is far better than anything we have at the moment.” But it has languished since the monkey experiment, perhaps based on fears that it would prevent later transplants, cause rejection during pregnancies, and fail to catch a handful of HIV particles before they replicate and thus incorporate self-MHC.

Mark Feinberg (Emory University, Atlanta, GA) warns, “for a protective vaccine, the regulatory environment is exceedingly conservative, because you are dealing with healthy people.” Even if concerns such as transplantation are of little importance in the developing world, a vaccine developed in the industrialized world will have to follow the exacting standards of bodies such as the US Food and Drug Administration (FDA). Unfortunately, says Feinberg, “the FDA goes off in one direction, and the epidemic goes off in another.” ■

References: Gould, S.J., et al. 2003. *Proc. Natl. Acad. Sci. USA*. 10.1073/pnas.1831413100. Amara, A., and D.R. Littman. 2003. *J. Cell Biol.* 162:371–375.

Centromere errors get chewed out

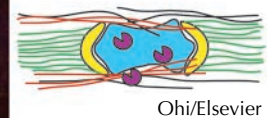
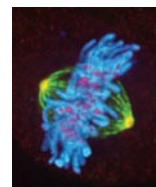
Microtubule (MT) ends that invade into the inner centromere may get chewed up, say Ryoma Ohi, Timothy Mitchison (Harvard Medical School, Boston, MA), and colleagues. The process should help prevent MTs emanating from a single pole from attaching to both sister kinetochores.

Ohi proposes that the chewing is performed by the KinI kinesin MCAK. He found a new MT-binding protein, ICIS, that binds to MCAK, relies on it for localization at the inner centromere, and further activates MCAK’s MT-depolymerizing activity *in vitro*.

Although ICIS depletion causes widespread MT polymerization, probably because of co-depletion of MCAK, it almost certainly has a more specific function at the inner centromere. Just away from the inner centromere—specifically near the kinetochore—a high density of MTs is desirable if

the cell is to ensure kinetochore capture. “But it’s also dangerous,” says Ohi. Slightly errant MTs can skirt around the closest kinetochore, cross the inner centromere, and attach to the more distant kinetochore. Ohi predicts that ICIS-stimulated MCAK intercepts these MTs before they can reach their incorrect target. He now proposes to test whether interference with the MCAK/ICIS system causes attachment errors, as his model predicts. ■

Reference: Ohi, R., et al. 2003. *Dev. Cell.* 5:309–321.



Ohi/Elsevier

ICIS (red, left) helps destroy invading microtubules (red, right).