Centrosomes deliver the death blow

Just as a deadly martial arts master channels his inner chi to deliver a fatal strike, cytotoxic T cells (CTLs) channel their toxic secretory granules to strike an infected target cell. New work by Jane Stinchcombe, Gillian Griffiths, and colleagues (Sir William Dunn School of Pathology, Oxford, UK) reveals that centrosomes do this channeling, going right to the plasma membrane to deliver their secretory granule death blows.

A CTL targets an infected cell by making transitory contact via an immunological synapse. Lytic protein–containing secretory granules are then released at the synapse to kill the target. Trafficking of the granules to the synapse was known to require transport along microtubules, but just how granules were delivered was unknown.

The general assumption was that CTLs would deliver their secretory granules in the same way that melanocytes deliver pigment for secretion—by transporting it along microtubules, transferring it to the actin cytoskeleton, and then delivering it to the membrane. Griffiths’s group thus looked at actin in CTLs, but found that it is completely cleared away from the synapse.

The authors found that secretory granule movement toward the minus ends of microtubules was sufficient for killing target cells. Granules thus move toward the centrosome, which associates with microtubule minus ends, not toward plus ends at the plasma membrane.

The team observed that the centrosome itself associates with the membrane in a large number of synapses. They hypothesize that the action of clearing the actin might, via actins’ attachment to microtubules, pull the centrosome close enough to the synapse membrane to send out the granules directly. Griffiths proposes that such direct delivery, without the need for transfer to the actin cytoskeleton, might also explain how the same CTL can engage and disengage synapses rapidly to kill multiple target cells, much like Bruce Lee rapidly defeats multiple opponents when surrounded.

Reference: Stinchcombe, J.C., et al. 2006. Nat. Cell Biol. doi:10.1038/nature05071.
HIV rides the tRNA train to the nucleus, according to Lyubov Zaitseva, Richard Myers, and Ariberto Fassati (University College, London, UK).

For HIV to propagate inside cells, it must first enter the nucleus and, using its reverse transcription complex (RTC), integrate into the host genome. Fassati and his team previously showed that a nuclear import protein called importin 7 was partly responsible for HIV RTC transport to the nucleus.

The team has now set about an unbiased task to find other nuclear import factors. Through multiple cell fractionation steps, they identified an RNA component capable of supporting nuclear import of HIV RTC. Sequencing revealed that the component was tRNA. Sure that tRNAs—instrumental for cytoplasmic protein translation—could not be responsible, Fassati thought, “Oh no! It’s all wrong, we’ve got to start all over again.” Only after multiple repetitions was the team convinced that the tRNA was not merely a contaminant.

Virtually all the tRNAs isolated from the active fraction (the one capable of nuclear import) had defective 3′ ends and were thus incapable of supporting translation. Wild-type tRNAs, on the other hand, had very little nuclear import activity.

Fassati speculates that perhaps the defective tRNAs get shuttled back to the nucleus for repair or degradation. Nuclear import costs energy, but the expense is probably worthwhile to ensure undisturbed protein translation. Whatever the host cell’s cost, HIV enjoys a free ride. JCB

Reference: Zaitseva, L., et al. 2006. PLoS. 4:1689–1706.

Ubp6 delays force destruction

The destructive force of the proteasome is tempered by one of its own components, report John Hanna, Daniel Finley, and colleagues (Harvard Medical School, Boston, MA).

The traditional view of the proteasome was, says Finley, “like a pencil sharpener,” mindlessly chewing away at ubiquitinated proteins. The characterization of one proteasome-associated factor now changes that view. Ubp6, the team shows, actually delays the rate of protein destruction. Proteasomes purified from yeast Ubp6 deletion mutants degraded ubiquitinated cyclin B protein faster than did those from their wild-type counterparts.

Ubp6 is a deubiquitinase, but this activity was not responsible for delaying degradation. Inhibiting its deubiquitinase active site did not speed up degradation. Ubp6 also needed to be bound to the proteasome to delay degradation, which would not be necessary if the delay tactic was simply to prevent targeting of proteins to the proteasome by removing ubiquitin moieties.

Instead, Ubp6 seems to delay degradation, at least in part, by inhibiting the action of a second proteasome component, called Rpn11. Rpn11 is itself a deubiquitinase whose activity is strictly coupled with degradation, unlike Ubp6.

Though Rpn11 inhibition might not be the sole cause for the degradation delay, it is clear that the proteasome is a more finely self-tuning machine than was first thought. JCB

Reference: Hanna, J., et al. 2006. Cell. 127:99–111.