In This Issue

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Cytomegalovirus sticks it to MHC

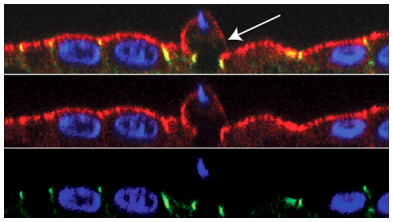
Viruses have numerous tricks for dodging the immune system. Stagg et al. reveal a key detail in one of these stratagems, identifying a protein that enables cytomegalovirus to shut down an antiviral defense.

Cytomegalovirus, which most people contract at some point in their lives, eludes immune system surveillance by targeting the protein MHC I. When we're sick, MHC I captures bits of viral proteins and presents them to cytotoxic T cells, which respond by killing cells that harbor the virus, stanching the infection. However, two cytomegalovirus genes dupe cells into ubiquitinating MHC I and demolishing it in the proteasome, the cellular garbage disposal. To trigger MHC I ubiquitination, the genes co-opt a cellular protein called the E3 ligase. Researchers haven't been able to pin down the identity of this protein, which could be one of several hundred enzymes.

Stagg et al. sifted 373 candidates by depleting them one by one with RNAi. Knocking down a ligase called TRC8 spared MHC I from destruction, the team found. Mutant versions of TRC8 that curtail ubiquitination allow MHC I to return to duty. Researchers know little about the function of the protein except that it is mutated in some rare hereditary and sporadic kidney tumors. That could mean that one of the normal targets of TRC8 helps spur cancer.

Stagg, H.R., et al. 2009. *J. Cell Biol.* doi:10.1083/jcb.200906110.

Putting the squeeze on apoptotic cells



A dying epithelial cell makes an apical exit.

A dying epithelial cell doesn't receive tender treatment from its neighbors. They collaborate to evict it. Now, Slattum et al. reveal how epithelial layers force unwanted cells to leave in a specific direction.

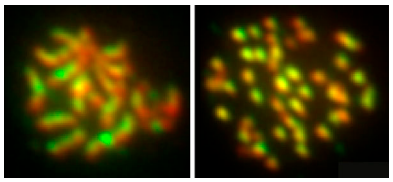
An apoptotic cell sends a warning to its epithelial neighbors. They respond by weaving an intercellular band of actin and myosin that contracts, popping the cell out of the epithelial layer. By closing a potential gap, ejection maintains the layer's integrity. Banished cells can exit the layer from the upper, or apical, surface. Or they can leave from the basal surface, slipping into the underlying tissue. The benefits of basal ejection aren't clear—it might allow recycling of the cell. Slattum et al. probed another mystery about the process—what determines which way the cell departs.

By labeling epithelial cells with tags that recognize only active myosin, the researchers discovered that the two exit routes require different contraction patterns. As little as 10% of the time, evicted cells leave basally. In those cases, only myosin in the upper portion of the surrounding cells clenches, pushing the apoptotic cell down. For an apical escape, myosin also contracts in the portions of the neighboring cells that face the sides and bottom of the dying cell. This compression lifts the apoptotic cell.

What enlists the additional myosin fibers required for an apical exit? The team found that when an upward push is needed, microtubules align toward the sides and bottom of the neighboring cells. The filaments direct p115 RhoGEF toward these cellular surfaces. In turn, p115 RhoGEF switches on RhoA that locally activates myosin. An unanswered question is whether cancer cells exploit the eviction mechanism to spread to other sites in the body.

Slattum, G., et al. 2009. *J. Cell Biol.* doi:10.1083/jcb.200903079.

Stopping sister synapses



Homologous chromosomes synapse in control cells (left) but fail to pair up when Pds5 is absent (right).

Sister chromatids act like homologous chromosomes when the meiotic protein Pds5 is missing, Jin et al. show. The work reveals that the protein ensures that only homologous chromosomes pair up during meiosis.

Meiosis ends with chromosome separation, but it starts with togetherness. Homologous chromosomes synapse, pairing up with help from the synaptonemal complex. Sister chromatids also get close, as the cohesin complex fuses them along their length. One protein that helps sisters stay together is Pds5. But probing Pds5's function has been tricky because loss of the protein is lethal. Jin et al. were able to engineer yeast cells that only switch off Pds5 during meiosis.

Plenty went wrong in the cells, the researchers found. The chromosomes were abnormally short and dense, meiosis stalled during prophase I, and homologous chromosomes didn't synapse. Although the cells created the double-stranded chromosome breaks that allow crossing over, they didn't repair the fractures.

But the most striking defect was that sister chromatids attempted to synapse—the synaptonemal complex formed between sister chromatids instead of between homologues. Sister chromatids are closer together than are homologues, so the cell presumably has to prevent them from synapsing so that homologues can line up. The researchers found that Pds5 works by suppressing Rec8, a cohesin component. They now want to tease out the rest of the molecular mechanism.

Jin, H., et al. 2009. *J. Cell Biol.* doi:10.1083/jcb.200810107.