In This Issue

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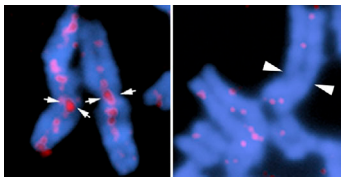
Vpr loosens chromatid ties



Compared to cells lacking Vpr (left), the cohesin Rad21 (red) is prematurely lost from centromeres (arrowheads) in the presence of Vpr (right).

An HIV-1 protein promotes chromosome missegregation by epigenetically modifying centromeric chromatin, Shimura et al. report.

Lymphocytes infected with HIV-1 display premature chromatid separation (PCS), in which sister chromatids come apart too early in mitosis, increasing the possibility of missegregation into the wrong daughter cell. This genomic instability may explain the increased incidences of certain cancers in HIV-1 patients, though how HIV-1 induces PCS is unknown.

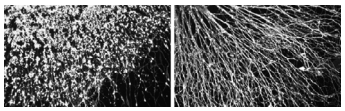
Shimura et al. found that viruses lacking the small accessory gene *vpr* didn't disrupt chromatid cohesion, whereas expression of Vpr alone was sufficient to induce PCS. Cohesin proteins, which link sister chromatids together until anaphase, were prematurely lost from the centromeres of mitotic chromosomes, probably because hSgo1, a protein that protects cohesins from dissociation, was displaced in the presence of Vpr.

hSgo1 is recruited to centromeres by heterochromatin proteins of the HP1 family. Shimura et al. saw that HP1-α and HP1-γ were displaced from centromeric chromatin by Vpr and that depleting HP1 proteins by RNAi caused similar levels of PCS. Vpr localized to chromosomes—especially at centromeres—and displaced HP1-α and -γ by recruiting the histone acetyltransferase p300 to modify the surrounding chromatin. Depleting or inhibiting p300 prevented Vpr from displacing HP1 proteins and inducing PCS.

Blocking the interaction between Vpr and p300 may therefore reduce genomic instability in long-term HIV-1 patients. Senior author Mari Shimura now wants to investigate how the Vpr protein localizes to host cell chromosomes.

Shimura, M., et al. 2011. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201010118.

DLK makes neuronal cutbacks



In the absence of NGF, control axons degenerate (left), whereas axons lacking DLK continue to thrive (right).

Sengupta Ghosh et al. describe how the kinase DLK activates a specific pool of JNK molecules to promote neuronal degeneration during development.

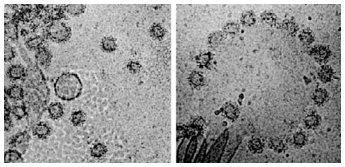
Developing sensory neurons compete for nerve growth factor (NGF); the losing cells die or retract their axons, thereby refining the innervation of peripheral targets. Sengupta Ghosh et al. generated mice lacking the mixed lineage kinase DLK and found that cell death was reduced in the peripherally projecting neurons of these animals. Dorsal root ganglion neurons isolated from DLK-null mice grew normally but were protected from axon degeneration and apoptosis after NGF withdrawal.

The researchers looked for signaling pathways altered in DLK-null neurons and found that, in the absence of DLK, NGF withdrawal failed to stimulate JNK, a MAP kinase that promotes neuronal degeneration. Yet basal levels of JNK activity—essential for normal neuronal function—remained unchanged in DLK-null neurons, indicating that DLK activates a subset of JNK molecules after NGF removal.

DLK bound to JIP3, a scaffold protein that also interacts with JNK. Neurons lacking JIP3 were also protected from JNK activation and neuron degeneration in the absence of NGF, suggesting that DLK and JIP3 form a specific signaling complex that activates JNK to promote axon degeneration and cell death without affecting other JNK functions. JNK promoted neuronal death by phosphorylating c-Jun, but this transcription factor wasn't required for axon degeneration. Senior author Joseph Lewcock now wants to investigate how NGF withdrawal stimulates DLK's activity.

Sengupta Ghosh, A., et al. 2011. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201103153.

Arf1 doubles up to release vesicles



Coatomer and wild-type Arf1 generate COPI vesicles from liposomes (left), but coatomer and dimerization-deficient Arf1 only induce coated vesicle buds (right).

The Arf1 GTPase and vesicle coat proteins catalyze distinct steps in the budding and release of COPI vesicles from the Golgi, Beck et al. reveal.

Arf1 recruits several types of vesicle coats to membranes, including the coatomer complex that forms COPI vesicles at the Golgi. Both the GTPase and the vesicle coat can deform membranes. Arf1 is thought to accomplish this by inserting an amphipathic helix into the outer leaflet of the lipid bilayer. Beck and colleagues previously found that Arf1 dimerizes on membranes and that a mutant version unable to pair up couldn't bend membranes or support vesicle formation, even though it could still recruit coatomer.

To find out why Arf1 dimerization is required for COPI vesicle biogenesis, Beck et al. analyzed Arf1's effects on lipid membranes by cryo-electron microscopy. In the presence of coatomer, both wild-type and dimerization-deficient Arf1 prompted the formation of coated vesicle buds. But these buds were unable to separate from their donor membrane in the presence of mutant Arf1, suggesting that coatomer drives the initial budding of COPI vesicles before dimerized Arf1 pinches them off. Vesicle scission was restored if the mutant Arf1 was artificially dimerized using chemical cross-linking reagents.

The mechanism of membrane separation is not entirely clear. It is more difficult for Arf1 to insert its amphipathic helix at the bud neck, where lipid headgroups are more tightly packed. If dimeric Arf1 is kept in place via its interactions with coatomer, an energetically unfavorable situation would arise, which could be relieved by vesicle scission. Similar mechanisms may also apply to other types of GTPase-dependent vesicles.

Beck, R., et al. 2011. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201011027.