In This Issue

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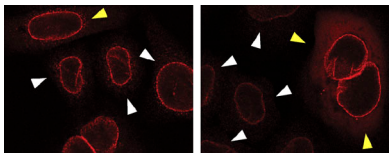
HIV-1 makes a pore adjustment



Nup62 (red) localizes to the nuclear envelope (left) but disperses into the cytoplasm in the presence of HIV-1 and Rev expression (yellow arrowheads, right).

HIV-1 induces extensive changes in its host cell's nuclear pores, Monette et al. reveal.

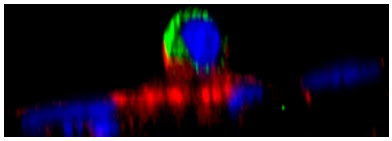
Like all viruses, HIV-1 hijacks the molecular machinery of its host cell to drive its own replication. One process disrupted by the virus is protein transport between the nucleus and cytoplasm. For example, HIV-1 prevents an RNA-binding protein called hnRNP A1 from entering the nucleus so that it can bind to the virus' RNA in the cytoplasm and initiate production of viral proteins. To learn more about HIV-1's effects on nucleocytoplasmic transport, Monette et al. isolated the nuclear envelopes of infected cells and analyzed their protein composition by mass spectrometry.

Viral infection altered the abundance of many nuclear envelope proteins, including the nuclear pore components called nucleoporins. At least one of these pore proteins—Nup62—relocalized to the cytoplasm of HIV-1–infected cells and was even incorporated into new HIV-1 virions budding from the plasma membrane. Nup62 is dislodged from nuclear pores at a late stage of the viral life cycle, when the virus' RNA is transported out of the nucleus. Viruses lacking the nuclear export protein Rev were unable to displace Nup62 into the cytoplasm. On the other hand, viral RNA was retained in the nuclei of host cells lacking Nup62, decreasing viral production and infectivity.

Author Andrew Mouland now wants to investigate whether the incorporation of Nup62 into budding virions aids their ability to infect new cells, for example by assisting the entry of viral genetic material into the nucleus. If so, a dual involvement in both early and late stages of HIV-1's life cycle would make Nup62 an attractive therapeutic target.

Monette, A., et al. 2011. *J. Cell Biol.* doi:10.1083/jcb.201008064.

Sphingolipid puts the squeeze on apoptotic cells



An apoptotic cell (green) is extruded from the zebrafish epidermis by a contractile actin ring (red).

Dying epithelial cells tell their neighbors to evict them by releasing the lipid sphingosine-1-phosphate (S1P), Gu et al. report.

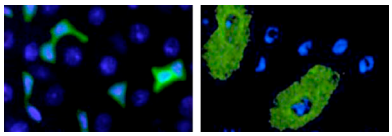
Healthy cells form an actomyosin ring around adjacent apoptosing cells to push them out of an epithelial layer without leaving any gaps in the tissue. But the signal sent by dying cells to their neighbors has remained mysterious. Gu et al. found that S1P—a lipid produced by apoptotic cells—was sufficient to induce actin cable assembly and that blocking S1P production by inhibiting sphingosine kinase prevented the extrusion of dying epithelial cells.

On the other hand, neighbors of the apoptotic cells needed the S1P receptor $S1P_2$ to expel the dying cells from their midst. Inhibiting or knocking down the receptor prevented epithelial monolayers from evicting dying cells in vitro, and zebrafish lacking $S1P_2$ couldn't extrude apoptotic cells from their epidermis. $S1P_2$ is a G protein–coupled receptor that likely stimulates actomyosin ring assembly by activating the Rho GTPase.

Gu et al. also found that surrounding cells take up the S1P produced by their dying neighbors. Since S1P promotes cell survival, this internalization may ensure that these cells stay alive to take the evicted cell's place. Senior author Jody Rosenblatt now wants to investigate how S1P is transferred between neighboring cells. She is also interested in whether defects in this pathway lead to dysfunctional epithelia in asthma and other diseases and whether S1P signaling contributes to the extrusion of living epithelial cells in both normal development and cancer metastasis.

Gu, Y., et al. 2011. *J. Cell Biol.* doi:10.1083/jcb.201010075.

Bigger isn't better



Intestinal stem cells (green) lacking TSC2 (right) grow larger than wild-type cells (left), which prevents them from proliferating.

Amcheslavsky et al. reveal that *Drosophila* intestinal stem cells lacking the tuberous sclerosis complex (TSC) grow too large to divide, resulting in defective gut epithelia.

TSC is a complex of two proteins that prevents the activation of the growth-promoting kinase target of rapamycin (TOR). TSC1 and TSC2 are considered to be tumor suppressors because they restrict cell growth and proliferation in tissues such as *Drosophila* imaginal discs. Amcheslavsky et al. identified TSC2 in a screen for regulators of adult intestinal stem cells. Gut precursors lacking TSC1 or TSC2 grew up to ten times larger than wild-type stem cells, but they failed to undergo cell division. TSC-deficient fly intestines had a thinner epithelial lining and were more sensitive to tissue-damaging agents such as bleomycin, presumably because injured cells could not be replaced by the daughters of mutant intestinal stem cells.

This unexpected defect in proliferation was caused by the stem cells' excessive growth. Feeding flies with the TOR inhibitor rapamycin or depleting the transcription factor Myc suppressed growth and restored normal rates of proliferation to intestinal stem cells lacking TSC.

It's unclear why TSC deficiency blocks the division of intestinal stem cells but stimulates the proliferation of other cell types. One possibility, says senior author Tony Ip, is that cells in imaginal discs and other developing tissues proliferate so rapidly that they can't grow big enough to block division. Adult intestinal stem cells cycle slowly, however, and may therefore be more sensitive to changes in cell growth rates.

Amcheslavsky, A., et al. 2011. *J. Cell Biol.* doi:10.1083/jcb.201103018.