In This Issue

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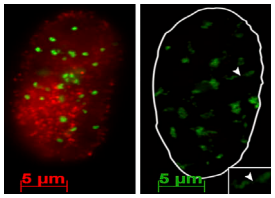
Senescent cells have a case of the SADS



α-Satellite DNA (green) is compact in a proliferative cell (left) labeled with BrdU (red) but distended in a nonproliferative senescent cell (right).

Cells unravel their centromeres as they enter senescence, Swanson et al. reveal.

Senescent cells are metabolically active but no longer capable of dividing. This permanent exit from the cell cycle can be induced by the telomere shortening associated with aging or by other stresses such as the expression of active oncogenes. Despite the importance of senescence for both aging and tumor suppression, however, researchers have failed to identify any cellular markers that are common to all types of senescent cell. Some human fibroblasts, for example, form compact heterochromatin foci called SAHFs as they enter senescence. But SAHFs aren't formed in mouse fibroblasts or in cells from patients with the premature aging disease Progeria, suggesting that there is not a unifying mechanism of cellular senescence.

Swanson et al. found that the satellite DNA found at human and mouse centromeres unraveled from its normal compact state as cells entered senescence. This unraveling—which the researchers termed senescence-associated distension of satellites, or SADS—occurred regardless of how senescence was induced and appeared to occur early in the process of cell cycle exit. SADS weren't formed in immortal, transformed cell lines. Nor were they seen in cancer cells in vivo, with the exception of a benign prostate tumor whose cells were senescent. Strikingly, cells from Progeria patients formed SADS as they exited the cell cycle, suggesting that these prematurely arrested cells follow the same senescence pathway as normally aging cells.

The satellites unraveled to a far greater extent than seen during ordinary chromosome decondensation. Indeed, there was no change in the levels of several histone modifications associated with compact heterochromatin. SADS therefore reflects a unique higher order unfolding of chromatin, which, say the authors, occurs at structures critical for cell division and could thus prove key to preventing proliferation.

Swanson, E.C., et al. 2013. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201306073.

T cells JAK up integrin activity

Montresor et al. describe how the JAK family of tyrosine kinases promotes leukocyte adhesion.

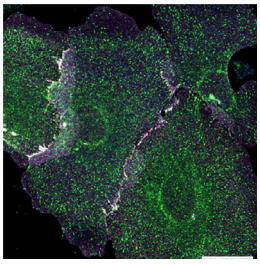
A key step in the recruitment of leukocytes to sites of damage or infection is the activation of integrin adhesion molecules by chemokines so that the cells can attach to blood vessel walls and exit the blood stream. The chemokine CXCL12, for example, shifts the T cell integrin LFA-1 to a high-affinity conformation by activating the GTPases RhoA and Rac1 and their downstream effectors phospholipase D1 (PLD1) and PIP5K1C. But how CXCL12 activates this Rho signaling module is unclear.

Janus kinases (JAKs) can activate signaling pathways downstream of chemokine receptors, and Montresor et al. found that JAK2 and JAK3 were activated in T cells treated with CXCL12. Knocking down or inhibiting these JAKs suppressed the activation of LFA-1 by CXCL12, reducing T cell adhesion in vitro and in vivo. JAKs activated the Rho signaling module by phosphorylating the guanine nucleotide exchange factor VAV1, the researchers found.

JAK signaling was also required for the activation of a second signaling module, involving the small GTPase Rap1, that has been independently implicated in chemokine-induced integrin activation. Surprisingly, Rap1 activation depended on RhoA and PLD1, indicating that Rap1 acts downstream of the Rho signaling module. Senior author Carlo Laudanna now wants to determine the mechanism by which RhoA and PLD1 control Rap1's activation and to investigate how these signaling pathways differ in other blood cells and in leukemias.

Montresor, A., et al. 2013. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201303067.

p120 CLASPs microtubules to junctions



CLASP2 (green) colocalizes with E-cadherin (red) and p120 (blue) at adherens junctions.

Shahbazi et al. describe how the adherens junction protein p120-catenin binds to the microtubule plus end–tracking protein CLASP2 to stabilize intercellular adhesions.

Microtubules are closely associated with the cadherin-based adherens junctions between neighboring epithelial cells and, depending on the precise cell type, are required for either junction assembly or turnover. But how microtubules interact with adherens junctions is not entirely clear.

Shahbazi et al. found that p120-catenin, which stabilizes cadherin molecules at the cell surface, bound to the microtubule plus end–tracking protein CLASP2 at the adherens junctions of keratinocytes. CLASP2's recruitment to junctions was reduced in keratinocytes lacking p120, whereas knocking down CLASP2 reduced p120's accumulation at intercellular contacts, delaying junction assembly and reducing junction dynamics and stability. Microtubules are usually stabilized when they contact junctions at the cell cortex. In the absence of CLASP2 or p120, however, fewer microtubules approached adherens junctions, and those microtubules that did grow near to adhesions weren't stabilized. This suggests that p120 and CLASP2 link microtubules to adherens junctions, thereby stabilizing both intercellular adhesions and the cytoskeleton.

Keratinocytes form a multilayered, stratified epidermis. CLASP2 only localized to intercellular adhesions in the basal layer, which contains proliferating epidermal stem cells. The junctions between terminally differentiating suprabasal cells, in contrast, appear to be linked to microtubule minus ends by a protein called Nezha. Senior author Mirna Perez-Moreno now wants to investigate whether the p120–CLASP2 interaction has a specific role in the maintenance of basal progenitor cells.

Shahbazi, M.N., et al. 2013. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201306019.