Sun and survival with Hif1α

Stabilized Hif1α helps cells to survive in the face of low oxygen. Now, Busca et al. (page 49) report that elevated cAMP, which occurs in melanocytes downstream of UV irradiation from the sun, also leads to higher Hif1α. This should help cells survive the sun’s insults, but may also aid in melanoma development.

Oxygen-dependent Hif1α regulation occurs primarily at the posttranslational level. But Busca et al. report that cAMP acts as an independent stimulant of Hif1α expression by increasing transcription of the Hif1α gene (which encodes Hif1α) in melanocytes.

The elevated cAMP up-regulates expression of MITF, a key melanocyte-specific transcription factor. When the team performed a series of reporter gene experiments using MITF and Hif1α constructs, they saw that MITF was necessary and sufficient to turn on Hif1α expression. Furthermore, MITF bound directly to Hif1α promoter DNA, based on ChIP analysis. Significantly, cells that had elevated cAMP were resistant to cell death triggers, but only when Hif1α was present.

Although cAMP-MITF activation of Hif1α was not detected in other cell types—presumably due to the absence of MITF—the scientists think similar transcriptional regulation of the Hif1α gene likely occurs elsewhere. If that is true, researchers may have one more tool to turn off Hif1α’s pro-survival role in tumor cells. JCB

Regulating the prostate

Prostate cancer and benign prostatic hyperplasia result from excessive proliferation of cells in this organ, likely due to deregulation of stem cells. Salm et al. (page 81) find that cells in the proximal region of the prostate, where the stem cells reside, respond differently to TGF-β relative to distal cells in mice. A regulatory teeter-totter between TGF-β expression, which inhibits cell proliferation and pro-growth cytokines, maintains stem cell quiescence in the healthy organ.

The researchers looked first at androgen-expressing animals. They found that cells in the proximal region of the prostate had more TGF-β-mediated signaling than did cells in the distal region. This should keep the stem cells quiescent, but the cells still survive, probably because of the high expression of anti-apoptotic Bcl-2 in the region.

The distal region normally has lower TGF-β signaling, but androgen withdrawal reversed the pattern. Now the high TGF-β in the distal region induced apoptosis, whereas the lowered TGF-β signaling in the proximal region allowed stem cells in this area to respond to pro-growth cytokines.

The balance between TGF-β and pro-growth cytokines likely maintains the quiescent state of stem cells in a healthy prostate, and deregulation may lead to prostate disease. A similar balancing act may also be present in the epidermal and hematopoietic stem cells already known to be regulated by TGF-β. JCB

The degranulation two-step

Degranulation of mast cells involves a two-step process, report Nishida et al. on page 115. First, antigen stimulation triggers microtubule polymerization and granule translocation to the cell surface in a calcium-independent process. Second, the granules fuse with the plasma membrane in a well-characterized calcium-dependent process.

Mast cells are so full of granules that degranulation was thought to occur through granule-to-plasma membrane fusion and granule-to-granule fusion, without the need for granule transport. However, inhibition of microtubule polymerization blocked degranulation.

In response to antigen stimulation, Nishida et al. found that tubulin staining increased and fluorescently tagged granules translocated to the cell surface before exocytosis. Removal of calcium from the culture medium prevented granule fusion to the membrane but had no effect on microtubule polymerization or granule movement, suggesting that the steps are distinct.

When the team stimulated mast cells deficient for Fyn or Lyn tyrosine kinase signaling proteins, the cells had reduced degranulation, as previously reported. However, only the Fyn mutant cells showed a disruption in microtubule polymerization and granule movement, suggesting that Fyn signaling directs microtubule polymerization.

The scientists are now looking for proteins that link granules to microtubules. They reason that such molecules might provide a relatively specific target for drugs aimed at blocking unwanted histamine release from mast cells. JCB