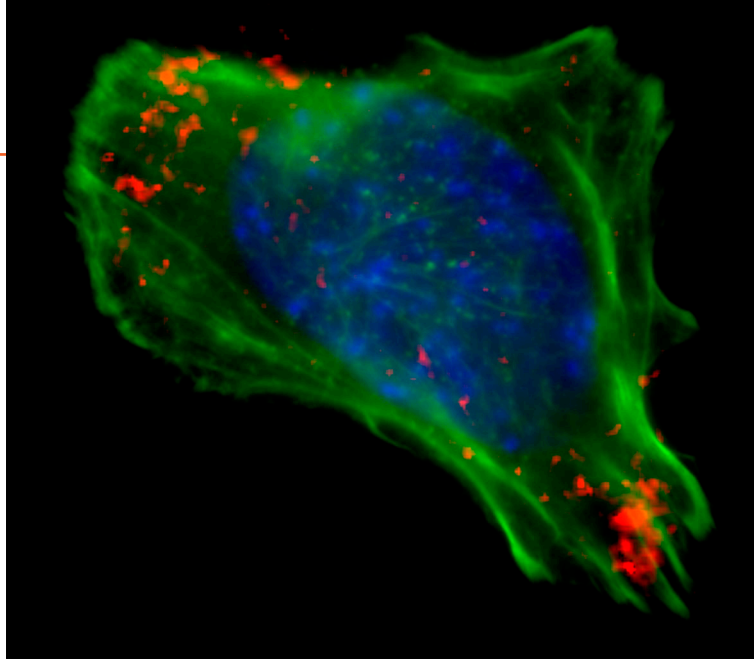
In This Issue



Late endosomes (red) scatter to the cell periphery when the p14 adaptor is missing.

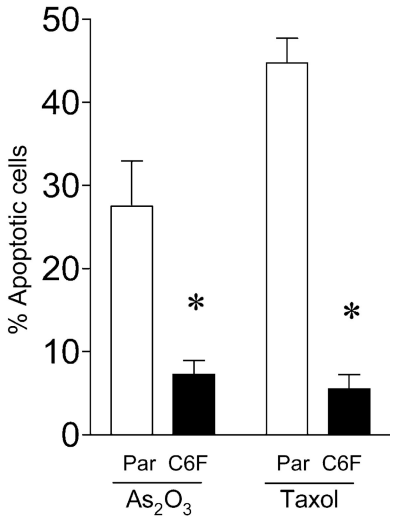
Essential adaptor

Receptors keep signaling long after they are endocytosed thanks to a variety of adaptor proteins. Now, Teis et al. show on page 861 that the loss of p14, a protein that helps attach active MAP kinase to endosomes, results in endosome positioning defects, cell cycle problems, and death.

Mice lacking p14 died as embryos. Fibroblasts from the embryos had normal early endosomes but, compared with wild-type cells, twice as many of their late endosomes and lysosomes were located far from the nucleus, and degradation of internalized EGF receptor was half as efficient.

Epidermal-specific deletion of p14 resulted in mice that were born alive but died soon after from dehydryation. EGF receptors, normally found only in basal cell layers, were not degraded properly and were therefore expressed even in suprabasal cell layers. The mice had thin skin, apparently because of the reduced proliferation that was evident in vitro for harvested keratinocytes. This defect could not be rescued by p14 forced to localize to the plasma membrane, suggesting that the endosome localization is necessary to build a fully comptetent signaling complex.

A paper in press at *Nature Medicine* (authored in collaboration with Teis et al.) identifies a hypomorphic allele of p14 as the explanation for a familial immunodeficiency. Here again, endosome dynamics are disturbed, possibly because one of the motors that brings adaptor proteins to endosomes also helps localize endosomes. Teis et al. now want to see whether inhibition of endosome-localized MAP kinase signaling might be more effective against proliferation-related diseases and have fewer side effects than inhibition of all MAP kinase signaling. JCB



Cells die less readily if they have mitochondrial mutations (black bars).

Surviving on low energy

Many cancer cells resort to inefficient glycolysis for their energy but can nevertheless survive, even when competing with their more energy-efficient noncancerous neighbors. One explanation, say Pelicano et al. (page 913), is that the altered metabolism can turn on an Akt survival pathway.

Most cells rely primarily on the rich energy harvest that comes from oxidative phosphorylation. But a switch to glycolysis can be induced by hypoxia, the loss of the tumor suppressor p53, expression of tumor inducers such as Myc and Ras, or mutation of certain mitochondrial enzymes.

Mitochondrial mutation is particularly common in cancer cells, which are under metabolic stress that generates mutagenic oxidants. Mitochondrial DNA is a prime target for these mutations as these organelles lack many of the safegard mechanisms that prevent and repair damage of nuclear DNA.

Pelicano et al. mutated mitochondrial DNA. The resultant cells grew better under hypoxic conditions and were less sensitive to common anticancer drugs. The cells produce high levels of NADH, which is normally consumed by oxidative phosphorylation, and this altered redox environment inactivated the PTEN phosphatase. With PTEN out of action, its target, Akt, was activated. This kinase is known to increase cell survival. In hypoxic or toxic conditions, this survival pathway may be used in normal cells to keep the cells healthy, but cancer cells have used it to survive despite their unorthodox metabolism.

When cells with mitochondrial mutations were treated to prevent the Akt activation, they once more became sensitive to anticancer drugs. Inhibition of the Akt pathway may also be a promising approach in the clinic, although it is not yet clear which protein in the Akt pathway would make the best target, or which anticancer drugs would make the best follow-up treatment. JCB