Old cells gone bad

The rising incidence of senescent cells during aging may promote cancer development, according to Judith Campisi (Lawrence Berkeley National Laboratory, Berkeley, CA) and colleagues. They propose that evolution may have selected a useful function for cellular senescence early in life—the switching-off of cells that are prone to becoming cancerous—without any consideration of how these cells might behave later on in life.

It is not the senescent cells themselves that become cancerous, however. Rather, these fibroblast cells produce soluble factors, matrix, and perhaps cell-surface molecules that cause cocultured preneoplastic or neoplastic epithelial cells to proliferate and form tumors in nude mice. Cocultured primary epithelial cells are not affected.

The effect on proliferation may be an unwanted byproduct of the senescence expression program, which includes increased levels of an odd mixture of molecules. Only a few of these molecules are involved in cell cycle arrest, but a number may promote epithelial proliferation.

Campisi says that the expression mix may have arisen when evolution co-opted an existing program involved in wound healing to shut down the cell division of senescent fibroblasts. Wounding eventually blocks fibroblast division, as is required during senescence, but it also results in production of matrix remodeling enzymes (to clear up the mess), cytokines (to recruit macrophages), and epithelial growth factors (to close the wound). These same factors, produced in increasing amounts by increasing numbers of senescent cells, may promote the development of epithelial cancers, which constitute the vast majority of late-onset cancers in humans.

Reference: Krtolica, A., et al. 2001. Proc. Natl. Acad. Sci. USA. 98: 12072–12077.

Sustained specificity

Many cell signaling circuits are not well insulated from one another: there are too many signals and too few signaling components for that. Now, researchers have found that mating and invasive-growth pathways in budding yeast may be differentiated by the extent of activation of the same components.

The two yeast pathways use the same upstream kinases to activate the two MAP kinases, Fus3 and Kss1. Thanks to a pathway-specific scaffolding protein, Fus3 was thought to be specific to the mating pathway, and Kss1 to the invasive-growth pathway. Fus3 was proposed to act as a specificity factor by sterically preventing the association of Kss1 with the mating-specific scaffolding protein.

Now, Lee Bardwell and colleagues of the University of California, Irvine, CA, report that Kss1 is activated during mating, although the period of activation is shorter than for Fus3. This limitation on Kss1 is dependent not only on the presence of Fus3 but also (contrary to previous results) on Fus3 activity. The relevant target of Fus3 has not yet been determined.

“The idea that the specificity involves transient versus sustained activation of MAP kinase opens up a whole series of parallels with mammalian systems,” says Bardwell. In rat neurons, for example, transient MAP kinase activation downstream of EGF results in proliferation, whereas sustained activation downstream of NGF results in differentiation.

The method by which sustained activation is decoded is unknown. One possibility is that a kinase must be active for long enough both to induce transcription and to phosphorylate the product of that transcription.

Reference: Sabbagh, W., et al. 2001. Mol. Cell. 8: 683–691.