In This Issue

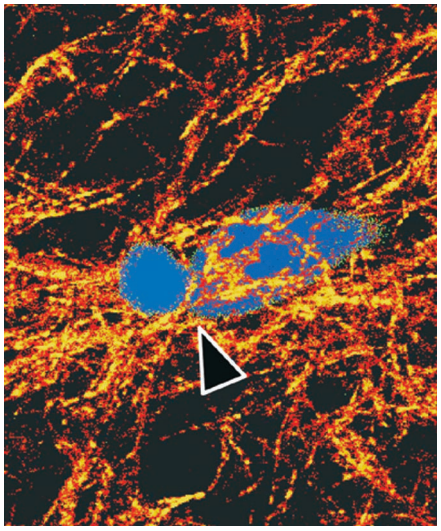
Tumor cells get primitive

When metastatic tumor cells migrate through connective tissue, they use proteases to chew a path for themselves. This finding led to the development of protease inhibitors as potential cancer therapies, but some animal and human clinical tests of these drugs have been disappointing. Wolf et al., reporting on page 267, may have found one reason why: when proteolysis is inhibited, tumor cells resort to an amoeboid type of movement that allows them to squeeze through cracks in the matrix. The results provide substantial new insight into cell migration in multicellular organisms.

Using both in vitro and in vivo cell migration systems, the authors investigated the effects of inhibiting proteases that degrade the extracellular matrix. Normally, transformed cells migrate through three-dimensional collagen matrices or the mouse dermis as individual, spindle-shaped cells, using several proteolytic enzymes and leaving trails through the matrix. When the proteases are shut down, cells undergo a striking change in their appearance, reminiscent of a transition toward amoeboid movement. The cells then continue to migrate through the matrix without breaking it down and without leaving trails.

The change in migration strategy, which Wolf et al. call the mesenchymal–amoeboid transition, suggests that the cells of multicellular organisms retain a more primitive migration system that is normally masked. This type of migration, similar to the movement of the soil amoeba *Dictyostelium discoideum*, could serve as a "salvage" pathway, allowing tumor cells to take a step backward in evolutionary time to continue migrating in the presence of protease inhibitors.

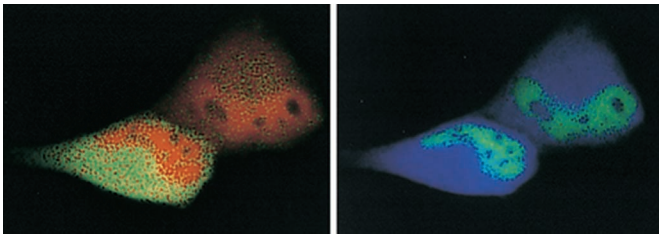
Amoeboid movement may also have more positive functions in multicellular organisms; in separate work, T lymphocytes have been shown to migrate through collagen matrices without using proteases. The authors are now trying to identify the regulatory pathways responsible for controlling the mesenchymal–amoeboid transition. Targeting this process while simultaneously inhibiting proteases might provide a salvage pathway for new tumor therapies as well. ■



Protease-inhibited cells squeeze through the matrix using ameboid-like movements.

Venus dye trap catches executioners

Fluorescence resonance energy transfer (FRET) between coupled fluorescent proteins is a promising tool for studying caspase activation during apoptosis. Unfortunately, current FRET systems are acutely sensitive to changes in pH and chloride ion concentration, and since these fluctuate considerably during apoptosis the results of FRET experiments are often difficult to interpret. Takemoto et al., whose report appears on page 235, developed a new FRET system that is resistant to acidification and chloride, and used it to obtain a detailed view of caspase-3 and caspase-9 activation in apoptosis. The new technique should also enable studies of caspase activity in vivo that were previously impossible.



Caspase 3 is activated first in the cytoplasm (left) and then in the nucleus (right).

To make a caspase-sensitive FRET system, two fluorescent proteins, a donor and an acceptor, are linked with a cleavage site that can be cut by a particular caspase. Caspase activity is then detected as a change in fluorescence. The authors used a new variant of enhanced yellow fluorescent protein called Venus as the acceptor, and linked it to a donor protein through either a caspase-3 or caspase-9 cleavage sequence. Both systems are resistant to acidification and high chloride ion concentrations.

The new systems show that, when apoptosis is induced, caspase-3 is activated rapidly in the cytosol and nucleus, reaching full activation before apoptotic morphological changes begin. This suggests that activated caspase-3 may enter the nucleus to induce the early structural changes. Caspase-9 is initially activated at the same time as caspase-3, but does not become fully activated until the morphological changes are well underway.

The authors have now developed a line of transgenic flies expressing the caspase-3 indicator system, and hope to have a transgenic mouse system soon. The ability to monitor caspase activity in whole tissues should make it possible to study the early steps of this important process, before the apoptotic cells are engulfed by their neighbors. ■