

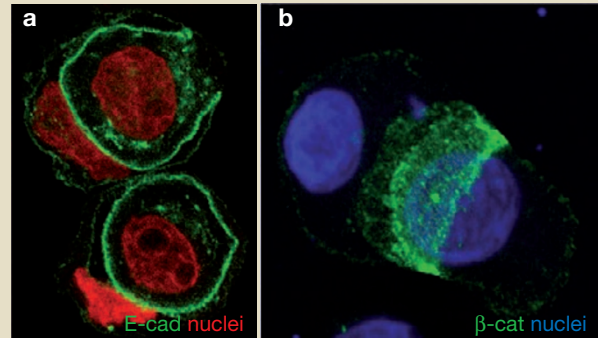
## Entosis: cell death by invasion

Most animal cells require attachment to an extracellular matrix for survival. Within the mammary gland, death of matrix-deprived cells underlies lumen formation during development and is also thought to act as a defence against the formation of breast tumours. It has long been known that epithelial cells detached from their extracellular matrix can undergo a process of apoptotic cell death called anoikis. Overholtzer *et al.* (*Cell* 10.1016/j.cell.2007.10.040; 2007) now report that detached epithelial cells can also take an alternative path to death which is driven by cell-in-cell invasion.

While observing mammary epithelial cells in suspension cultures, they found that these detached cells are often internalized into vacuoles within neighbouring cells. Following their internalization, most of these cells are eventually degraded by lysosomal enzymes; however, some of the captured cells are instead released. Surprisingly, a small percentage of cells may undergo cell division while entrapped within other cells.

Internalization is independent of apoptosis and instead occurs by a process the authors have named entosis, from the Greek *entos*, meaning inside or within. The study showed that live internalizing cells actively participate in the invasion process, in a manner dependent on signalling through the small GTPase Rho, which mediates actomyosin-mediated contraction. Overholtzer *et al.* also noticed that before internalization, cells establish E-cadherin–beta-catenin-mediated adherens junctions and the compaction of these junctions appears to directly mediate the entosis process. The authors propose that invasion is driven by unbalanced myosin II-dependent forces during compaction.

Is entosis an artefact of cells cultured in suspension or is it a physiologically relevant phenomenon that has thus far escaped the attention of cell biologists? To address this question, the authors



Entosis, or cell-in-cell invasion, occurs in cell populations detached from matrix. (a) Human mammary epithelial cells (MCF10A) undergo entosis when cultured in suspension. Nuclei are stained with TO-PRO-3-red and the extent of internalization is highlighted by anti-E-cadherin staining (green). The upper structure displays a partially internalized cell; the cell in the lower structure is completely internalized in its neighbour. (b) Entosis in a clinical metastatic breast tumour specimen (pleural effusion) showing  $\beta$ -catenin (green) and nuclei (DAPI in blue). Images courtesy of M. Overholtzer and J. Brugge.

obtained pleural fluid from breast metastatic tumours as well as solid primary breast tumour samples, as the features exhibited by internalized cells are reminiscent of ‘cell-in-cell’ or cell ‘cannibalism’ images observed in metastatic cells. They discovered that cells from both classes of tumours exhibit characteristics of entosis: cell-in-cell intermediates with high levels of adherent junction proteins were observed as well as cells inside the lysosomes of other cells.

The study by Overholtzer *et al.* suggests that a cytological feature known to clinicians for many years may be crucial for the growth of a wide variety of tumours, possibly as a tumour-suppressor mechanism that eliminates cells that have escaped their natural environment and are detached from the normal matrix. There is definitely more to entosis than just another way to die.

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