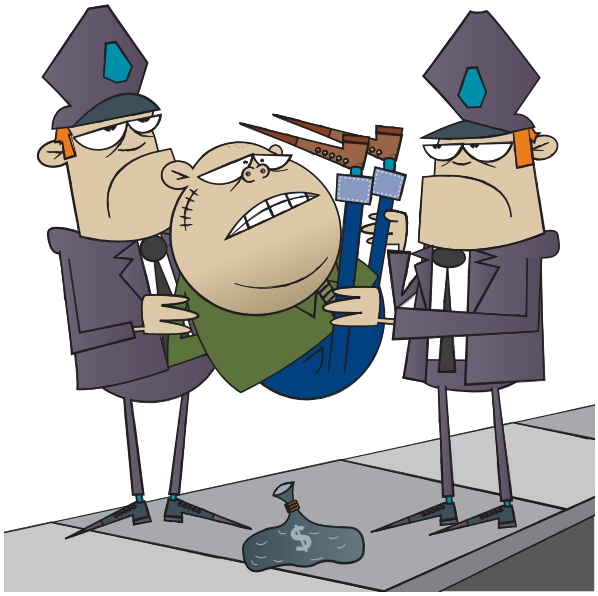
MICROENVIRONMENT

Enforced compliance



Understanding the initial changes that promote early, clonal tumour cell growth is essential both for the development of more effective cancer treatments and for cancer prevention. Cheuk Leung and Joan Brugge have found that processes that enable the extrusion of a mutant cell from a constraining epithelium are important in establishing clonal outgrowth.

> “processes that enable the extrusion of a mutant cell from a constraining epithelium are important in establishing clonal outgrowth.”

The use of three-dimensional (3D) culture conditions has vastly improved our understanding of tumour development in an epithelial environment. When MCF10A cells — a human, non-transformed mammary epithelial cell line — are grown in Matrigel, they form acinar-like structures that consist of an outer polarized epithelium that surrounds a hollow lumen. Using an inducible gene expression system to express oncogenes in only a single cell in an acinus, the authors found that potent oncogenes, such as *MYC*, myristolated AKT (myr*AKT*), E7 from human papilloma virus 16 and cyclin D1 (*CCND1*), did not result in clonal outgrowth, unlike the hyperproliferative growth that is evident when all cells in an acinus express these oncogenes. By contrast, expression of ERBB2, a receptor tyrosine kinase that is overexpressed in 30% of breast cancers, resulted in the extrusion of the ERBB2-expressing cell into the lumen and its proliferation. A similar result was seen in primary mouse mammary epithelial cells and an ovarian cell line that exhibits cellular polarity in 3D culture. Interestingly, the inhibition of cell proliferation did not block the extrusion of the ERBB2-expressing cells.

Downstream signalling from ERBB2 involves both the MAPK pathway and the PI3K pathway, and inhibitors of these pathways indicated that activation of the MAP2K1–ERK pathway was involved in ERBB2-mediated extrusion. Indeed, the ERK transcriptional target *ETS1* also promotes cellular extrusion. Expression of this transcription factor drives the expression of matrix metalloproteinases (MMPs), and inhibition of MMP activity suppressed cellular extrusion that was driven by ERBB2, a constitutively active MAP2K1 mutant and ETS1. Importantly, this also prevented the proliferation of ERBB2-expressing cells, and expression of MMP14 in single cells was sufficient to induce cellular extrusion, but not proliferation within the lumen.

The authors noted that the basement membrane surrounding single ERBB2-expressing cells in an acinus was disrupted and that ERBB2-expressing cells had impaired adhesion to plates coated with Matrigel. Moreover, disruption of cell–matrix adhesion through the knockdown of talin 1 enabled cells to move into the lumen. These results indicate that disruption of the epithelial environment could be key to facilitating the outgrowth of cells that harbour oncogenic mutations. In support of this, enforced extrusion (using expression of MMP14) of single cells expressing myrAKT resulted in clonal outgrowth. Similar results were not evident for the cells overexpressing MYC, probably because these cells exhibited high rates of apoptosis once they had entered the lumen, indicating that suppression of apoptosis at this stage is important. In addition, the disruption of cell–cell interactions through knockdown of p120-catenin allowed single myrAKT- or MYC-expressing cells to proliferate in the context of the disrupted acinar epithelium.

These results indicate that cells with pro-proliferative oncogenic mutations are likely to be kept in check when remaining in a structured and intact epithelium. However, the movement of cells out of this environment, such as could occur as a result of inflammation or injury, is permissive for proliferation.

Nicola McCarthy

ORIGINAL RESEARCH PAPER Leung, C. T. & Brugge, J. S. Outgrowth of single oncgene-expressing cells from suppressive epithelial environments. *Nature* 8 Feb 2012 (doi:10.1038/nature10826)

© 2012 Macmillan Publishers Limited. All rights reserved