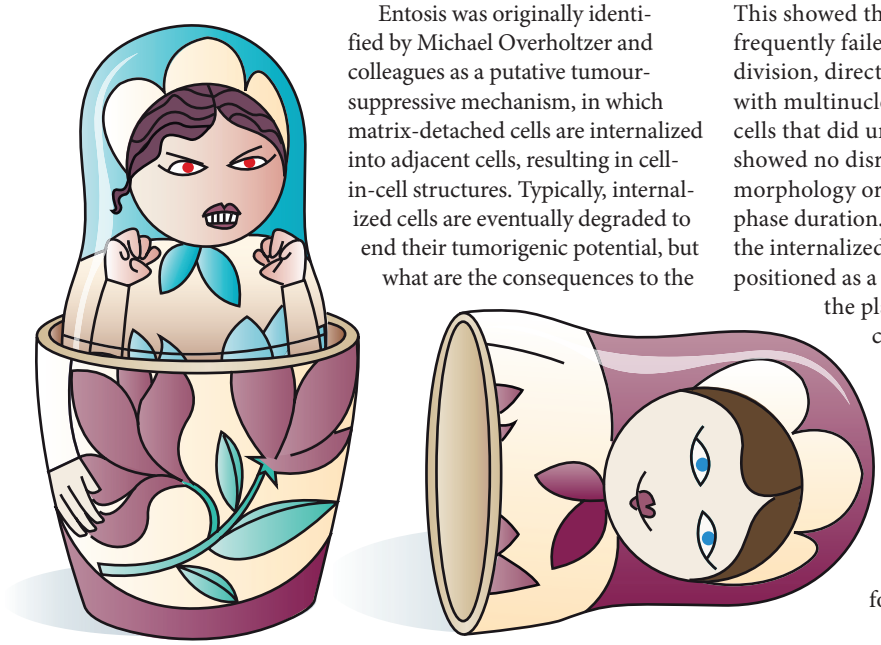
Nature Reviews Cancer | AOP, published online 17 March 2011; doi:10.1038/nrc3048

CHROMOSOME INSTABILITY

Chaos from within

> on balance, entosis might be a tumour-promoting phenomenon



Aneuploidy, the gain or loss of chromosomes, is thought to primarily arise from mutations that disrupt mitosis or that alter centrosome numbers. However, routes to aneuploidy might actually be more varied. Cell fusion has been suggested as an alternative route, and a new study proposes entosis as an important path to aneuploidy without a prior requirement for mutations.

Entosis was originally identified by Michael Overholtzer and colleagues as a putative tumour-suppressive mechanism, in which matrix-detached cells are internalized into adjacent cells, resulting in cell-in-cell structures. Typically, internalized cells are eventually degraded to end their tumorigenic potential, but what are the consequences to the host cell in the interim? In their latest work, the authors examined cell-in-cell structures in primary cancer samples and cell lines, and found that multinucleation of entosis host cells was tenfold more common compared with adjacent single cells.

Time-lapse microscopy was used to track immortalized or fully transformed breast and bronchial cell lines over many cell divisions. This showed that entosis host cells frequently failed to undergo cell division, directly linking entosis with multinucleation. Entosis host cells that did undergo mitosis showed no disruptions of spindle morphology or prophase to anaphase duration. However, when the internalized cell was by chance positioned as a physical barrier to the plane of attempted cleavage, failed cytokinesis and binucleated, tetraploid cells resulted. Even partially internalized cells were found to serve as barriers to cytokinesis. Staining for phosphorylated myosin light chain 2 showed that the internalized cells caused incomplete formation of the contractile ring in the host cell, explaining why the cleavage furrow and cytokinesis were impeded.

Tetraploidy is a common intermediate of aneuploid cell lineages: does this progression hold true for these binucleated host cells? Fluorescence *in situ* hybridization for chromosomes 8 and 12 revealed that binucleated intermediates of different cell lines did produce aneuploid derivates.

Confirming previous observations, the authors found a positive correlation between cell-in-cell frequency and advancing clinical grade of tumour samples, indicating that, on balance, entosis might be a tumour-promoting phenomenon.

Although entosis can be considered as a non-genetic route to aneuploidy, it will be interesting to determine whether there are indeed cancer-relevant mutations that predispose to entosis in addition to those, such as the loss of *TP53*, that tolerate the resultant tetraploid state and drive its progression to aneuploidy.

Darren J. Burgess

ORIGINAL RESEARCH PAPER Krajcovic, M. *et al.* A non-genetic route to aneuploidy in human cancers. *Nature Cell Biol.* **13**, 324–330 (2011)