TUMORIGENESIS

To the death!

In the early stages of tumour initiation in the epithelium, when only a few cells are transformed, evidence suggests that normal and transformed cells that are in close proximity compete for space in which to grow, causing the 'loser' cells to undergo JNK-dependent apoptosis. This phenomenon is known as cell competition and can be tumour suppressive if the losers are transformed cells. Two papers now provide further insight into how this process might function in tumorigenesis.

Lethal (2) giant larvae (*l(2)gl*) is a tumour suppressor in *Drosophila melanogaster* that, when mutated in a mosaic tissue (surrounded by normal cells), causes these *l(2)gl*$^-$ cells to become the losers in cell competition. L(2)GL is a scaffold protein, and Tamori and colleagues identified HIV-1 Vpr-binding protein (VPRBP) as a new binding protein of L(2)GL2 by immunoprecipitation in human MCF7 breast cancer cells and MDCK canine epithelial cells. They also identified a homologue in *D. melanogaster* that they named Mahjong (MAHJ) that bound L(2)GL. Using the FLP–FRT system the authors generated mosaic flies so that equal numbers of *mahj*$^{-/-}$ and normal cells were produced. The *mahj*$^{-/-}$ cells were eliminated from wing discs and further analysis revealed that *mahj*$^{-/-}$ cells adjacent to normal cells had activated caspase 3 and were undergoing JNK-dependent apoptosis. This suggests that loss of *mahj*, like loss of *l(2)gl*, causes such cells to be the losers in cell competition with normal cells. Similarly, co-culture of VPRBP-deficient MDCK cells with normal MDCK cells induced caspase-dependent apoptosis in 45% of the VPRBP-deficient cells, which were subsequently extruded from the apical surface, demonstrating that cell competition also occurs in mammalian cells.

So, how could cell competition function in tumorigenesis? Menéndez and colleagues showed that *l(2)gl*$^-$ cells that are induced in normal wing discs undergo JNK-dependent apoptosis. The overexpresssion of the oncogenic *ras*^{v12} mutant in *l(2)gl*$^-$ cells allowed the overgrowth of *l(2)gl*$^-$ cells in normal wing discs. Furthermore, the authors found that the Hippo pathway was suppressed, and that yorkie (YKI) — a transcription factor that is suppressed by the Hippo pathway — was consequently activated in these cells. Furthermore, the authors found that overexpression of *yki* in *l(2)gl*$^-$ cells also caused overgrowth in mosaic wing discs, suggesting that suppression of the Hippo pathway is sufficient to allow *l(2)gl*$^-$ cells to form tumours in wing discs.

It has been proposed that the losers in cell competition are determined by a slower growth rate than the competing cells. However, although the expression of *ras*^{v12} or *yki* increased the growth rate of the *l(2)gl*$^-$ cells, apoptosis was still apparent in the patches of growing *l(2)gl*$^-$ *ras*^{v12} or *l(2)gl*$^-$ *yki* cells at the regions adjacent to normal cells. Indeed, the authors found that more than half of the *l(2)gl*$^-$ *ras*^{v12} cells were eliminated from the mosaic wing discs, indicating that growth rate does not determine the losers. Further analyses suggest that peripheral apoptosis in patches of transformed cells is a general feature of cell competition and that cells evade apoptosis from competition with adjacent normal cells by growing together, which reduces the number of cells that are exposed to the surrounding normal cells.

Together these papers have further defined the interesting phenomenon of cell competition, and additional understanding of this process could identify possible targets for prevention and therapy.

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ORIGINAL RESEARCH PAPERS Tamori, Y. *et al.* Involvement of Lgl and Mahjong/VprBP in cell competition. *PLoS Biol.* **8**, e1000422 (2010) | Menéndez, J. *et al.* A tumor-suppressing mehanism in *Drosophila* involving cell competition and the Hippo pathway. *Proc. Natl Acad. Sci. USA* 2 Aug 2010 (doi:10.1073/pnas.1009376107)

CORBIS

> “demonstrating that cell competition also occurs in mammalian cells.”