TUMORIGENESIS

Neighbourhood watch

> host tissues possess intrinsic tumour-suppressive activity that can eliminate premalignant cells

Multiple observations suggest that host tissues possess intrinsic tumour-suppressive activity that can eliminate premalignant cells (a type of cell competition). However, the mechanisms by which this occurs are unknown. Igaki and colleagues now show that Jun N-terminal kinase (JNK)-mediated engulfment of pre-malignant cells, by their surrounding wild-type neighbours, may be one such mechanism.

In *Drosophila melanogaster* imaginal epithelia, clones of cells in which the tumour suppressor genes *scribble* (*scrib*) or *discs large* (*dlg*) are mutated are outcompeted by surrounding wild-type cells and undergo JNK-dependent cell death. Using *D. melanogaster* eye-antennal discs, Ohsawa *et al.* analysed wild-type cells juxtaposed to *scrib*- or *dlg*-mutant clones to study the mechanisms of this tumour-suppressive activity. They found evidence of activated JNK signalling not only in mutant clones, but also in the wild-type neighbours. However, unlike JNK activation in mutant clones, JNK activation in surrounding wild-type cells was non-apoptotic. Intriguingly, blocking JNK signalling in the surrounding cells, by RNA interference or expression of a dominant-negative mutant of the Jun kinase Basket (BSK^{DN}), suppressed elimination of *scrib*-mutant clones. The authors hypothesized that the cell surface tumour necrosis factor ligand Eiger, which was previously shown to activate JNK within *scrib*- and *dlg*-mutant clones, could also be upstream of JNK activation in wild-type neighbours. Indeed, overexpression of *eiger* in surrounding wild-type cells enhanced elimination of *scrib*-mutant clones. Together, these results indicate that Eiger–JNK signalling in normal cells promotes the elimination of neighbouring premalignant cells.

Next, Ohsawa *et al.* sought to identify effectors downstream of Eiger–JNK signalling. Guided by a candidate screen for proteins that regulate the actin cytoskeleton, a known outcome of JNK signalling, the authors found that PDGF- and VEGF-receptor related (PVR) is upregulated in both mutant clones and the surrounding wild-type cells, in a pattern similar to JNK activation. Knockdown of *pvr* in surrounding wild-type cells suppressed the elimination of *scrib* clones. Moreover, *pvr* knockdown in surrounding cells that overexpressed *eiger* prevented their ability to outcompete *scrib* clones, thereby placing PVR downstream of Eiger–JNK signalling.

How does Eiger–JNK–PVR signalling in wild-type cells lead to the elimination of premalignant neighbours? Live imaging of imaginal discs revealed that *scrib*-mutant cells are engulfed by their wild-type neighbours. Overexpression of *eiger* or *pvr* in surrounding wild-type cells enhanced the engulfment of *scrib*-mutant clones, whereas this was reduced in *eiger*-mutant discs. Finally, the authors showed that knockdown of engulfment and cell mobility (*elmo*) in surrounding wild-type cells suppressed the elimination of *scrib*-mutant clones, thereby implicating the ELMO–myoblast city (MBC) pathway, which mediates cytoskeletal rearrangement during phagocytosis, in this phenomenon.

These results show that activation of Eiger–JNK–PVR signalling in surrounding wild-type cells promotes ELMO–MBC-mediated engulfment of premalignant neighbours. It will be interesting to determine whether JNK-mediated cell engulfment is an evolutionarily conserved form of cell competition that eliminates premalignant cells from epithelia.

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ORIGINAL RESEARCH PAPER Ohsawa, S. *et al.* Elimination of oncogenic neighbours by JNK-mediated engulfment in *Drosophila*. *Dev. Cell* **20**, 315–328 (2011)

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