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TUMORIGENESIS

Influencing those around you

Tumour cells do not exist in a vacuum: they proliferate within the confines of a normal tissue, but the full extent of the effects that abnormally proliferating cells have on the cells that surround them is not well understood. Using *Drosophila melanogaster* as a model system, Tatsushi Igaki and colleagues have shown that mitochondrial defects in cells expressing oncogenic RAS^{V12} can induce the cells that surround them to proliferate owing to effects on the Hippo pathway.

The authors used mosaic analysis with a repressible cell marker (MARCM) to induce homozygous mutations in cells expressing a green fluorescent protein–Ras^{V12} construct and isolated the mutations that induced growth of the surrounding normal cells in larval eye discs. The mutated genes were all involved in mitochondrial respiratory function and included *Pdsw*, a component of complex I; *mRpL4*, which encodes y mitochondrial ribosomal protein; and *CoVa*, a component of complex IV. Additional experiments indicated that neither the mitochondrial mutations nor RAS^{V12} alone was able to induce proliferation of surrounding normal cells, but RAS^{V12} expression combined with any of the mitochondrial mutations induced non-autonomous growth.

The authors used additional genetic screens to delineate the pathway that was responsible for this effect. They found that the mitochondrial mutations resulted in the generation of reactive oxygen species, which activated JUN N-terminal kinase (JNK). JNK combined with an active RAS^{V12} signalling pathway inactivated the Hippo tumour suppressor pathway. This resulted in Yorkie-mediated transcription of unpaired (*upd*), an interleukin-6 homologue that activates the JAK–signal transducer and activator of transcription (STAT) pathway, and wingless (*wg*), a WNT homologue, and these proteins induce the proliferation of the surrounding wild-type cells.

Interestingly, the authors also found that, in addition to inducing proliferation, UPD and possibly WG can also induce the invasive growth of RAS^{V12}-expressing cells that do not have mitochondrial mutations. Reduction of STAT levels blocked this invasive behaviour.

> “RAS^{V12} expression combined with any of the mitochondrial mutations induced non-autonomous growth.”

These results indicate that, in flies, RAS^{V12} tumours, which are normally benign, can become malignant owing to the effects of mitochondrial mutations in a subset of the cells expressing RAS^{V12}. Although the mitochondrial mutations are unlikely to benefit the cells in which they arise — such mutations often result in growth arrest — they lead to the expression of factors that influence cell migration and proliferation, and hence contribute to tumour progression.

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ORIGINAL RESEARCH PAPER Ohsawa, S. *et al.* Mitochondrial defect drives non-autonomous tumour progression through Hippo signalling in *Drosophila*. *Nature* 30 Sep 2012 (doi:10.1038/nature11452)