PCI-02

Mitochondrial defect drives non-autonomous tumour progression through Hippo signalling in *Drosophila*

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Abstract

Mitochondrial respiratory function is frequently impaired in human cancers. However, the mechanisms by which mitochondrial dysfunction contributes to tumour progression remain elusive. Here we show in *Drosophila* imaginal epithelium that defects in mitochondrial function potently induce tumour progression of surrounding tissue in conjunction with oncogenic Ras. Our data show that Ras activation and mitochondrial dysfunction cooperatively stimulate production of reactive oxygen species, which causes activation of c-Jun amino (N)-terminal kinase (JNK) signalling. JNK cooperates with oncogenic Ras to inactivate the Hippo pathway, leading to upregulation of its targets Unpaired (an interleukin-6 homologue) and Wingless (a Wnt homologue). Mitochondrial dysfunction in Ras-activated cells further cooperates with Ras signalling in neighbouring cells with normal mitochondrial function, causing benign tumours to exhibit metastatic behaviour. Our findings provide a mechanistic basis for interclonal tumour progression driven by mitochondrial dysfunction and oncogenic Ras.