CELL DEATH

E2Ffects on mitochondria

E2F transcription factors (E2F–DP (differentiation-related polypeptide) heterodimers) have a crucial role in the induction of apoptosis following DNA damage in *Drosophila melanogaster* by directly regulating the transcription of key apoptotic genes. However, *Dp*-mutant *D. melanogaster* cells, in which E2f1 is functionally inactivated, fail to undergo cell death in response to irradiation despite apoptotic gene induction. This study shows that E2f1 also regulates mitochondrial function that is required for cell death, in addition to its role in pro-apoptotic gene expression.

Gene expression analysis of larval eye discs from wild-type and *Dp*-mutant *D. melanogaster* showed that the *Dp*-mutant cells induce the same set of apoptotic genes as wild-type cells in response to irradiation, and the level of expression of apoptotic genes was the same or higher in irradiated *Dp*-mutant cells. So, the failure of *Dp*-mutant cells to undergo apoptosis is not the result of a failure to induce pro-apoptotic gene transcription.

Of the genes that were downregulated in *Dp*-mutant but not wild-type eye discs after irradiation, there was a marked enrichment of mitochondrial genes associated with metabolic and oxidative phosphorylation pathways. Dp and E2f1 were shown to bind directly to the promoters of many of these *D. melanogaster* genes, and eight human homologues of these genes also bound E2F1 in a DP-dependent manner. So, in *D. melanogaster* and mammalian cells, mitochondria-associated genes are directly regulated by E2F1–DP.

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The authors next showed that DP mutation leads to mitochondrial defects in both *D. melanogaster* and human cells. Mitochondrial membrane potential was decreased in *Dp*-mutant compared with wild-type *D. melanogaster* eye discs. Also, the mitochondria of *Dp*-mutant *D. melanogaster* cells, and of human cells in which E2F1 was inactivated, were more globular and swollen. The downregulation of mitochondria-associated direct gene targets of E2f1–Dp was sufficient to partially phenocopy these mitochondrial defects and to mediate protection from irradiation-induced apoptosis, with the severity of the defects correlating well with the degree of protection.

The results show that E2F transcription factors regulate mitochondrial function in *D. melanogaster* and human cells. The mechanism by which mitochondrial dysfunction provides protection against irradiation-induced apoptosis remains to be determined.

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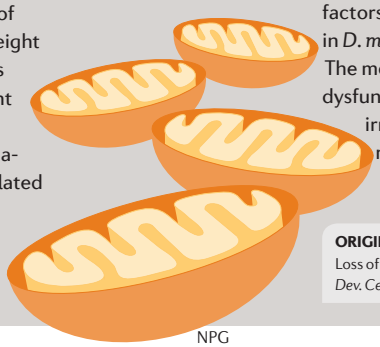

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ORIGINAL RESEARCH PAPER Ambrus, A. M. *et al.* Loss of dE2F compromises mitochondrial function. *Dev. Cell* **27**, 438–451 (2013)