CELL SIGNALLING

Balancing act

The disruption of key regulators that orchestrate the commitment of cells to enter the G1 phase of the cell cycle, such as retinoblastoma (RB) and members of the E2F family of transcription factors, is commonly associated with tumorigenesis. E2F transcription factors can activate genes that promote proliferation and, paradoxically, genes that induce apoptosis. Joseph Nevins and colleagues have clarified the importance of the balance between E2F1-dependent proliferation and apoptosis in cancer.

The capacity of E2F1 to transactivate different subsets of target genes to orchestrate either proliferation or apoptosis seems to depend on whether the serum-induced, pro-survival phosphatidylinositol 3-kinase (PI3K)–Akt signalling pathway is active. To verify this, Nevins and colleagues undertook DNA microarray analyses of quiescent Ref52 rat fibroblasts expressing E2F1 in the presence of serum and/or the PI3K inhibitor LY294002. Serum addition to E2F1-expressing cells gave the expected increase in expression of genes involved in proliferation; however, a subset of E2F1 target genes, many of which were previously unidentified E2F1 targets, were repressed after serum addition and this was dependent on PI3K activity. These findings were also verified in human tumour and non-tumour cell lines.

One of the E2F1 target genes that is repressed by the PI3K–Akt pathway is *AMPK α 2* (also known as *PRKAA2*), the kinase subunit of AMP-activated protein kinase, which can induce growth arrest in response to low ATP levels and nutrient

deprivation. Ectopic expression of *AMPK α 2* alone was not sufficient to induce apoptosis in quiescent human diploid fibroblasts, but *AMPK α 2* expression synergized with sub-apoptosis-inducing levels of E2F1. Consistently, they showed that treatment of cells with the *AMPK α 2*-activating drug AICAR increased E2F1-dependent apoptosis and this was reversed when *AMPK α 2* — and other E2F1 target genes found in the apoptotic subset — were depleted by short hairpin RNA, indicating that these genes commit cells to E2F1-dependent apoptosis.

Disruption of oncogene-induced apoptosis is common to many cancers. So, is the PI3K-repressed subset of E2F1 target genes relevant? Analyses of two breast cancer data sets and an ovarian cancer data set using the gene clusters that were identified from the Ref52 microarrays revealed two mutually exclusive expression patterns: tumours that express higher relative levels of the PI3K-repressed E2F1 target genes and tumours that express higher relative levels of E2F1 target genes involved in proliferation; these subsets correlated with high and low levels of predicted PI3K activity, respectively. Importantly, the reduced expression of PI3K-repressed E2F1 target genes correlated with a poor prognosis for patient survival in each of the data sets.

This study reveals a bipartite transcriptional programme for E2F1 that activates proliferative or apoptotic gene sets in a mutually exclusive manner. The commitment to apoptosis can be repressed by the PI3K–Akt pathway and Nevins and colleagues showed that this

is favoured in advanced tumours with poor prognoses. Therefore, administration of PI3K inhibitors and/or AMPK activating drugs (such as AICAR or the diabetes drug metformin) to such patients could restore sensitivity to E2F1-dependent apoptosis.

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ORIGINAL RESEARCH PAPER Hallstrom, T. C., Mori, S. & Nevins, J. R. An E2F1-dependent gene expression program that determines the balance between proliferation and cell death. *Cancer Cell* **13**, 11–22 (2008)

FURTHER READING Chau, B. N. & Wang, J. Y. Coordinated regulation of life and death by RB. *Nature Rev. Cancer* **3**, 130–138 (2003)