What doesn't kill you makes you stronger – *bcl-2* promotes survival independent of proliferation

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TITLE	*Bcl-2* gene promotes haemopoietic cell survival and cooperates with *c-myc* to immortalize pre-B cells
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Combination therapy with the BCL-2 inhibitor, venetoclax, and hypomethylating agents produces high response rates in elderly patients with acute myeloid leukemia unfit for induction chemotherapy, setting a new standard of care for these patients.[1] These clinical results build on decades of fundamental, translational, and clinical research into BCL-2 and apoptosis.

The *bcl-2* gene (now known as *BCL2*) was originally discovered in 1984 by Yoshihide Tsujimoto in Croce's laboratory; he identified it as the fusion partner with the immunoglobulin heavy chain locus in patients with B-cell malignancies and the t(14;18) translocation.[2] Subsequently, Reed *et al.* reported that *bcl-2* was an oncogene, the first oncogene identified without a viral counterpart. However, the biological function and mechanism by which *bcl-2* promoted malignancy remained unknown.

In a landmark paper published in 1988, Drs. Vaux, Cory and Adams described the first cellular mechanism of action of *bcl-2*.[3] In their letter to Nature, a paper with three figures and neither supplementary material nor volumes of extended data, they showed that overexpression of *bcl-2* prevented cell death. Interleukin (IL)-3-dependent FDC-P1 myeloid cells were transduced with human *bcl-2* cDNA and then IL-3 was withdrawn. All control and *c-myc*-transduced FDC-P1 cells died 4 days after IL-3 withdrawal. In contrast, 60% of the cells overexpressing *bcl-2* remained viable. Although viable, cells overexpressing *bcl-2* did not proliferate and did not become tumorigenic when injected into mice. The authors concluded that *bcl-2* functions as an oncogene by promoting prolonged cell survival, independent of its effects on cell proliferation. Subsequently, *bcl-2* was shown to protect cells from a specific mechanism of cell death, called apoptosis.

Over the following years and decades, a clearer picture of the mechanisms of action of *bcl-2* emerged. A family of pro- and anti-apoptotic proteins structurally related to BCL-2 were identified. BCL-2 and its family members were localized to the mitochondrial outer membrane where they regulated mitochondrial membrane potential. Inhibiting BCL-2 led to a collapse of mitochondrial membrane potential and release of mitochondrial proteins, including cytochrome c, which triggered apopto-

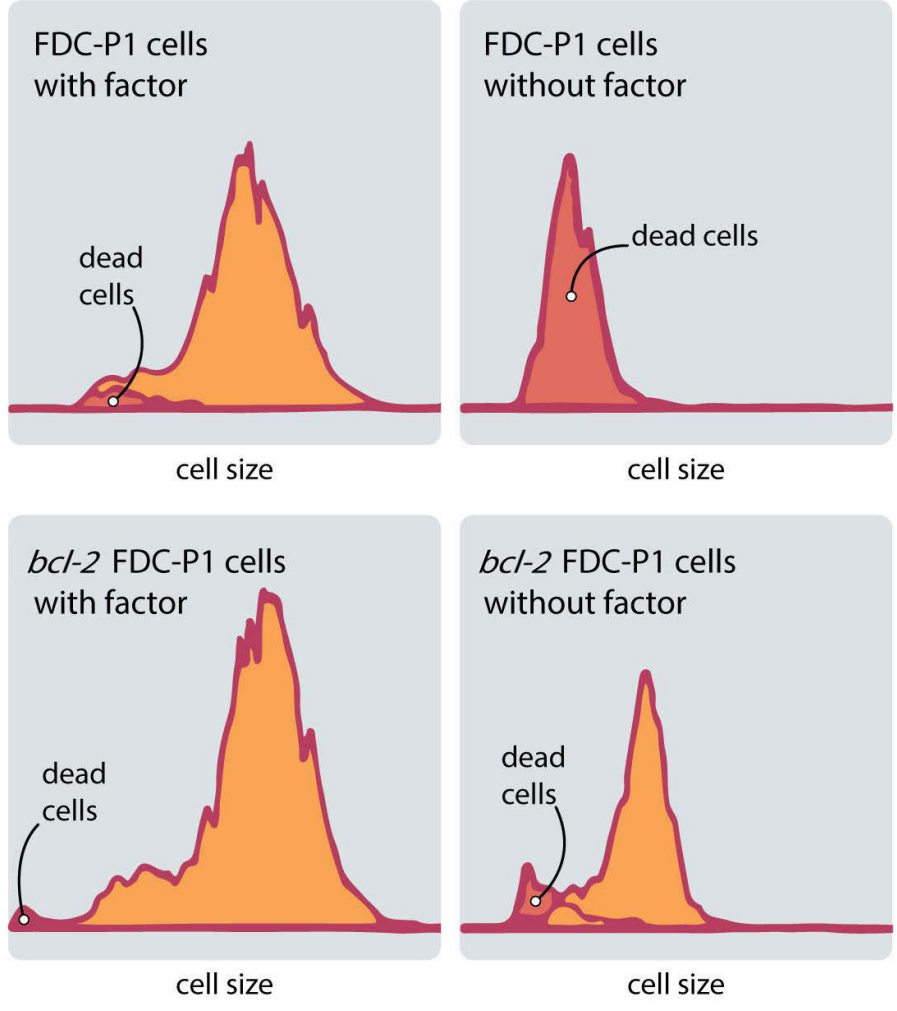

Figure 1. Overexpression of *bcl-2* protects cells from cell death. Interleukin (IL)-3-dependent FDC-P1 myeloid cells were transduced with *bcl-2* cDNA. After transduction, cells were washed to remove IL-3 from the culture media. Cell viability was measured by flow cytometry. Overexpression of *bcl-2* protected cells from death after IL-3 withdrawal.

sis. However, the book on *bcl-2* is not yet closed. Even 30 years later, new functions for *bcl-2* continued to be identified, including its ability to regulate T-cell immune function.

In 2001, the three-dimensional structure of BCL-2 was solved, paving the way for the identification of small molecules that bind BCL-2 and block its interaction with inhibitory pro-apoptotic proteins. Through iterative rounds of structure-guided medicinal chemistry, the selective BCL-2 inhibitor venetoclax was identified. Thirty-six years after the original identification of *bcl-2* by Tsujimoto, a randomized clinical trial demonstrated the superiority of venetoclax in combination with azacitidine over azacitidine alone in elderly patients with newly diagnosed acute myeloid leukemia.[1]

Until Vaux's discovery, the prevailing opinion was that mutations in cancer-associated genes promoted malignancy by causing uncontrolled cellular proliferation. For the first time, Vaux *et al.* showed that oncogenes could act by blocking cell death. This discovery provided a new hallmark of cancer – the ability of cancer cells to resist cell death. It helped spark research into cell death mechanisms of cancer, and strategies to selectively target cell death pathways in cancer cells.

Disclosures

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