Insights from Bcl-2 and Myc: Malignancy Involves Abrogation of Apoptosis as well as Sustained Proliferation

Suzanne Cory, David L. Vaux, Andreas Strasser, Alan W. Harris, and Jerry M. Adams

The Walter and Eliza Hall Institute of Medical Research, PO Royal Melbourne Hospital, Victoria 3050, Australia

Abstract

The chromosome translocations typifying Burkitt’s lymphoma and follicular lymphoma deregulate very different oncogenes, myc and bcl-2.

It is indeed an enormous honor and pleasure to introduce Drs. Suzanne Cory and Stanley Korsmeyer, this year’s winners of the Mott Prize.

I think no one would question the view that their seminal experiments radically changed the way we think about the process of cancer. If we look back about 10 or 15 years, programmed cell death was a very interesting phenomenon, but we had no idea what this meant in terms of cancer, although suggestions were made. It was certainly interesting in terms of development, but we had no idea about the mechanisms involved.

Of course, all this has changed enormously over the last decade, and in terms of cancer particularly, through the seminal contributions of Suzanne Cory and Stan Korsmeyer and their colleagues. Now we know that not only do cancer cells have to escape proliferation controls, they also have to abolish cell death pathways. Not only is this incredibly important for our understanding of the mechanisms underlying cancer, but the way we think about therapy has been radically altered.

And as was said already, it is very exciting and a great coincidence, perhaps, that the Sloan Prize this year is awarded to Bob Horvitz who has used very elegant genetics to dissect cell death pathways in C. elegans. And, of course, what is particularly exciting is the convergence of the studies on bcl-2 in humans and mice with those in C. elegans to show these pathways are conserved. What an exciting combination of studies.

So, now, to introduce Dr. Suzanne Cory. Suzanne has made many seminal contributions over the years, and I would say one thing that has typified her approach has been to use pioneering transgenic experiments to dissect gene interaction in cancer—together with her collaborator over many years, Dr. Jerry Adams, who is here in the audience.

Suzanne got her degree at the University of Melbourne in Australia and then made a very visionary and wise choice in coming to Britain to do her Ph.D. I wasn’t going to crack any jokes, just a slight one... to do her Ph.D., as she says, in the Department of One Called Francis Crick.

She survived that experience and came out with a very important paper on sequencing transfer RNA which was a breakthrough at the time.

After a productive post-doctoral period in Switzerland, Suzanne then set up a joint laboratory with Jerry Adams in the Walter and Eliza Hall Institute in Melbourne. First, they concentrated on normal B cell development and identified immunoglobulin gene clusters, showed that deletions were important in rearranging those clusters in B cells to bring about the formation of the immunoglobulin genes, and then they moved to pathology and made a very important observation, that in mouse plasmacytomas and Burkitt’s lymphoma, the myc gene is deregulated by translocations.

However, they went one step further than that. They actually recreated the myc rearrangements in transgenic animals which then developed lymphomas, proving causality which is a very important thing we all have to do.

The next move that they made was to use transgenic approaches to look at the interaction of different oncogenes and how they cooperate in oncogenesis in mice. Then, in terms of this particular prize, the seminal finding, after the isolation of the bcl-2 oncogene by Stan Korsmeyer and other groups, was the study published in Nature in 1988. Together with David Vaux and Jerry Adams, Suzanne Cory showed that the introduction of bcl2 into B-cells in culture increased their survival. This was, of course, a very, very important observation.

Suzanne then went on to pursue aspects of the biology of bcl-2, showing for example that bcl-2 can cooperate with myc in oncogenesis in transgenic animals, and has continued to study the function of bcl-2 and interacting partners.

Suzanne is now the director of the Walter and Eliza Hall, a very famous, wonderful institute in Melbourne, and she has had many honors over the years, including election to the Royal Society in London in 1992, and foreign membership of the National Academy of Sciences in 1997. She has also won the Burnet’s Medal and shared the 1998 Australia Prize of the Australian Academy of Sciences.

Nicholas D. Haste
Medical Research Council
Human Genetics Unit
Western General Hospital
Edinburgh, United Kingdom

Transgenic mouse models have illuminated how each contributes to lymphomagenesis. Constitutive myc expression provokes sustained cell proliferation and retards differentiation. However, the resulting expansion in cell number is self-limiting, because the cells remain dependent on cytokines and undergo apoptosis when these become limiting. In contrast, bcl-2 is the prototype of a new class of oncogene that enhances cell survival but does not promote proliferation. Coexpression of these genes leads to the rapid transformation of lymphocytes, probably because each can counter an antioncogenic aspect of the other. Several close homologues of Bcl-2 also enhance cell survival and are thus potential oncogenes; each is essential for maintenance of particular major organs. More distant Bcl-2 relatives instead promote apoptosis and can be regarded as tumor sup-

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2To whom requests for reprints should be addressed.

3Co-recipient of the Mott Prize along with Stanley Korsmeyer, whose article can be found on pages 1693s–1700s of this supplement.

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pressors. For many but not all apoptic signals, the balance between these competing activities determines cell survival. Learning how to adjust the apoptotic threshold in cancer cells should promote development of more effective therapeutic strategies.

Introduction

Many leukemias and lymphomas are hallmarked by specific karyotypic abnormalities, the first recognized being the Philadelphia chromosome of chronic myeloid leukemia (1), produced by a reciprocal translocation between chromosomes 9 and 22 (2). Such abnormalities have been the rosetta stone for identifying causative oncogenic mutations.

By modeling in transgenic mice the translocations specific to Burkitt’s lymphoma and follicular lymphoma, we showed that these B-lymphoid malignancies stem from fundamentally different types of oncogenic mutation. The Burkitt’s mutation, deregulation of c-myc, results in loss of control of cell division, whereas in follicular lymphoma, deregulation of bcl-2, results in decreased susceptibility to cell death. Importantly, these mutations can act in concert, driving the inexorable and rapid development of lymphoma. The lessons learned are relevant to diverse neoplasms.

**myc: An Oncogene That Provokes Loss of Growth Control**

Burkitt’s lymphoma is an aggressive malignancy common in children in equatorial Africa and Papua New Guinea. The majority of these tumors exhibit a translocation involving chromosomes 8 and 14; its murine counterpart is the t(12;15) found in most of the plasmacytomas arising in BALB/c mice injected with mineral oil (3). As reviewed previously (4), several laboratories, including ours, independently established in the early 1980s that both these translocations result from a reciprocal recombination event involving c-myc and the immunoglobulin heavy chain (Igh) locus (5–11). As Ohno et al. (12) first hypothesized, these interchromosomal recombination events appear to be an accidental by-product of the intrachromosomal rearrangement of Igh genes obligatory in normal B-lymphoid ontogeny.

The critical outcome of the reciprocal translocation (13) is constitutive expression of c-myc, enforced by its subjugation to an Igh enhancer (14). The c-myc gene product is a basic/helix-loop-helix transcription factor that regulates several genes that maintain cells in cycle. The oncogenic potential of myc had already been flagged by retrovirus studies. Indeed, its name derives from avian myelocytoma virus, the genome of which bears a mutated form of the gene, and retroviral activation of the cellular gene is frequent in chicken B lymphomas (15) and in murine T lymphomas (16).

Despite the tight association of the myc translocation with Burkitt’s lymphoma and murine plasmacytoma, the case for an etiological role remained circumstantial. To obtain direct proof, we generated mice bearing a transgene comprised of myc linked to the intronic Igh enhancer (Eμ), to mimic the translocation and enforce constitutive Myc production throughout the B-lymphoid compartment. The Eμ-myc transgene proved a potent, heritable lymphomagenic agent; within the first year of life, all of the mice acquired disseminated lymphoma accompanied by leukemia (17, 18). Similar findings were made by Leder’s laboratory (19). The oncogenic potential of myc was not confined to a single differentiation stage, because both pre-B and B lymphomas developed, and some Eμ-myc mice treated with mineral oil succumbed to plasmacytoma (20). These experiments established beyond doubt that the deregulation of myc contributes to the development of most Burkitt’s lymphomas and plasmacytomas. A minor subclass of such tumors bearing variant translocations involving immunoglobulin light chain loci probably also activate myc albeit from a greater distance (4, 21).

Close analysis of the Eμ-myc mouse model was enlightening. Although newborn mice were healthy and devoid of transplantable tumor cells, they showed clear evidence of a preneoplastic condition: a marked increase in pre-B cells, most of which were in cycle, accompanied by a reduction in mature B cells (22). Thus, enforced myc expression had promoted proliferation and retarded differentiation. The lymphomas that subsequently arose stochastically were monoclonal and highly transplantable. Furthermore, the kinetics of their onset suggested that the myc-driven pre-B cells became malignant at a frequency of about 1 per 10^10 cell divisions (18). The strong implication was that tumor onset required one or two somatic mutations as well as constitutive myc expression. Genetic background also played a significant role; tumor onset on a BALB/c background was considerably faster than on a C57BL/6 background (Fig. 1). Such background effects in transgenic models should prove valuable in the coming search for genes modifying susceptibility to human cancer.

The myc mice provided a fertile testing ground for identifying synergistic oncogenic mutations. Some 10% of the lymphomas harbored mutated ras (N- and K-ras) genes (23). The inferred myc-ras synergy, noted earlier in other cell types (24, 25), was proven by showing that mice bearing both an Eμ-N-ras and an Eμ-myc transgene succumbed to lymphomas much faster than those bearing either alone (20). In an alternative approach for identifying synergistic mutations, neonatal Eμ-myc mice were infected with Moloney murine leukemia virus, which can activate and thereby tag a cellular protooncogene. The proviral insertion sites associated with accelerated lymphomagenesis included pim-1, which encodes a ser/thr kinase, and a novel gene dubbed bmi-1 (26, 27), which encodes a transcriptional repressor of certain homeotic genes. How these proteins collaborate with Myc is still unclear, but it is intriguing to speculate that Bmi-1, for example, might repress certain homeobox genes necessary for differentiation.

Finally, it is noteworthy that lymphocytes from Eμ-myc mice remained dependent on cytokines and in fact died faster than those

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**Fig. 1. Rate of Eμ-myc transgene-induced lymphomagenesis varies with genetic background.**

![Graph showing the rate of Eμ-myc transgene-induced lymphomagenesis at different ages.]
**Bcl-2: An Oncogene That Regulates Cell Death**

Following the paradigm established by Burkitt's lymphoma, the karyotypic abnormalities in many leukemias and lymphomas have been cloned as aberrant rearrangements of immunoglobulin or T cell receptor genes (31). Among these was the 14;18 translocation found in the relatively indolent but common follicular lymphoma. Studies by Tsujimoto et al. (32), by Bakhshi et al. (33), and by Cleary et al. (34) revealed that the gene brought into the IgH locus was a novel one, and it was dubbed bcl-2 (B-cell lymphoma gene 2). As in the myc translocation, the bcl-2 coding region remained intact, and the critical outcome was constitutive production at high levels of Bcl-2 in the affected B cell and its clonal progeny. The Bcl-2 protein was found to be associated with cytoplasmic membranes (35) [more specifically, the endoplasmic reticulum and the outer membranes of mitochondria and the nucleus (36)], but apart from a hydrophobic COOH terminus, thought to be a membrane anchor, its amino acid sequence revealed no recognizable motifs.

The function of Bcl-2 remained a mystery, until Vaux et al. (37) introduced the gene into interleukin 3-dependent cell lines. Most unexpectedly, withdrawal of the cytokine revealed that the dependency had now been altered (Fig. 2). Although the cells still could not multiply in the absence of interleukin 3, they survived for many days and proliferated again when resupplied with cytokine. This now-classic experiment demonstrated that cell survival is regulated separately from proliferation and that the function of Bcl-2 is to inhibit apoptosis. Thus, Bcl-2 became the prototype of a new class of oncogene, one that exerts its action by enhancing cell survival rather than stimulating cell division.

Studies of bcl-2 transgenic mice developed by us and by Korsmeyer's group (38–41) confirmed and extended these observations. The B-lymphoid compartment was expanded 4- to 5-fold, but in contrast to the myc mice, the cells were not in cycle. B and T lymphocytes from normal mice when deprived of cytokines (28). The clear implication was that cells forced to cycle by myc die rapidly when cytokines become limiting, thus accounting for the plateau in lymphocyte numbers observed in vivo and in vitro. Askew et al. (29) and Evan et al. (30) subsequently established that myc promotes programmed cell death (apoptosis) under adverse growth conditions.

**Fig. 2.** Bcl-2 enhances cell survival. A, interleukin 3 (IL-3)-dependent FDC-P1 myeloid cells and a derivative line expressing bcl-2 retrovirus were cultured for 3 days with and without IL-3. In the presence of IL-3, both lines proliferated and remained viable (e.g., left panel). In the absence of IL-3, the parental cells died rapidly (center panel). Those expressing the bcl-2 retrovirus survived well in the absence of IL-3 (right panel) but withdrew from cycle, as evidenced by their smaller size.

B, viability of independent clones of parental FDC-P1 myeloid cells and LyH7 pro-B cells (open symbols) and bcl-2 virus-infected derivatives (closed symbols) after 3 days in the absence of IL-3.

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expressing the bcl-2 transgene proved remarkably robust in the face of diverse cytotoxic insults. The normally fragile CD4⁺CD8⁻ thymocytes, for example, were recalcitrant to treatment with ionizing radiation, glucocorticoids, phorbol ester, or calcium ionophore.

As predicted, the bcl-2 transgene proved oncogenic, albeit less so than myc. The incidence of B-lymphoid tumors was higher in the bcl-2 mice than their nontransgenic littermates, although the penetrance was low (10–15% over 12 months), and the latency was long (42, 43). Thus, the transgenic models paralleled the human diseases; Myc produced an aggressive malignancy, whereas Bcl-2 produced an indolent one.

Another oncogenic mutation that can enhance survival of certain cell types is loss or inactivation of the tumor suppressor p53. Such cells normally undergo apoptosis when p53 levels increase in response to DNA damage (44). The protection against DNA damage proffered by Bcl-2, however, is broader than that conferred by loss of p53; Bcl-2 inhibits apoptosis of both resting and cycling T cells, whereas the absence of p53 protects only the quiescent cells (45). High levels of Bcl-2 in tumor cells may therefore be a graver impediment to genotoxic cancer therapy than loss of p53.

Dangerous Liaisons

Many of the tumors arising in bcl-2 mice exhibited a rearranged myc gene, implicating collaboration between myc and bcl-2 (42, 43). That synergy had first been inferred from the demonstration that infection of bone marrow cells from pretumorous myc mice with a bcl-2 retrovirus yielded immortal tumorigenic pre-B cell lines (37). Striking evidence emerged from crosses of myc and bcl-2 mice (46). Young bitransgenic offspring had copious pre-B cells, with blood leukocyte levels 50–100-fold higher than normal and even 25-fold higher than littermates bearing only the myc transgene. Importantly, however, these cycling bcl-2-myc pre-B cells were not fully malignant; despite their greatly enhanced survival in the absence of cytokines (Fig. 3A), they were not transplantable. Thus, even this potent oncogene combination does not fully transform lymphoid cells. Nevertheless, every bcl-2-myc mouse went on to develop a transplantable lymphoma before 7 weeks of age (Fig. 3B). Unexpectedly, each tumor had the phenotype of a primitive progenitor cell and retained both B-lymphoid and macrophage differentiation potential (46, 47). Presumably, additional mutation(s) were involved, but it remains unclear
why a rare stem cell is so susceptible to transformation by the myc/bcl-2 combination.

Curiously, despite this clear potential for synergy, no bcl-2 translocations were detected in lymphomas arising spontaneously in myc mice (23). However, inactivation of p53 was detected in some 10–20% of early passage lines derived from the Eμ-myc tumors and in a significant proportion of Burkitt’s lymphomas (48, 49). In accord with that finding, introduction of the Eμ-myc transgene into a heterozygous p53+/− background by breeding led to very early lymphoma (Fig. 4A). Remarkably, almost every tumor had lost the wild-type p53 allele (e.g., Fig. 4B), as well as also observed by Hsu et al. (50). Clearly, loss of p53, like gain of Bcl-2, synergizes very effectively with constitutive Myc expression to transform lymphocytes.

These studies indicate that the combination of an oncogenic mutation that suppresses the intrinsic cell death program with one that overrides the physiological brakes on cell division is a potent recipe for cancer. Most likely, mutations that enhance cell survival counter the “safety net” of apoptosis, which normally swings into action when cells are induced to divide under adverse or restrictive conditions (29, 30).

The Expanding Bcl-2 Family

A great deal is now known about Bcl-2, although its biochemical mode of action remains controversial (51–54). Bcl-2 is in fact but one of a complex family of proteins regulating apoptosis (Fig. 5). The 15 or so members fall into three subfamilies. Some, like Bcl-2, enhance cell survival, and each of these is a potential oncogene. Other rather similar proteins, such as the prototype Bax, discovered by Oltvi et al. (55), counter this survival function and even promote apoptosis when expressed at high concentrations. A third, more recently recognized group comprises proteins largely unrelated to each other or to Bcl-2, except for a short (9–16 amino acids) central domain known as BH3. These “BH3-only” proteins are potent inducers of apoptosis. Indeed, Bim, a novel BH3-only protein we identified recently, is so potent that stable lines cannot be isolated from cells transduced with bim cDNA unless they also overexpress bcl-2 (56). The pro- and antiapoptotic cousins can heterodimerize and seemingly titrate one another’s function, suggesting that their relative concentration acts as a rheostat for the suicide program (55). Heterodimerization involves insertion of the BH3 domain of the prodeath proteins into a pocket created by three conserved domains of the prosurvival proteins, as shown by Fesick and co-workers (57, 58). The ability of BH3-domain and Bax family members to counter Bcl-2 action suggests that the proapoptotic proteins may act as tumor suppressors, and indeed, many human gastrointestinal cancers and some leukemias have been shown recently to contain mutations of bax (59).

A Bcl-2 Homolog Essential for Spermatogenesis

The two closest homologs of Bcl-2 are Bcl-xL (60) and Bcl-w, discovered in our laboratory (61). All three protect cells from the same array of cytotoxic agents and do so equally well, when expressed at a comparable concentration (62). Nevertheless, gene disruption has revealed tissue-specific requirements. Whereas Bcl-2 is essential for the maintenance of the mature lymphoid system (63) and Bcl-xL for the development of erythroid and neuronal cells (64, 65), Bcl-w is necessary for spermatogenesis (66, 67). In bcl-w-null mice, testicular development and prepubertal spermatogenesis are largely unaffected, but adult seminiferous tubules are disorganized, Sertoli cells and germ cells of all types are reduced in number, and there are no mature sperm. Most likely a particular prosurvival gene is required in certain tissues because it is the sole guardian expressed there. However, it also remains possible that individual inhibitors block certain cell death pathways more effectively than others.

The Bcl-2 Family Controls Many but not All Roads to Death

How does the Bcl-2 family control apoptosis? The engine driving cellular suicide is a family of proteases homologous to Ced-3, the product of one of three genes (ced-3, ced-4, and egl-1) shown by Horvitz and co-workers (68, 69) to be essential for developmental cell deaths in Caenorhabditis elegans (Fig. 5). These proteases, now called caspases, cleave their targets after aspartate residues. To protect the cell, they are synthesized as almost inactive zymogens. Activation requires cleavage at sites that are themselves caspase consensus sites; therefore, apoptosis entails a caspase cascade (70).

In C. elegans, the ced-9 gene inhibits programmed cell death by antagonizing the action of ced-4 and ced-3 (71). Importantly, Vaux et al. (72) and Hengartner and Horvitz (73) found that human bcl-2 can inhibit cell death in the nematode, a striking demonstration of the evolutionary conservation of the machinery of apoptosis (74). How Bcl-2 and Ced-9 function remains uncertain. In keeping with the localization of Bcl-2, some evidence links its function to the permeability or integrity of organelles, particularly the mitochondrion (75). An alternative view, aligned more obviously with the C. elegans genetics, favors a more direct role for the prosurvival molecules. Some recent evidence has suggested that the prosurvival proteins may function by binding to and inhibiting Ced-4-like adaptor molecules needed to facilitate aggregation and autocatalysis of caspases (reviewed in Refs. 54 and 76). The conserved NH2-terminal BH4 region of Bcl-2 homologs, required for their prosurvival activity, may be critical for any such interaction (77). In mammalian cells, proapoptotic cousins such as Bax and Bim may act by binding to Bcl-2 homologues, thereby allowing Apaf-1 homologues to induce death via caspase-9 (Fig. 5). Other putative adaptors may similarly activate other caspases. Likewise, in nematodes, the BH3 domain protein Egl-1 interacts with Ced-9, probably releasing the adaptor Ced-4 to activate Ced-3 (69). The very divergent sequences of the BH3-domain subfamily may hint that each responds to a distinct death/survival signal, one to a damaged cytoskeleton, for example, and another to damaged DNA. Some may also preferentially target subsets of the death effectors.

Bcl-2 is not a panacea for mammalian cell death. In several cell lines and activated normal T cells (78) and in cells targeted by cytotoxic T cells (40, 62, 79), it is ineffectual against the signal induced by “death receptors” such as CD95 (Fas/APO-1) and other members of the tumor necrosis factor receptor family. Ligand-induced aggregation of these receptors leads, via the adaptor protein FADD/Mort1, to activation of caspase-8 (80; Fig. 5). This pathway appears to be independent of Apaf-1 and caspase-9 (81, 82). Additional mammalian death pathways undoubtedly remain to be discovered, because neither gain of Bcl-2 nor inactivation of FADD/Mort1 prevents, for example, the culling of autoreactive thymocytes (40, 79, 83).

A Restraint on Entry into Cell Cycle

Bcl-2 and its homologs not only control cell survival but can also modulate the cell cycle. An early hint of this connection was the quiescence of Bcl-2-expressing cells that survived cytokine withdrawal (37), and their reentry into cycle on restimulation was subsequently found to be retarded (84, 85). Furthermore, thymocyte turnover is slowed in bcl-2 transgenic mice, as is the mitogenic response of their lymphocytes (86–89). Bcl-2 also hastens withdrawal from cycle (90). Importantly, the inhibitory effect of Bcl-2 on cell cycle entry is genetically separable from its survival function; the former but not the latter is ablated by mutation.

* Our unpublished results.

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of a tyrosine residue near the NH₂-terminal BH4 domain (91) or by a deletion in the adjacent nonconserved loop (92). Inhibition of cell cycle entry might involve a protein that can bind to this region, such as the phosphatase calcineurin (93). Whatever the mechanism, the cell cycle inhibitory effect may have evolved to reduce the oncogenic impact of Bcl-2. It seems pertinent that progressed follicular lymphomas often display missense mutations in the relevant NH₂-terminal region (94).

**Concluding Remarks**

The long-observed multistage development of malignancy is now seen to be due to the sequential acquisition of the diverse genetic alterations needed to subvert controls on critical cellular processes. Deciphering the molecular basis of karyotypic abnormalities has revealed key mutations underlying many neoplasms, and transgenic models (95–97) have provided valuable insight into how specific mutations thrust cells from normalcy toward malignancy. Separate mutations may be needed to prevent terminal differentiation, to allow more autonomous growth, and to extend clonal life span (98).

Most notably, delineation of role of the bcl-2 translocation in follicular lymphoma has resulted in a fundamentally altered view of malignant transformation. The realization that bcl-2 exerts its oncogenic effect through suppression of cell death (37) rather than enhancing cell proliferation or blocking cell differentiation has great import for approaches to therapy.

The dramatic synergy between myc and bcl-2 demonstrated for lymphoma (46) and mammary carcinoma (99) may reflect the ability of each gene to counter an antioncogenic impulse of the other. Under limiting growth conditions, Myc overexpression elicits an apoptotic cell response as well as proliferation, whereas Bcl-2 encourages cell cycle arrest and extends clonal life span (98). Under limiting growth conditions, Myc overexpression elicits an apoptotic response as well as proliferation, whereas Bcl-2 encourages cell cycle arrest and extends clonal life span (98).

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