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Unmasking the Mysteries of MYC

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In the early 1980s, when the oncogenic potential of MYC was established, the scientific community was somewhat perplexed (1). Contrary to other oncogenes known at the time, such as HRAS, which induced neoplasia only if it harbored mutations in the open reading frame, MYC-induced neoplastic transformation was possible from the activation of a nonmutated form (1). Chromosomal translocation into the IgH locus is one mechanism by which MYC is overexpressed to cause cancer and is present in virtually all cases of Burkitt lymphoma in humans and plasmacytomas in rodents (2). Another important and unexpected discovery in the early 1980s was the detection of transcriptional enhancers, first in the genome of the SV40 virus and subsequently in IgH (3). Indeed, the landmark paper published by Jerry Adams and colleagues (4) modeled the Burkitt lymphoma chromosomal translocation by creating the Eμ-*myc* mice, which involved coupling the *MYC* gene to the IgH enhancer (this article is available at https://www.nature.com/articles/318533a0). This transgene converted MYC into a potent oncogene in vivo and predisposed the Eμ-*myc* mice to B lymphoid lymphoma/leukemia with 100% penetrance (4). Ever since, the Eμ-*myc* mouse model has proven invaluable in establishing causal links between this genetic anomaly and the imbalance in downstream processes involving cellular division, differentiation, and apoptosis, which eventually lead to tumorigenesis.

Eμ-*myc* mice invariably developed tumors, and these tumors corresponded to different stages of B cell ontogeny, including pre-B, immature B, mature B, or mixed pre-B/immature B (4). The endogenous *MYC* gene in Eμ-*myc* tumors is transcriptionally silent, just as in Burkitt lymphoma, likely due to negative feedback regulation by MYC expressed from the translocated allele (4), indicative of tight regulation of MYC in untransformed cells. Further characterization of these mice revealed that most young Eμ-*myc* mice exhibited a variable period of benign overgrowth of pre–B cells, whereas mature B cells developed in reduced number despite increased cell proliferation (5). Thus, the MYC-induced proliferative potential and the availability of a large pool of rapidly dividing cells likely promoted tumorigenesis (5, 6). This observation was consistent with early studies showing that mitogenic stimulation of cells induced the expression of MYC in a cell cycle–dependent manner (7) and that MYC played a key role in DNA replication (8, 9).

Interestingly, constitutive expression of MYC alone was not sufficient to transform B cells. B cell lymphomas arose in Eμ-myc mice in a stochastic manner between 6 and 83 wk of age (4, 6). In addition, the tumors were mainly monoclonal, but from different stages of B cell development (4). Together, these results suggested that further somatic mutations were required for tumorigenesis and triggered the search for genetic events that cooperate with MYC-induced tumorigenesis in the Eμ-myc murine model.

One hallmark of most, if not all, types of cancers is acquired resistance to apoptosis (10). In the early 1990s, the thinking behind the oncogenic mechanism of MYC changed when its role was extended beyond cellular proliferation and implicated in activation-induced apoptosis (11). This finding explained the early nonlymphomatous state in Eμ-*myc* mice, in which MYC-induced rapid cellular proliferation was likely offset by MYC-induced apoptosis, thereby protecting Eμ-*myc* mice from tumor development (4, 12). Subsequent studies showed that deregulated MYC induced apoptosis by activating the tumor suppressor p53 via ARF, which ultimately triggered a cohort of genes involved in apoptosis and cell cycle arrest (13, 14). Hence, it was hypothesized that secondary mutations might allow B cells to circumvent MYC-induced apoptosis, likely resulting in clonal tumors. Indeed, the Eμ-*myc* murine model was critical in identifying MYC-induced pathways that promote apoptosis (15); more than half of tumors arising in Eμ-*myc* mice had inactivated the ARF–Mdm2–p53 apoptotic axis (15). Consistent with these findings, Eμ-*myc* mice heterozygous for p53 or ARF showed accelerated lymphomagenesis (16). However, almost one fourth of the analyzed tumors did not have any conspicuous signs of perturbations in ARF, p53, or Mdm2, implying that multiple pathways were involved (15).

In 1983, Land et al. (17) showed that primary rat embryo fibroblasts only became transformed when MYC was introduced along with RAS, thus pioneering the concept of oncogene cooperation. Based on these results, the Adams Laboratory showed that BCL-2, which, on its own, was weakly transformative, greatly promoted the immortalization of B lineage cells from Eμ-*myc* mice in vitro (18). Thus, whereas MYC provided cells with proliferative potential, BCL-2 provided cells with a survival capacity, and their synergy promoted lymphocyte tumorigenesis (18). MYC-dependent oncogene cooperation was, for the first time, shown in vivo in 1990 with the creation of doubly transgenic Eμ-bcl-2/*myc* mice, which developed tumors much faster and more synchronously than their Eμ-*myc* littermate

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counterparts, producing tumors with a more primitive lymphoid origin (12). Consistent with these findings, half of high-grade lymphomas arising from single *Bcl-2* transgenic mice harbored somatic translocations that activated MYC (19). Subsequent studies showed that apoptosis is controlled by the interplay between proapoptotic and antiapoptotic proteins. In 2004, Egle et al. (20) reported that in the absence of Bim, which is a major physiological antagonist of Bcl2, Eμ-myc mice showed accelerated MYC-induced lymphomagenesis, the kinetics being similar to the gain of Bcl2 (12). Further characterization revealed that the p53 apoptotic pathway was intact in Bim-deficient Eμ-myc tumors, indicating that loss of apoptosis due to Bim reduction could be an independent alternative to loss of p53 function during tumorigenesis. These studies have collectively helped the clinical development of Bcl2 inhibitors as therapeutic agents of different malignancies (21, 22).

Eμ-*myc* tumors arise from early stages of B cell development, whereas human Burkitt lymphomas and murine plasmacytomas exclusively arise from germinal center B cells and plasma cells, respectively. In 2008, Mori et al. (23) reported that several forms of B cell tumors are found in Eμ-*myc* mice. They used previously developed expression signatures of oncogenic pathways to characterize the heterogeneity of Eμ-*myc* tumors and reported that early-onset and late-onset tumors have gene expression characteristics corresponding to Burkitt lymphomas and diffuse large B cell lymphoma, respectively (23). Together, with results that further dissected the spectrum of tumors, the Eμ-*myc* mouse model has been used to understand the complexity of the molecular processes of other B cell malignancies and to help develop diagnostics and therapeutics (23).

MYC overexpression occurs in almost half of human tumors and is associated with more clinically aggressive tumors that have a worse prognosis (24). In addition, MYC is estimated to bind to thousands of sites in the human genome (25). Thus, the Eμ-*myc* model described in this landmark paper (4) has a potential to help identify many other MYC-affected cellular processes in addition to continuing to be a widely appreciated model of MYC-induced transformation and tumorigenesis.

Disclosures

The authors have no financial conflicts of interest.

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