MYC and the Control of Apoptosis

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MYC expression is tightly correlated with cell-cycle progression in normal tissues, whereas unchecked MYC expression is among the most prominent hallmarks of the hyperproliferation associated with most forms of cancer. At first glance it might seem counterintuitive that MYC is also among the most robust agents of programmed cell death (apoptosis) in mammalian cells. However it is clearly beneficial for a multicellular organism to have a mechanism for triggering death in cells that express potentially oncogenic levels of MYC. Decades of intense study have begun to provide an understanding of the mechanisms that regulate MYC's seemingly split personality. Key features of MYC-induced apoptosis will be discussed here along with examples of how our understanding of this pathway might be exploited for the therapeutic benefit of cancer patients.

INITIAL LINKS BETWEEN MYC EXPRESSION AND APOPTOTIC CELL DEATH

As described elsewhere in this collection, the first decade of study of MYC focused on its role in promoting phenotypes classically associated with malignancy. This included studies that documented its role in promoting cell-cycle progression and in blocking terminal differentiation. However, in the late 1980s and early 1990s, hints began to emerge that this monolithic view of MYC might not reflect the true complexity of its biological properties. For example, in 1987, Wyllie, Spandido, and their colleagues reported that rodent fibroblasts expressing *ras* and MYC oncogenes had a much higher rate of cell death than those expressing only *ras* (Wyllie et al. 1987). Similarly, Neiman and colleagues observed in 1991 that stimuli that triggered cell death in normal B lymphocytes

were made appreciably more potent by the ectopic expression of MYC (a viral form of MYC in this case) (Neiman et al. 1991). The heightened sensitivity to apoptosis caused by ectopic MYC expression was observed in premalignant cells, but not after malignant transformation. This last observation foreshadowed the critical concept discussed below that tumor cells have acquired specific mechanisms for blunting the apoptotic effects that MYC exerts in their normal counterparts.

Later that year, Askew, Cleveland, and colleagues began the shift from these early descriptive observations correlating MYC expression and apoptosis to a more mechanistic understanding of this important link (Askew et al. 1991). This shift was the result of their studies of a myeloid cell line whose growth is dependent on the cytokine IL-3. On IL-3 withdrawal, these cells respond by undergoing an acute growth

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arrest. During this process, expression of the endogenous MYC gene is essentially shut off. Remarkably, enforcing MYC expression in these IL-3 deprived cells induced robust apoptosis.

This landmark study highlighted at least three important concepts that have remained pillars of our understanding of the pathway linking MYC to apoptosis. First, not only can the inherently oncogenic viral form of MYC induce apoptosis (as evident from Wyllie et al. 1987), but the normal MYC proto-oncogene can also cause apoptosis. Rather than the sequence of the gene product, the absolute levels or perhaps kinetic pattern of MYC expression appears to play a central role in determining the cellular response to MYC. Second, the cellular response to elevated MYC levels is dictated in large part by the environment in which the cell finds itself. For example, cells bathed in adequate concentrations of growth factors respond to heightened MYC with more rapid proliferation, whereas cells experiencing conditions in which growth factors are limited may respond to MYC by undergoing apoptosis. This apparent ability of growth factor signaling pathways to toggle the cellular response to MYC between proliferation and death continues to fuel excitement over the therapeutic potential of targeting MYC transformed cells in patients. This is partly based on the fact that, unlike normal cells in which growth factor deprivation triggers a feedback loop to decrease MYC levels, tumor cells have constitutively elevated MYC that is no longer susceptible to feedback control. A third critical concept raised by the studies of Neiman et al. (1991) and codified by Askew et al. (1991), is that normal cells have response mechanisms in place that allow them to sense elevated MYC levels and to respond by undergoing apoptosis. Conversely, transformed cells often acquire the ability to resist the apoptotic effects of elevated MYC and respond only to its pro-proliferative signals.

In 1992, a series of studies expanded these previous observations to the point where there arose a widespread appreciation that MYC has potent and acute effects on both cell-cycle progression and programmed cell death. In the first of these, Evan, Hancock, and colleagues report-

ed that the activation of a conditional allele of MYC in growth factor-deprived fibroblasts is sufficient to induce apoptosis, regardless of the phase of cell cycle in which the trigger is pulled (Evan et al. 1992). Another advance provided by these investigators stemmed from their observation that the domains of the MYC protein essential for apoptosis overlap quite well with the domains required for other known activities of MYC (e.g., transformation, DNA binding, and MAX dimerization, transcriptional activation).

Another of the early, high profile studies capitalized on the fact that apoptosis is a process that is important in several normal physiological settings, as well as in response to oncogene activation and genotoxic insults. One of the normal processes that require apoptosis is the elimination of self-reactive lymphocytes that might otherwise mount an autoimmune response. In a study also published in 1992, Shi, Green, and their colleagues showed that this form of apoptosis requires expression of the endogenous MYC gene (Shi et al. 1992). This highlights the point that the pathological apoptotic response observed in some scenarios when MYC is over-expressed likely represents an adaptation of a normal function that MYC exerts in some biological contexts, even when expressed at endogenous levels.

Collectively, these studies defined the basic elements of MYC's apoptotic potential and served as a foundation for the numerous subsequent studies that have shed additional light on the paradox that the most potent pro-proliferative agent encoded in our genome is also among the most potent agents of cell death.

The ability of MYC (and certain other oncoproteins like E1A and E2F) to induce cell death in some contexts has been referred to as latent or intrinsic tumor suppressor activity (Lowe et al. 2004). Elevated expression of MYC, and hence increased MYC function, is a nearly universal hallmark of human cancer (Huang and Weiss 2013; Roussel and Robinson 2013; Gabay et al. 2014; Schmitz et al. 2014). The possibility that tumors harbor the seeds of their own destruction in the form of elevated MYC, and that normal cells are generally not susceptible to MYC-triggered apoptosis, has led to decades of effort

aimed at dissecting the molecular mechanisms that control MYC-driven apoptosis. Ultimately, the goal of these studies has been to gain sufficient understanding of MYC-driven apoptosis that therapeutic strategies can be designed that convert the effects of oncogenic levels of MYC from pro-proliferative to proapoptotic.

BIOCHEMICAL MECHANISMS THAT CONTROL THE APOPTOTIC RESPONSE TO MYC

As alluded to above, a number of important advances have been made in our understanding of how a cell decides whether to respond to MYC activation by proliferating or by engaging the apoptotic machinery. These mechanisms are interrelated and most involve some aspect of the proapoptotic p53 pathway, the prosurvival BCL-2 pathway, or both. What follows are examples of key observations linking MYC to other apoptotic regulators.

BCL-2 Activation as a Common Mechanism for Evading MYC-Driven Apoptosis

Both experimental models and genetic studies of cancer patients have firmly established the link between the MYC and BCL-2 oncoproteins. In human tumors, MYC is often overexpressed owing to amplification or translocation (Vita and Henriksson 2006). Frequently these MYC alterations are accompanied by rearrangements in the BCL-2 locus. In germinal center B-cell lymphomas with an IGH:BCL-2 translocation, IGH:MYC fusions or MYC amplifications have been documented (Martin-Subero et al. 2005). Similarly BCL-2 locus translocations in follicular lymphomas are transformed to high-grade lymphomas upon subsequent rearrangement of MYC (Knezevich et al. 2005; Mukhopadhyay et al. 2005). Numerous other forms of cancer have been documented to carry simultaneous elevation of both BCL-2 and MYC levels (e.g., supraglottic squamous cell carcinoma [Ozdek et al. 2004] and acute lymphoblastic leukemia [Berger et al. 1996]). The conclusion most frequently drawn from these lines of evidence is that human tumors are able to tolerate the nor-

mally apoptotic effects of MYC elevation only when they have simultaneously blunted the death pathway by compensatory overexpression of the potent prosurvival agent BCL-2. This raises the possibility that therapeutic agents that antagonize BCL-2 might unmask the true apoptotic effects of MYC overexpression.

It is also worth noting that the broad but still correlative data implicating BCL-2 overexpression as a promoter of MYC-mediated transformation in human cancers have been more formally linked in elegant animal models. For example, in the classic E μ -*myc* transgenic mouse model, lethal lymphomas appear at ~6 mo of age (Adams et al. 1985; Jacobsen et al. 1994). However, *Bcl-2/c-myc* double transgenic mice succumb to immature lymphoblastic leukemia typically within a few days of birth (Strasser et al. 1990). Conversely, conditional knock-out of the *Bcl-2* allele in *MYC* transgenic mice induces massive apoptosis (Letai et al. 2004), adding additional support to the model that *Bcl-2* overexpression is required to block the apoptotic program in MYC overexpressing animals.

Other BCL Family Events that Participate in Regulating MYC-Driven Apoptosis

Translocation of the MYC gene to one of the immunoglobulin gene loci is a primary transforming event in Burkitts lymphoma. However, the *myc* allele in these lymphoma cells can acquire secondary, missense mutations in a region that comprises a phosphoacceptor domain (Johnston et al. 1991; Bhatia et al. 1993; Yano et al. 1993). This domain participates in a number of critical aspects of MYC function, including the regulation of MYC protein stability (Sears et al. 1999). This region has also acquired similar mutations in the acutely oncogenic viral versions of the *myc* gene. In addition to a role in protein stability, several studies have shown that at least one of the more common mutations, T58A, has a dramatic effect on the ability of MYC to induce apoptosis. For example, using in vitro platforms Chang et al. (2000) showed that a T58A version of the MYC protein showed both increased transforming potential and decreased ability to induce apoptosis. In subse-

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quent studies using animal models, Hemann et al. (2005) showed that tumors induced by the T58A allele of MYC were more deadly than those induced by WT MYC. Consistent with the in vitro studies of Chang et al. (2000), this increase was correlated with a decrease in apoptotic potential. Hemann and colleagues mapped this effect to the BCL-2 pathway and specifically showed that the decreased apoptotic potential of the T58A allele was linked to a defect in the ability of MYC to induce expression of the proapoptotic BCL family member Bim. Although it remains unclear how the T58A conversion alters this specific transcriptional circuit, these in vitro and in vivo data further support the critical role of both prosurvival (BCL-2) and proapoptotic (Bim) family members in balancing cell-cycle progression and apoptosis in MYC expressing cells.

An additional link between regulation of the BCL-2 pathway and MYC's apoptotic effects was shown in recent studies from our group that identified the BAG-1 gene product as a critical, direct downstream target of MYC (Zhang et al. 2011). BAG-1 was first isolated as a BCL-2 chaperone that has potent prosurvival effects (Takayama et al. 1995). In animal tumor models, loss of even a single copy of the BAG-1 gene decreases tumor formation (Gotz et al. 2004), presumably owing to heightened apoptosis of the nascent tumor cells. Our analysis showed that induction of BAG-1 by MYC is a critical event in dampening the latent apoptotic effects that MYC overexpression otherwise exerts (Zhang et al. 2011). Although BAG-1 is expressed as multiple protein isoforms with potentially distinct functions and has many client proteins beyond BCL-2 (Wang et al. 1996; Luders et al. 2000; Cato and Mink 2001; Lin et al. 2001; Arhel et al. 2003), these studies provide further evidence that modulating the pro-survival/proapoptotic balance in the BCL pathway is an important means by which MYC controls its biological effects. These data also highlight the possibility that there exist multiple nodes within this pathway that might serve as therapeutic targets for agents whose mode of action involves the activation of MYC's apoptotic potential.

MYC Activation Levels as a Determinant of Apoptotic Potential

An important advance in our understanding of the distinction between MYC-driven proliferation and MYC-driven apoptosis came from in vivo studies by Murphy et al. (2008). These investigators used genetic platforms to establish a scenario in which MYC levels could be tightly controlled in a rheostat-like manner. Upon modest elevation of MYC, transformation was enhanced as expected. In contrast, robust overexpression of MYC led to a dramatic increase in apoptosis. Given MYC's role as transcription factor the investigators suggested two interesting alternatives that might explain how modest and extreme levels of ectopic MYC result in distinct biological outcomes. First, very high levels of MYC might engage a new set of MYC target genes that are not regulated by lower levels of MYC. These genes might be preferentially skewed toward targets with proapoptotic functions. Alternatively, MYC might engage the same set of target genes regardless of expression levels and only the extent of target gene transcription is altered. In this scenario, modest elevation of MYC, although leading to enhanced transformation, might also be engaging the apoptotic machinery at some low level. These models are of course impacted by more recent studies that show MYC functions as a general amplifier of preexisting transcriptional programs (Lin et al. 2012; Nie et al. 2012), rather than an agent that directly dictates distinct and targeted transcriptional outcomes (see Levens 2013; Rahl and Young 2014). It is worth noting, however, that the constitutive activation of at least some level of apoptosis by both modest and extreme levels of MYC is consistent with historical findings in both culture systems and human tumor samples that populations of cells often simultaneously show both a high mitotic index and a significant fraction of apoptotic cells (Topham and Taylor 2013).

Role of p53 in the Apoptotic Effects of MYC

As the central tumor suppressor in higher organisms, TP53 encodes a transcription factor

that works in part by inducing rampant apoptosis in cells that have activated one of a variety of stress-responsive pathways (Levine and Oren 2009). For example, p53 is activated in response to genotoxic insults that arise in normal cells and which could lead to transformation if the cell were allowed to survive. A great deal is known about how p53 responds to upstream stress signals such as DNA damage response pathways. Similarly, the apoptotic effector mechanisms of p53 are well characterized and largely involve regulation of the transcription of BCL family members, including the proapoptotic members BAX, BAK, and PUMA/BBC3. p53 also regulates BCL family member function via direct protein–protein interactions that do not depend on alterations in transcription (Haupt et al. 1997). By modulating the ratio of active prosurvival and proapoptotic BCL family members, p53 induction results in oligomerization of proapoptotic members at the mitochondrial outer membrane, thus facilitating release of caspase-activating molecules such as cytochrome *c* and APAF1. In addition to DNA damage signaling pathways, p53 is stimulated to induce these proapoptotic events by activation of oncogenes like MYC. Oncogene activation induces p53 via a pathway that involves enhanced function of the p14ARF/CDKN2A tumor suppressor, which in turn blocks the function of the p53 inhibitor hMDM2 (Kamijo et al. 1997, 1998; de Stanchina et al. 1998; Zindy et al. 1998). As loss of p53 is a very common event in human cancer, the implications for MYC-driven apoptosis are equally broad. Indeed much of MYC's apoptotic potential is dependent on the downstream activation of p53.

Although examples abound, among the most elegant settings in which a role for p53 pathway function in MYC-driven tumors comes from the E μ -*myc* transgenic mouse model discussed above. In this model, several important observations have been made linking tumorigenesis to decreased apoptotic activation by p53. The 6-mo latency period for tumors in the E μ -*myc* transgenic mouse model suggests that secondary genetic changes must occur subsequent to MYC overexpression. Interestingly, these animals display high levels of apoptosis in

their B-lymphocyte compartment when young, suggesting that a proapoptotic response to elevated MYC is responsible for keeping the tumors in check (Jacobsen et al. 1994). For a large percentage of the tumors that ultimately arise in these animals, that secondary genetic change appears to inactivate the p53 pathway (Eischen et al. 1999). This inactivation occurs in roughly equal proportions by loss-of-function mutations in either p53 itself or in the p14ARF locus. Overexpression of MDM2 also contributes to inactivation of this pathway in some animals. Moreover, targeted deletion of one or both alleles of either p53 or p14ARF greatly accelerates tumor formation as well. Similar findings had been reported previously in cell culture models as well (Zindy et al. 1998). These and numerous other examples clearly show that, in at least some settings, the potent apoptotic potential of MYC is enforced via the p14ARF/p53 axis. Furthermore, the ability to circumvent activation of this pathway by MYC drives the frequent alterations that arise in p53, p14ARF, MDM2, and other regulatory proteins during tumor progression

Perhaps more intriguing than p53-dependent induction of apoptosis by MYC, are scenarios in which MYC drives apoptosis in a manner that does not require p53. This p53-independent apoptosis is of particular interest because it provides a basis for the suggestion that reactivation of MYC's latent apoptotic potential might be a viable therapeutic strategy even in the large proportion of human tumors in which p53 function has already been lost. Among the best characterized of p53-independent apoptosis induction by MYC is the murine myeloid leukemia system (Amanullah et al. 2000). In culture, these cells proliferate aggressively, yet can be induced to undergo terminal differentiation by IL-6 treatment. This differentiation is accompanied by a decrease in the expression of endogenous MYC, and enforced MYC expression actually blocks the induction of differentiation by IL-6. Ultimately these cells undergo apoptosis, in a manner that does not require p53. p53-independent induction of apoptosis by MYC is not limited to myeloid lineage cells, as similar results have been documented in mouse

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Figure 1. Apoptotic signaling pathways in normal and malignant cells. Fundamental differences in MYC-linked signaling pathways distinguish normal and malignant cells. (*Left*) In normal cells whose environment has adequate nutrients and growth factors, surveillance mechanisms such as p53 activation are not triggered. This is due in part to lack of flux through stress signaling pathways and in part to negative autoregulation that allows elevated MYC levels to trigger a block in further MYC expression. Unbridled MYC expression can activate the oncogene-stress pathway that signals via the p14ARF/MDM2 pathway to stimulate p53-mediated apoptosis. However, MYC levels in normal cells typically do not reach levels high enough to activate the p14ARF tumor suppressor. (*Center*) When growth factors are limiting, cells with high MYC levels experience activation of surveillance mechanisms, such as p53 induction. These changes ultimately culminate in apoptosis, as a means of eliminating incipient tumor cells from the organism. (*Right*) Tumor cells have constitutively elevated MYC, generally as the result of chromosomal translocation, MYC gene amplification, or tonic WNT signaling. By loss of surveillance mechanisms (e.g., p14ARF or p53 mutation, MDM2 overexpression) and/or by gain of pro-survival signals (e.g., BCL-2 and NF-κB pathway alterations), tumor cells are able to tolerate constitutively elevated MYC and avoid apoptosis. At least conceptually, the restoration of MYC-driven apoptosis signaling pathways in tumor cells yields promise as an anticancer therapy.

embryo fibroblasts, kidney epithelial cells, and B lymphocytes (Sakamuro et al. 1995; Trudel et al. 1997; Hagiyaama et al. 1999; Boone et al. 2011).

The ability of normal cells to sense oncogenic levels of MYC and eliminate themselves from the organism so as not to cause potentially lethal tumor, is mirrored by a noncell autonomous phenomenon. In this phenomenon, termed cell competition, those cells expressing elevated MYC overgrow those expressing low MYC by two converging mechanisms. First,

the elevated MYC levels drive more rapid proliferation, as expected. Second, and more unexpected, the high MYC cells provide an outward signal that causes the apoptotic death of their low MYC neighbors. MYC regulated cell competition has been described in insects and mammals and its biochemical triggers are still being elucidated (de la Cova et al. 2004; Claveria et al. 2013). Our current understanding of this enigmatic MYC function is described in detail elsewhere in this volume (see Johnston 2014).

SUMMARY

From the examples discussed above a model emerges that places the most ubiquitous human oncogene MYC at the head of a cascade that ultimately triggers apoptosis (see Fig. 1). In fact, the evidence suggests that the default function of MYC may be to drive cell death rather than cell-cycle progression and it is only by carefully orchestrating changes in the apoptotic machinery that MYC is able to transform cells. These changes that allow cells to tolerate elevated MYC without undergoing death include increased expression of the prosurvival BCL-2 and BAG-1 proteins and loss of p53 function via direct lesions in the TP53 locus, loss of p14ARF, or overexpression of the hMDM2 oncogene. We now have the ability to therapeutically modulate the activity of some of these players (e.g., BCL-2 and hMDM2) (Vassilev 2004; Tse et al. 2008). This raises the possibility that as we gain the ability to modulate these proteins in a predictive and more sophisticated manner, we may be able to acutely disrupt the protective role they play in MYC expressing tumor cells. Coupled with the findings from Murphy et al. (2008), that only high levels of MYC induce robust apoptosis, this may provide a viable therapeutic window in which normal cells could be spared during such therapy. This model also raises a cautionary note regarding recent advances in our ability to directly target MYC with inhibitory compounds (Delmore et al. 2011; Mertz et al. 2011; Ott et al. 2012). At face value, blocking the function of this ubiquitous oncogene seems like an eminently reasonable approach that could have profound benefits to cancer patients. However, given the robust apoptotic trigger that MYC provides to tumor cells when expressed at high levels, blocking its function may have negative consequences. This may become of particular relevance when combining MYC inhibition strategies with more standard treatments like chemotherapy and radiation that are designed to trigger cell death.

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