Oncogenes in Cell Survival and Cell Death

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The transforming effects of proto-oncogenes such as *MYC* that mediate unrestrained cell proliferation are countered by “intrinsic tumor suppressor mechanisms” that most often trigger apoptosis. Therefore, cooperating genetic or epigenetic effects to suppress apoptosis (e.g., overexpression of *BCL2*) are required to enable the dual transforming processes of unbridled cell proliferation and robust suppression of apoptosis. Certain oncogenes such as *BCR-ABL* are capable of concomitantly mediating the inhibition of apoptosis and driving cell proliferation and therefore are less reliant on cooperating lesions for transformation. Accordingly, direct targeting of *BCR-ABL* through agents such as imatinib have profound antitumor effects. Other oncoproteins such as *MYC* rely on the anti-apoptotic effects of cooperating oncoproteins such as *BCL2* to facilitate tumorigenesis. In these circumstances, where the primary oncogenic driver (e.g., *MYC*) cannot yet be therapeutically targeted, inhibition of the activity of the cooperating antiapoptotic protein (e.g., *BCL2*) can be exploited for therapeutic benefit.

Proto-oncogenes perform physiological functions that are necessary for normal cellular homeostasis. In particular, proto-oncogenes govern the processes of growth, proliferation, and survival that a cancer cell can exploit to gain competitive advantages over its non-neoplastic counterparts (Hanahan and Weinberg 2011). During malignant transformation, an emerging clone must circumvent the antineoplastic countermeasures that usually regulate the activity of proto-oncogenes (Hanahan and Weinberg 2011). Tumor cells can then use the beneficial properties of an oncogene (e.g., enhanced proliferation) without the negative effects of “fail-safe” countermeasures that have

been otherwise overridden (Lowe et al. 2004). Indeed “intrinsic tumor suppression” activities such as cellular senescence or apoptosis are triggered when a cell is driven to uncontrolled proliferation through the inappropriate activity of an oncogene (Lowe et al. 2004). One of the best examples of such a fail-safe mechanism is detailed later in this review through the focus on *c-MYC* that concomitantly induces cell proliferation and apoptosis. In this instance, cooperating lesions that inhibit apoptosis (e.g., loss of function of p53 or overexpression of *BCL2*) are required to facilitate *MYC*-driven tumorigenesis (Fig. 1). In contrast, an oncogene such as *BCL2* may have the capacity to inhibit apoptosis but

Editors: Eric H. Baehrecke, Douglas R. Green, Sally Kornbluth, and Guy S. Salvesen
Additional Perspectives on Cell Survival and Cell Death available at www.cshperspectives.org

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Cite this article as *Cold Spring Harb Perspect Biol* 2012;4:a009829

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Figure 1. Cellular transformation through concomitant stimulation of cell proliferation and inhibition of apoptosis. (A) Oncogenes such as *MYC* induce cellular proliferation, however, intrinsic “fail-safe” apoptotic mechanisms such as those induced by the ARF/MDM2/P53 pathway counteract the mitotic stimulus mediated by *MYC* and suppress transformation. (B) Oncogenes such as *BCL2* are potent inhibitors of apoptosis but poor inducers of cell proliferation and are, therefore, insufficient to drive tumorigenesis as a single oncogenic event. (C) The cooperative activity of oncogenes such as *MYC* and *BCL2* suppress apoptosis and drive proliferation resulting in cellular transformation. (D) Certain oncogenes such as *BCR-ABL* can activate signaling pathways that simultaneously induce cell proliferation and suppress apoptosis, thereby leading to transformation.

does not contain strong intrinsic mitogenic activity and therefore cooperating oncogenes that drive cell proliferation (e.g., *RAS*, *MYC*) are required for cellular transformation (Strasser et al. 1990; Lee et al. 2007) (Fig. 1). Finally, there are oncoproteins that engage multiple signal transduction pathways (e.g., *BCR-ABL*) that can concomitantly activate both cell proliferation and cell survival (reviewed by Druker 2008). Such oncoproteins may therefore be less reliant on secondary genetic or epigenetic hits to initiate tumorigenesis (Fig. 1).

Oncogenes are identifiable by their capacity to transform a cell in the context of deregulated expression or function. Mechanisms of oncogene activation are diverse and include upregulated expression of a normal gene product, expression of mutant protein with enhanced stability or altered functionality or altered recruitment or subcellular localization of a normal gene product through interaction with an

aberrantly expressed or mutant binding partner. Perhaps the simplest illustrations of deregulated oncogene expression in malignant transformation can be found in B-cell lymphomas. Here, as a lymphocyte undergoes genomic V(D)J rearrangement to generate antibody specificities, oncogenes may be switched on by “accidental” rearrangement alongside powerful immunoglobulin gene enhancer elements (Kuppers and Dalla-Favera 2001). The resulting “switch-translocations” define lymphomas at a chromosomal level, and strongly implicate the rearranged oncogenes as initiating lesions in lymphomagenesis (Table 1). Classical examples include immunoglobulin heavy chain (*IGH*)-*cMYC* translocations in Burkitt lymphoma and *IGH-BCL2* translocations in follicular lymphoma. *MYC* and *BCL2* are considered prototypic oncogenes and their diverse mechanisms of transformation will be highlighted in this review. Neoplastic transformation is a multistep

Table 1. Examples of oncogenes revealed by IGH-switch translocations

Oncogene	Disease	Gene product (protein) function	Effects
<i>BCL2</i>	Follicular lymphoma	Prevents mitochondrial outer membrane permeabilization	Antiapoptotic
<i>BCL6</i>	Diffuse large B-cell lymphoma	Transcription factor	Proliferative, differentiation block
<i>BCL10</i>	Extranodal marginal zone lymphoma	Caspase-recruiting domain containing protein	Activation of prosurvival signaling (e.g., NF- κ B), proapoptotic
<i>CCND1</i>	Mantle cell lymphoma	Activates cyclin dependent kinases	Proliferative
<i>CDK6</i>	Splenic marginal zone lymphoma	Cyclin dependent kinase	Proliferative
<i>FGFR3</i>	Plasma cell myeloma	Receptor tyrosine kinase	Proliferative, activation of prosurvival signaling (e.g., PI3K, MAPK)
<i>cMAF</i>	Plasma cell myeloma	Transcription factor	Proliferative, altered interactions with tumor microenvironment
<i>MALT1</i>	Extranodal marginal zone lymphoma	Protease/paracaspase	Activation of prosurvival signaling (e.g., NF- κ B)
<i>cMYC</i>	Burkitt lymphoma	Transcription factor	Proliferative, proapoptotic, prosenescent

process involving cooperating activation of oncogenes and/or silencing of tumor suppressors in order for a clone to achieve full malignant potential (Hanahan and Weinberg 2000). Accordingly, deregulation of a single oncogene is usually insufficient to transform a cell.

INITIATING LESIONS AND THE CONCEPT OF “ONCOGENE ADDICTION”

The genetic complexity of neoplastic transformation varies from tumor to tumor. Whereas lymphomas arising from *IGH* switch translocations may be relatively monomorphic in their genetic make-up, carcinomas often have complex aneuploid DNA harboring multiple aberrancies (Kinzler and Vogelstein 1996, 1998). As such, the initial oncogenic event that spawned a genetically complex cancer can be difficult to determine. However, certain malignancies clearly evolve in a stepwise fashion that builds on an initiating oncogenic “hit.” As this stepwise progression rests on the beneficial effects of a primary oncogene, the developing cancer becomes increasingly dependent on that oncogene for viability. At this point, the cancer is considered “oncogene-addicted” because of its heightened reliance on the offending gene products (Wein-

stein 2002). Selective targeting of an oncogene of addiction is a major goal in cancer therapeutics, in which oncogene dependency represents a potential vulnerability in cancer cell survival (Weinstein 2002).

MECHANISMS OF COOPERATIVE ONCOGENIC TRANSFORMATION

Oncogenes show diversity in their proneoplastic effects and in the regulatory fail-safes that protect against transformation. Some oncogenes such as *BCR-ABL* possess a near-complete repertoire of proneoplastic properties, requiring less assistance from cooperative mutations (reviewed by Perrotti et al. 2010). Other oncogenes have a narrow spectrum of biological activity (e.g., *BCL2*) or simultaneously trigger cell proliferation and cell death/senescence (e.g., *MYC*) and therefore cannot transform a cell without cooperating lesions that blunt or inhibit the intrinsic tumor suppressor mechanisms. In this way, the disruption of a specific prosurvival effector can combine with broader oncogenic hits to potentially accelerate the development of cancer. For example, deregulation of *MYC* drives cell growth and proliferation, but its net effect is countered by increased rates of

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apoptosis (Evan et al. 1992). If deregulated, *Myc* activity is then combined with *Bcl2* overexpression, the apoptotic fail-safe is removed in a synergistic route to transformation (Strasser et al. 1990) (Fig. 1). This paradigm is illustrated by the ability of *MYC* to cooperate with a range of antiapoptotic proteins in experimental models of lymphomagenesis (Beverly and Varmus 2009; Whitecross et al. 2009; Campbell et al. 2010). Moreover in the clinic, “double-hit” lymphomas containing *MYC* and *BCL2* translocations are recognized as a distinct entity with poorer prognosis (Aukema et al. 2011).

MYC—AN EXAMPLE OF A TWO-EDGED SWORD IN ONCOGENESIS

Deregulation of *MYC* gene expression is one of the most frequently encountered events in human cancer, implicated in over half of all malignancies (reviewed by Vita and Henriksson 2006). Signal transduction pathways activated in response to nutrients, growth factors, and mitogenic stimuli relay signals from phosphorylation cascades directly to *MYC*. For example, ERK, the canonical downstream effector of the RAS/RAF/MEK/ERK pathway stabilizes *MYC* by phosphorylation of serine 62 (Sears 2004; Gustafson and Weiss 2010). Conversely, glycogen synthase kinase (GSK)-3 β mediated phosphorylation of *Myc* at serine 58 has a destabilizing effect (Sears 2004). GSK-3 β is antagonized by AKT, a nodal effector in the phosphatidylinositol-3-kinase (PI3K) pathway. Therefore, RAS/RAF and PI3K/AKT signaling cooperate to promote *MYC* protein stability in response to optimal growth conditions.

The *MYC* gene promoter receives input from many transcription factors and is normally switched on in response to mitogenic stimuli. In particular *MYC* is transactivated by E2F transcription factors released from RB in response to phosphorylation by cyclin/cyclin dependent kinase (CDK) complexes (Oswald et al. 1994). *MYC* gene-targets are implicated in most aspects of cellular physiology, however, those involved in growth and proliferation feature prominently. The proliferative effects of *MYC* are evident at multiple points in cell-cycle regulation. For ex-

ample, *MYC* activates transcription of D-type cyclins and CDKs to promote cell cycle checkpoint progression (Hermeking et al. 2000; Bouchard et al. 2001). At the same time, *MYC* represses the expression of CIP/KIP family cyclin/CDK inhibitors (Seoane et al. 2002). To prepare the cell for division, *MYC* augments the processes of ribosomal biogenesis (Gomez-Roman et al. 2006) and 5' cap-dependent translation (Lin et al. 2009), allowing a cell to manufacture protein and accumulate biomass. *MYC* also modulates specific metabolic pathways integral to cell growth, such as glucose and iron homeostasis (Adhikary and Eilers 2005).

Unbridled *MYC* activity is a potent oncogenic stimulus, requiring stringent regulation at every possible level from transcriptional control to protein stability. *MYC* also possesses inherent proapoptotic and prosenescent properties that must be overcome before neoplastic transformation can occur. As discussed in detail below, *MYC* activates p53-driven apoptosis programs through the ARF tumor suppressor protein (Lowe et al. 2004). These dual proneoplastic and cancer-protective properties make *MYC* a “two-edged sword” in oncogenesis.

CANCER-PROTECTIVE PROPERTIES OF MYC

MYC-Induced Apoptosis

MYC's inherent proapoptotic properties safeguard against malignant transformation. To a large extent, *MYC*'s apoptotic activity is underpinned by its capacity to initiate a DNA-damage response (DDR) and activate the MDM2-ARF-p53 tumor suppressor pathway (Lowe et al. 2004; Meyer and Penn 2008). Proposed mechanisms for DDR activation include generation of genotoxic reactive oxygen species and formation of aberrant DNA replication intermediates (Vafa et al. 2002). Upregulation of ARF in response to *MYC* stabilizes p53 expression by antagonism of MDM2. Augmented p53 activity counteracts the proliferative effects of *MYC* and activates p53-dependent apoptotic effectors such as PUMA and Noxa. *MYC* also up-regulates the p53-independent expression of proapoptotic BIM (Hermann et al. 2004). The importance of *MYC*'s

interaction with the DDR and apoptosis is highlighted in experimental models of MYC-transformation and human Burkitt lymphoma. Genetic interrogation of these cancers reveals the majority contain perturbations in the MDM2-ARF-p53 pathway as a means to bypass MYC-induced apoptosis (Eischen et al. 1999). Accordingly, genetic crosses of *Myc* transgenic mice with *p53*-, *p19 Arf*-, or *Atm*-deficient mice results in accelerated tumorigenesis by inhibition of *Myc*-induced apoptosis (Schmitt et al. 1999; Reimann et al. 2007). Moreover, knockdown or knockout of *Puma* (Hemann et al. 2004) and to a lesser extent *Noxa* (Michalak et al. 2009) also accelerates *Myc*-induced lymphomagenesis. Conversely, genetic manipulation to overexpress Bcl2 family proteins (Schmitt et al. 2002; Beverly and Varmus 2009; Whitecross et al. 2009; Campbell et al. 2010) or delete *Bim* (Egle et al. 2004) in preneoplastic *Myc*-overexpressing stem cells greatly enhances the oncogenic activity of *Myc* and concomitantly relieves the pressure to mutate *p53* or *p19 Arf* in *Myc*-driven tumorigenesis. These data provide compelling evidence that suppression of *Myc*-induced apoptosis in the presence of a strong pro-proliferation signal by *Myc* cooperate to drive tumorigenesis.

ONCOGENIC SIGNAL TRANSDUCTION PATHWAYS AND REGULATION OF APOPTOSIS

Diverse signal transduction pathways can be activated by upregulated expression of oncoproteins or gain-of-function mutations leading to abnormal protein activity. For example, gain-of-function receptor mutations can initiate ligand-independent receptor tyrosine kinase (RTK) or G-protein coupled receptor (GPCR) activity. Similarly, activating mutations of RAS and *PI3K* can amplify the responses to upstream receptor ligation or cause ligand-independent pathway activation (Vivanco and Sawyers 2002; Engelman 2009). Moreover, chromosomal translocations can give rise to aberrant fusion proteins with oncogenic enzymatic activity (e.g., *BCR-ABL*). A common feature of these oncogenic signaling molecules is their ability to simultaneously stimulate cellular proliferation and sup-

press apoptosis. Although reductionist scientific approaches describe canonical linear signaling cascades, in reality complex networks of communicating proteins exist within a cell. Oncogenic activation of one prosurvival “pathway” can lead to compensatory downregulation of another. For this reason, a combination of upstream genetic lesions (e.g., mutation of *PI3K* and *RAS*) can cooperate by circumventing regulatory modulation by negative feedback loops between networks. It is now recognized that virtually all cancers show either activation of an oncogenic kinase and/or silencing of a tumor-suppressor phosphatase. Below we will provide examples of oncoproteins that either alone or in combination activate a diverse array of signaling pathways to provide the dual transforming effect of uncontrolled cell proliferation and inhibition of apoptosis.

BCR-ABL AND THE CHRONIC MYELOPROLIFERATIVE NEOPLASMS

The initiating lesion of CML arises by reciprocal translocation of *c-ABL1* on chromosome 9 with the *BCR* gene on chromosome 22 to generate the *BCR-ABL* fusion protein with greatly enhanced cABL-1 kinase activity. Acquisition of this *BCR-ABL* fusion is sufficient to transform hematopoietic stem cells (Kharas et al. 2008; Perrotti et al. 2010). The effects of constitutive *BCR-ABL* activity are pleiotropic and include enhanced cellular proliferation, evasion of apoptosis, and increased capacity for cell self-renewal (Druker 2008). Enhanced proliferation and survival are variably attributable to concomitant and coordinated activation of *PI3K*, *JAK/STAT*, and *RAS/RAF/MEK/ERK* pathways (Druker 2008). At the same time, *BCR-ABL* sets the scene for acquisition of new oncogenic lesions by promoting genomic instability and downregulating tumor suppressors (Nowicki et al. 2004; Koptyra et al. 2008). Clonal evolution to blast crisis is most commonly accompanied by mutations of the MDM2-ARF-p53 axis and transcription factors including *RUNX1* and *IKZF1* (Perrotti et al. 2010). Although these secondary lesions cluster within the terminal phenotypes of myeloid and

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lymphoid blast crises, they do not follow a consistent pattern between patients. Therefore, it appears deregulated BCR-ABL expression provides a “fertile soil” for further oncogenic devolution, and these secondary events occur stochastically and additively to convey a more aggressive phenotype.

GROWTH-FACTOR RECEPTOR MUTATIONS IN EPITHELIAL CANCERS

Deregulated expression or activity of members of the epidermal growth factor receptor (EGFR) family underlies development of a range of epithelial tumors across numerous tissues (Wheeler et al. 2010). These cell surface proteins function as RTKs, and EGFR (ERBB1/HER1) and HER2/NEU (ERBB2) are the most extensively studied members of the family. EGFR activation results in an explosion of intracellular signaling including triggering of the RAS/RAF/MEK/ERK and PI3K/AKT/MTOR pathways, as well as activation of Src tyrosine kinases, PLC γ , and STATs 3 and 5 (Marmor et al. 2004). The net result of simultaneous activation of these pathways is enhanced cellular proliferation, suppression of apoptosis, and cellular transformation that is conceptually and somewhat mechanistically similar to that described above for *BCR-ABL* (Fig. 1).

PI3K AND AKT

PI3K is a lipid kinase that integrates afferent signals from GPCRs, RTKs, RAS, and other drivers of oncogenic signal transduction to activate downstream targets implicated in growth, proliferation, and evasion of apoptosis (reviewed by Engelman et al. 2006). As such, PI3K plays an important role in facilitating GPCR, RTK, and RAS-initiated oncogenesis. Indeed, pharmacological or genetic silencing of PI3K severely impairs the ability of *BCR-ABL* to transform hematopoietic stem cells (Kharas et al. 2008) and induces apoptosis in epithelial tumors “addicted” to EGFR and HER2 (Faber et al. 2009). However, PI3K is much more than a passive yet important conduit in oncogenesis, as aberrant PI3K activation by mutation or gene amplifica-

tion is observed in a range of solid-organ malignancies.

Within the PI3K family, class IA PI3K is the most closely associated with cancer. Class IA PI3K consists of a catalytic (p110) and regulatory (p85) subunit. There are four p110 isoforms (α , β , γ , δ) encoded by the *PIK3CA*, *PIK3CB*, *PIK3CG*, and *PIK3CD* gene loci, respectively. The *PIK3R1* gene encodes the p85 regulatory subunit that has a suppressive effect on p110 catalytic activity that is relieved by an interaction with phosphorylated Tyr residues on RTKs. *PIK3CA* and *PIK3R1* have been identified as oncogenes and somatic-activating mutations of *PIK3CA* occur in 30% of epithelial cancers and precursor lesions (reviewed by Engelman 2009). *PIK3CA* mutations increase lipid kinase activity in the absence of receptor activation, promoting cell transformation in vivo (Engelman 2009). The oncogenic activity of PI3K has largely been attributed to its ability to activate mammalian target of rapamycin complex (MTORC)-1 and AKT (Engelman 2009). MTORC-1 is considered a master controller of cell growth, as it modulates the processes of ribosomal biogenesis and 5' cap-dependent translation (Schmelzle and Hall 2000).

AKT itself is an oncogene, first identified as the cellular homolog of a virally encoded protein (vAKT) implicated in the etiology of rodent T-cell lymphoma (Staal et al. 1977). AKT has both proliferative and antiapoptotic effects whereas negatively regulating tumor suppressors including p53, GSK-3 β , and the forkhead-box family of transcription factors (FOXOs) (Liu et al. 2009). The proliferative effects of AKT are conveyed by antagonism of p53-mediated growth arrest and inhibition of CIP/KIP family cyclin/CDK inhibitors. AKT directly inhibits apoptosis by promoting the cytoplasmic sequestration of BAD (Datta et al. 2000) and downregulating the transcription of BIM (which is normally transactivated by FOXOs). AKT also stabilizes the levels of endogenous IAP proteins (Dan et al. 2004), whereas AKT-mediated phosphorylation of caspases can increase resistance to cleavage (Cardone et al. 1998).

The functional relationship between MYC, AKT, and MTOR provides a further example of the duality of MYC and the potential for MYC

to cooperate with other oncogenes (Fig. 2). MYC transcriptionally represses TSC-2 expression (Ravitz et al. 2007), the regulatory complex that bridges AKT and MTORC-1 in canonical PI3K signaling (Astrinidis and Henske 2005). TSC-2 downregulates MTORC-1 but is required for full activation of the second rapamycin insensitive MTOR complex (MTORC-2) (Huang et al. 2008). As MTORC-2 cooperates with PI3K to activate AKT, the net effect of MYC expression is to promote MTORC-1 while suppressing MTORC-2/AKT. This “binary switch” protects against the oncogenic effects of MTORC-1 activation by dampening upstream AKT phosphorylation. Interestingly, chronic pharmacological MTORC-1 antagonism can prevent the onset of lymphoma in experimental *Myc*-driven lymphoma. Conversely genetic activation of AKT by myristoylation (similar to vAKT) dramatically accelerates *Myc*-driven transformation, putatively by counteracting the normally suppressive effects of MYC on MTORC-2/AKT (Wendel et al. 2004).

Figure 2. The interplay between MYC AND PI3K/MTOR. The MYC-regulated transcriptional network interacts with canonical PI3K/AKT/MTOR signaling at multiple levels with opposing “counter-regulatory effects.” In one example, MYC represses the activity of TSC to activate MTORC-1 and enhance the cell’s capacity to translate MYC-mRNA in what is postulated to represent an oncogenic feed-forward loop (+). The concurrent regulatory “fail-safe” is that TSC is required for full activation of the AKT hydrophobic motif-kinase, MTORC-2. In this way, MYC activates MTORC-1 while dampening MTORC-2/AKT activity (–). Consequently, oncogenic activation of AKT by MTORC-2 independent mechanisms dramatically accelerates MYC-driven oncogenesis.

ONCOGENIC RAS

The RAS proto-oncogenes (*HRAS*, *NRAS*, *KRAS*) encode small monomeric GTPases. Wild-type RAS proteins are conformationally activated when bound to GTP and become inactive by the process of hydrolyzing GTP to GDP. Oncogenic RAS is resistant to GAPs, locking the protein into its GTP-bound active conformation. Activating mutations in RAS genes occur in >30% of all tumors (Fernandez-Medarde and Santos 2011). GTP-bound RAS binds and activates a range of effector proteins, most notably PI3K (p110) and RAF (Castellano and Downward 2010). Mutant RAS and *PIK3CA* have the potential to cooperate in PI3K pathway activation and colorectal tumors with genetic lesions in both the RAS/RAF/MEK/ERK and PI3K pathways have been reported (Yuan and Cantley 2008). In contrast, mutations of RAS and RAF are thought to be mutually exclusive in human cancer, suggesting functional redundancy (Sensi et al. 2006). RAF is a Ser/Thr kinase that initiates a phosphorylation cascade including MEK and MAPK. Oncogenic RAF mutations are implicated in the pathogenesis of melanoma and colorectal cancer (Davies et al. 2002). Engagement of the PI3K/AKT is a major mechanism of RAS-mediated inhibition of apoptosis (Castellano and Downward 2010). In addition, various downstream effectors including TBK1, AKT, and Rac can facilitate RAS-induced activation of NF- κ B signaling to suppress apoptosis that may be p53-dependent and -independent depending on the cellular context (Mayo et al. 1997; Cox and Der 2003; Barbie et al. 2009; Meylan et al. 2009). Through multiple molecular mechanisms, RAS concomitantly enhances cellular proliferation and inhibits apoptosis (Castellano and Downward 2010). However, cooperating genetic lesions are required for RAS-induced transformation, indicating the presence of intrinsic fail-safe mechanisms to suppress tumorigenesis. In the case of RAS, induction of senescence may play a protective role against its combined oncogenic proliferative and antiapoptotic effects in vivo. Whereas ectopic expression of RAS in normal cells promotes a senescent phenotype, this is dependent to a varying extent of intact p53/DDR

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detection mechanisms (Serrano et al. 1997). Hence, loss of DDR-related tumor suppressors is one cooperative mechanism by which RAS-induced senescence may be overcome in transformation.

INDUCTION OF APOPTOSIS THROUGH TARGETING ONCOGENES

If suppression of apoptosis is key for oncoproteins to mediate their tumorigenic effects then one would predict that targeted inhibition of the transforming oncoprotein, or of the cooperating protein that suppresses oncogene-induced apoptosis, would result in a robust proapoptotic response. This is indeed the case when the Abl-kinase inhibitor, imatinib, is used against *BCR-ABL*-addicted cells (O'Dwyer and Druker 2000), when the EGFR inhibitor, gefitinib, is used to treat tumors addicted to activated EGFR (Takeuchi and Ito 2010), and when the PI3K/AKT pathway is targeted using MTOR inhibitors in the context of constitutive AKT activation (Wendel et al. 2004). At present, direct pharmacological inhibitors of RAS and MYC have not yet been developed. However, transgenic mouse models of inducible *Myc*- or *Ras*-induced oncogenesis, showed dramatic apoptosis and subsequent tumor regression when these proteins were “turned off” (Chin et al. 1999; Felsher and Bishop 1999; Jain et al. 2002) indicating that this would be an effective cancer therapy strategy should these proteins or key downstream effectors be targeted. Moreover, we and others have shown that *Myc*-driven tumors that coexpress BCL2 or BCLXL resulting in accelerated tumorigenesis are highly sensitive to apoptosis ABT-737, the small molecule inhibitor of BCL2 and BCLXL, resulting in an effective therapeutic response (Mason et al. 2008; Whitecross et al. 2009). This provides proof-of-principle that targeting a second, cooperating apoptotic lesion may be effective against tumors that are addicted to a different “driver” oncogene.

CONCLUDING REMARKS

It is well recognized that two important cooperating hallmarks of tumorigenesis are unre-

strained cell proliferation and resistance to apoptosis. Whereas certain proto-oncogenes such as *BCR-ABL* may be capable of concomitantly inducing both of these important effects, others such as *MYC* must circumvent intrinsic fail-safe mechanisms that have evolved to counter unrestrained cell proliferation. Accordingly, genetic lesions that cooperate with *MYC* to facilitate cellular transformation are most often those that inactivate regulatory proapoptotic pathways such as the ARF/MDM2/p53 axis. Understanding the molecular interplay between genes and signaling pathways that cooperate to drive cell proliferation and inhibit apoptosis have provided important mechanistic insight into the complex process of cellular transformation. Importantly however, such scientific detail has provided the impetus to develop novel therapeutic agents that target the “apoptotic arm” of a driver or cooperating oncogene. Accordingly, successful treatment of an “oncogene-addicted” tumor may not necessarily require direct inhibition of the proto-oncogene itself, but may be achieved through inactivation of the cooperating anti-apoptotic countermeasure that is by definition essential for survival of the neoplastic cell.

ACKNOWLEDGMENTS

R.W.J. is a principal research fellow of the National Health and Medical Research Council of Australia (NHMRC) and is supported by NHMRC Program and Project Grants, the Susan G. Komen Breast Cancer Foundation, the Prostate Cancer Foundation of Australia, Cancer Council Victoria, the Victorian Cancer Agency, the Leukemia Foundation of Australia, Victorian Breast Cancer Research Consortium, and the Australian Rotary Health Foundation. J.S. is supported by the Leukaemia Foundation of Australia and the Cooperative Research Centre for Biomedical Imaging Development.

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