MYC Activation Is a Hallmark of Cancer Initiation and Maintenance

Meital Gabay, Yulin Li, and Dean W. Felsher

Division of Oncology, Departments of Medicine and Pathology, Stanford University School of Medicine, Stanford, California 94305

Correspondence: dfelsher@stanford.edu

The MYC proto-oncogene has been implicated in the pathogenesis of most types of human tumors. MYC activation alone in many normal cells is restrained from causing tumorigenesis through multiple genetic and epigenetically controlled checkpoint mechanisms, including proliferative arrest, apoptosis, and cellular senescence. When pathologically activated in a permissive epigenetic and/or genetic context, MYC bypasses these mechanisms, enforcing many of the "hallmark" features of cancer, including relentless tumor growth associated with DNA replication and transcription, cellular proliferation and growth, protein synthesis, and altered cellular metabolism. MYC mandates tumor cell fate, by inducing stemness and blocking cellular senescence and differentiation. Additionally, MYC orchestrates changes in the tumor microenvironment, including the activation of angiogenesis and suppression of the host immune response. Provocatively, brief or even partial suppression of MYC back to its physiological levels of activation can result in the restoration of intrinsic checkpoint mechanisms, resulting in acute and sustained tumor regression, associated with tumor cells undergoing proliferative arrest, differentiation, senescence, and apoptosis, as well as remodeling of the tumor microenvironment, recruitment of an immune response, and shutdown of angiogenesis. Hence, tumors appear to be "addicted" to MYC because of both tumor cell–intrinsic, cell-autonomous and host-dependent, immune cell–dependent mechanisms. Both the trajectory and persistence of many human cancers require sustained MYC activation. Multiscale mathematical modeling may be useful to predict when tumors will be addicted to MYC. MYC is a hallmark molecular feature of both the initiation and maintenance of tumorigenesis.

The MYC proto-oncogene was first discovered as an etiologic agent of retrovirally mediated tumorigenesis. Later, MYC was illustrated to be activated through chromosomal translocation in Burkitt lymphoma (see Conacci-Sorrell et al. 2014). MYC is also commonly activated in tumorigenesis as a consequence of both oncogenic and epigenetic events (Boxer and Dang 2001; Eilers and Eisenman 2008; Dang 2012). Indeed, MYC is overexpressed and/or activated in more than half of human cancers (Escot et al. 1986; Ladanyi et al. 1993; Gamberi et al. 1998; Kawate et al. 1999; Stock et al. 2000; Boxer and Dang 2001).

MYC largely functions as a transcription factor that coordinates many biological processes

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(Dang et al. 1999). MYC activation can usurp these programs, resulting in the cardinal hallmark features of cancer. Thus, MYC activation contributes to autonomous proliferation and growth, relentless DNA replication, increased protein biogenesis, global changes in cellular metabolism, activation of the angiogenic switch, suppression of the response to autocrine and paracrine regulatory programs, and a restraint of host immune responses (Felsher 2003; Shachaf and Felsher 2005; van Riggelen et al. 2010b; Bachireddy et al. 2012; Dang 2012). Hence, MYC activation appears to be a molecular hallmark of cancer.

In this review, we examine the notion that MYC activation is one of the necessary events for the initiation of tumorigenesis and frequently results in tumor survival being dependent on high levels of MYC, herein referred to as MYC addiction.

MYC AS AN INITIATOR OF TUMORIGENESIS

MYC is one of the most potent oncogenes as measured by many in vitro and in vivo assays for cell transformation phenotypes (Sheiness et al. 1978; Alitalo et al. 1983). However, MYC activation alone generally cannot induce tumorigenesis. Indeed, when MYC was first observed to induce neoplastic "transformation," this was detected only in specific cell lines that were pre-

sumed to have acquired other genetic events that rendered them permissive (Spencer and Groudine 1991; Dang 1999). Thus, although it is one of the most commonly activated oncogenes implicated in the pathogenesis of human cancers, MYC overexpression alone is surprisingly incapable of inducing cellular proliferation or neoplastic transformation of most normal human cells. Instead, MYC overexpression in normal cells can have no effects or can be highly destructive, culminating in proliferative arrest, senescence, and/or apoptosis (Fig. 1) (Evan et al. 1992; Gibson et al. 1995; Felsher and Bishop 1999b; Grandori et al. 2003; Nilsson and Cleveland 2003; Hoffman and Liebermann 2008).

MYC overexpression has been observed to enforce DNA replication and entry into S phase (Cerni et al. 1986; Mai et al. 1996; Felsher et al. 2000; Dominguez-Sola et al. 2007). Indeed, MYC is part of the replication complex (Dominguez-Sola et al. 2007; Srinivasan et al. 2013; see Dominguez-Sola and Gautier 2014 and Kuzyk and Mai 2014). However, MYC alone cannot cause mitotic cellular division (Felsher et al. 2000). In some cases MYC causes normal cells to grow and replicate DNA, but they cannot divide; rather, these cells become polyploid (Mai et al. 1996; Dang 1999; Johnston et al. 1999; Felsher et al. 2000; Neto-Silva et al. 2010). Moreover, MYC overexpression can enforce replication in a manner that results in DNA breaks
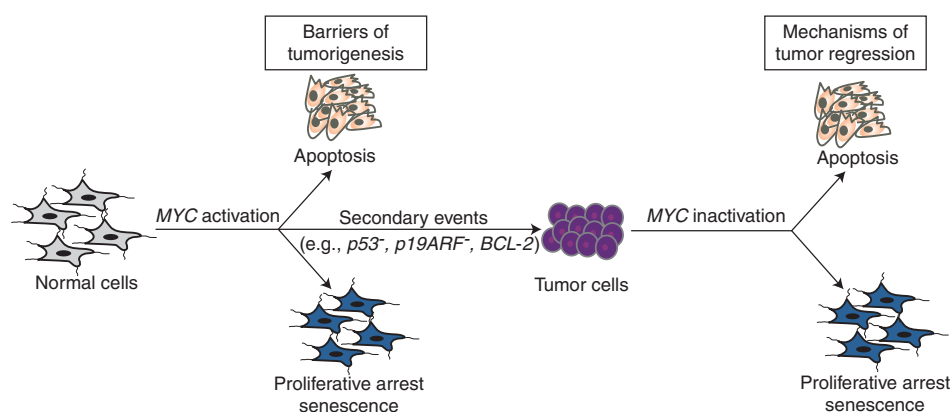

Figure 1. MYC-induced cancer initiation and maintenance. MYC induces tumorigenesis by evading multiple tumor-suppressing checkpoint mechanisms, including proliferative arrest, apoptosis, and/or senescence. On MYC suppression these barriers are restored, enabling sustained tumor regression.

Cite this article as *Cold Spring Harb Perspect Med* 2014;4:a014241

(Karlsson et al. 2003a). This appears to be the consequence of several mechanisms. MYC may directly block double-stranded DNA repair and/or increase oxidative damage, causing DNA damage (Vafa et al. 2002; Karlsson et al. 2003a; Ray et al. 2006). MYC overexpression can cause normal cells to undergo proliferative arrest under some circumstances (Felsher et al. 2000) and cellular senescence in other cases (Grandori et al. 2003). Thus, MYC deregulation alone cannot force complete transit through the cell division cycle.

The consequences of MYC overexpression in a normal cell are also dependent on epigenetic and genetic contexts. MYC overexpression in the embryonic liver induces cellular proliferation, whereas in adult liver it promotes cellular growth without mitotic division that is associated with polyploidy (Beer et al. 2004). Circumstances in an adult host that promote hepatocytes to proliferate, such as a partial hepatectomy or treatment with a liver toxin, can enable MYC to induce cellular proliferation in adult hepatocytes more readily (Makino et al. 1984; Beer et al. 2004). Similarly, the loss of the tumor suppressor p53 cooperates with MYC to induce cellular proliferation and tumorigenesis in adult hepatocytes (Beer et al. 2004). Thus, cellular context and specific genetic defects can enable MYC to more readily induce proliferation and tumorigenesis.

The gene dosage of MYC strongly influences the consequences of its activation. Highly robust activation of MYC is more commonly associated with DNA damage and apoptosis; conversely, less robust MYC activation appears to be associated with proliferative arrest and cellular senescence (Felsher et al. 2000; Grandori et al. 2003). Similarly, the gene dosage of MYC appears to strongly influence the consequences on cellular proliferation versus apoptosis (Murphy et al. 2008). Thus, the level and context of MYC dictate the consequences of its activation.

MYC COOPERATES TO INDUCE TUMORIGENESIS

MYC cooperates with many other oncogenic events to initiate tumorigenesis (Murray et al. 1983; Compere et al. 1989; DeoCampo et al. 2000; Welm et al. 2005; Clegg et al. 2011). Many oncogenes were first discovered as cooperating events in screens of MYC-induced tumor formation (Jonkers and Berns 1996; Mikkers et al. 2002; Mikkers and Berns 2003; Kool and Berns 2009; Mendrysa et al. 2010). Genetic events that abrogate cell-cycle checkpoints critical to the regulation of proliferative arrest, apoptosis, and/or senescence frequently synergize with MYC to induce proliferation as well as malignant transformation. Examples include the overexpression of BCL-2, loss of p53, or loss of p19ARF (Green 1997; Zindy et al. 1998; Jacobs et al. 1999; Schmitt et al. 1999; Schmitt and Lowe 2001). It is now axiomatic that normal cells possess multiple "intrinsic" mechanisms of tumor suppression that prevent malignant transformation by individual oncogenes such as MYC (Lowe et al. 2004).

Examination of the consequences of MYC activation using in vivo models has identified, in addition to cell-autonomous mechanisms, host-dependent mechanisms that influence MYC's ability to initiate tumorigenesis. Thus, toxins or carcinogens associated with the activation of cellular proliferation can cooperate with MYC to induce tumorigenesis (Beer et al. 2008). Similarly, autocrine mechanisms involving the expression of transforming growth factor-α as well as other cytokines are critical in tumor initiation and maintenance, as described below (Calvisi and Thorgeirsson 2005; Cavin et al. 2005). Both innate immunity (Reimann et al. 2010) and direct autocrine effects (van Riggelen et al. 2010a) contribute to the suppression of tumorigenesis.

Finally, the precise physiological state of the cell is likely to influence the consequences of MYC activation. The particular stage of differentiation of a cellular lineage may determine the consequences of MYC activation. For example, MYC activation in embryonic hepatocytes induces robust cellular proliferation, but in adult cells MYC activation induces DNA replication associated with mitotic arrest and results in hyperdiploid cells that cannot become malignantly transformed (Beer et al. 2004). Similarly, MYC expression in embryonic heart induces hyper-

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plasia, whereas in the adult heart MYC induces hypertrophy (DW Felsher, unpubl.). The mechanistic basis for these differences may relate to the recent findings that MYC amplifies the output of previously activated gene expression programs (Lin et al. 2012; Nie et al. 2012; see Levens 2013 and Rahl and Young 2014). Such expression programs would be expected to differ depending on cell type and stage of development. Thus, the phenotypic consequences of MYC expression may be influenced not just by cooperating genetic events but also perhaps by nongenetic or even epigenetic mechanisms.

Generally, MYC initiates tumorigenesis in a permissive epigenetic context that results from tumor-intrinsic mechanisms that regulate proliferation, apoptosis, and innate and adaptive immunity. Host programs may include modulation of the tumor microenvironment and the regulation of angiogenesis. Other genetic events may be required to perturb the normal regulation of the microenvironment, thus accelerating tumorigenesis. Changes in the microenvironment may create a circumstance that is more generally permissive for tumorigenesis. Thus, the local microenvironment may also contribute to susceptibility to MYC-induced tumorigenesis.

MYC-INDUCED TUMORS ARE ONCOGENE ADDICTED

The notion that cancer is a genetic disease associated with discrete and definable events that activate oncogenes and/or inactivate tumor suppressor genes suggested a rationale for the treatment of cancer. The repair of these mutant gene products could, in theory, reverse cancer (Bowden et al. 1994; Luo et al. 2009). Yet several questions arise: How does one decide which and how many events must be targeted? Will cancers exhibit genetic instability that enables the ready acquisition of compensatory mutations? Does an oncogene need to be mutated to be essential for maintenance of a neoplastic state? Could targeting oncogenes be toxic because most proto-oncogenes are essential?

To some investigators, the question of the potential efficacy of targeting oncogenes was

moot, because the use of antisense oligonucleotides has established the potential utility of oncogene addiction (Tamm et al. 2001; Dias and Stein 2002; Pastorino et al. 2004; Maksimenko and Malvy 2005; Stein et al. 2005). However, many critics have been dismissive and have postulated that these results were nonspecific, obtained largely through in vitro study and unlikely to be relevant to more complex human tumors.

To experimentally address whether cancer is reversible, many research groups examined whether the conditional activation of an oncogene could induce reversible tumorigenesis. The tactic has been to use transgenic mouse models with a conditional oncogene. Mouse models using the Tet system and/or chimeric gene products that could be activated in an on/off fashion are the two most common approaches (Giuriato et al. 2004; Arvanitis and Felsher 2005; Felsher 2006). Many investigators have focused on MYC.

The suppression of MYC was shown to reverse tumorigenesis. Similar results were seen in a wide variety of tumors, including hematopoietic tumors (T- and B-cell lymphoma and leukemia), epithelial tumors (hepatocellular, breast, squamous carcinoma), and mesenchymal tumors (osteogenic sarcoma) (Felsher and Bishop 1999a; Jain et al. 2002; Pelengaris et al. 2002; Marinkovic et al. 2004). Identical results have been observed for several other oncogenes (Table 1) (Chin et al. 1999; Felsher and Bishop 1999a; Huettner et al. 2000; D'Cruz et al. 2001; Fisher et al. 2001; Jain et al. 2002; Marinkovic et al. 2004; Shachaf et al. 2004; Lawlor et al. 2006; Ji et al. 2007; Li et al. 2007; Chakravarty et al. 2011). Importantly, in at least some cases, it was confirmed that these tumors were clonal and genetically complex (Karlsson et al. 2003b). In the experimental mouse model, MYC-induced tumorigenesis is reversible. Importantly, endogenous MYC was not suppressed in these experiments.

Yet it is important to note that MYC-induced tumorigenesis is not always reversible. In some genetic contexts MYC suppression resulted in the initial regression of a tumor that subsequently recurred. The introduction of ad-

Cite this article as *Cold Spring Harb Perspect Med* 2014;4:a014241

Table 1. Models illustrating MYC-associated oncogene addiction

Oncogene	Conditional mouse model	Reference
MYC	T-cell acute lymphoblastic leukemia	Felsher and Bishop 1999a
	Hepatocellular carcinoma	Shachaf et al. 2004
	Osteosarcoma	Jain et al. 2002
	T- and B-cell acute lymphoblastic leukemia	Marinkovic et al. 2004
	Mammary adenocarcinoma	D'Cruz et al. 2001
	Islet tumors	Lawlor et al. 2006
RAS	Melanoma (HRAS)	Chin et al. 1999
	Lung adenocarcinoma (KRAS)	Fisher et al. 2001
BRAF	Thyroid cancer	Chakravarty et al. 2011
	Lung adenocarcinoma	Ji et al. 2007
EGFR	Lung adenocarcinoma	Li et al. 2007
BCR-ABL	B-cell acute lymphoblastic leukemia	Huettner et al. 2000

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ditional genetic events, such as a mutant RAS, can abrogate the reversibility of MYC-induced breast adenocarcinoma (D'Cruz et al. 2001). Similarly, loss of p53 expression also prevents MYC-induced lymphoma from being reversible (Giuriato et al. 2006). However, when examined, all tumors that recurred after MYC suppression had reactivated MYC expression (Choi et al. 2011). Thus, tumors may not be able to completely escape MYC addiction.

Importantly, MYC-induced tumorigenesis may be reversible even when MYC is not the initiating oncogenic lesion. Using a dominant negative MYC, designated "omoMYC," investigators illustrated that conditional suppression of MYC appears to reverse RAS-induced tumorigenesis (Soucek et al. 2008, 2013). However, it is also possible that RAS is activating endogenous MYC, an event that could possibly explain why these tumors exhibit MYC dependence. Indeed, the mechanism of action of omoMYC is not entirely clear. Recent observations suggest

that omoMYC blocks some of the interactions between MYC and some of its partners (Savino et al. 2011). Less clear is whether it mediates effects independently of MYC. Further insight into the mechanism of omoMYC is likely to provide compelling clues to how best to target MYC therapeutically. Thus, addiction to MYC appears to be a feature of cancers driven by oncogenes other than MYC.

MECHANISMS OF MYC-ASSOCIATED ONCOGENE ADDICTION

Given that many experimental models demonstrated a dependency on continuous MYC expression for tumor progression, the key challenge to understanding MYC oncogene addiction is the delineation of the mechanisms underlying this dependency (Weinstein 2002; Sharma and Settleman 2007; Felsher 2008; Weinstein and Joe 2008). The inactivation of MYC is associated with sustained reversal of many of the hallmark features of tumorigenesis. On MYC inactivation, tumor cells appear to restore normal checkpoint mechanisms and undergo proliferative arrest, differentiation, apoptosis, and/or cellular senescence. In addition to cell-intrinsic mechanisms of MYC addiction, the tumor microenvironment is also remodeled on MYC inactivation, which results in the restoration of normal tissue architecture (Felsher and Bishop 1999a). Tumor angiogenesis is diminished with MYC withdrawal (Giuriato et al. 2006). Thus, there appears to be a restoration of normal physiologic programs both within the tumor cell and in the tumor microenvironment.

The specific mechanisms of MYC addiction appear to be tumor type specific (Fig. 2). Hematopoietic tumors appear to undergo proliferative arrest, differentiation, and senescence, followed by robust apoptosis on MYC withdrawal (Felsher and Bishop 1999a). In contrast, sarcomas undergo proliferative arrest, differentiation, and senescence with minimal if any evidence for apoptosis (Jain et al. 2002). Epithelial tumors appear to have two major fates; most tumor cells undergo proliferative arrest, senescence, and apoptosis, but a subpopulation
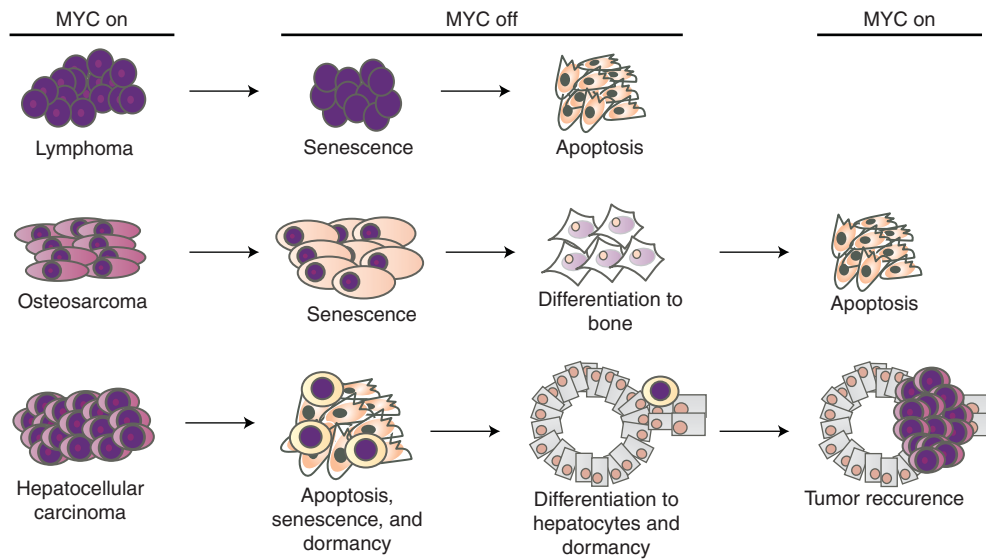
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Figure 2. Consequences of MYC inactivation in multiple types of cancer. MYC inactivation elicits oncogene addiction by multiple mechanisms that differ depending on tumor type. MYC inactivation in lymphoma induces proliferative arrest, differentiation/senescence, and widespread apoptosis. MYC inactivation in osteosarcoma induces proliferative arrest and differentiation/senescence but not apoptosis. MYC reactivation does not restore tumorigenesis. MYC inactivation in liver adenocarcinoma induces proliferative arrest, differentiation/senescence, and apoptosis. MYC reactivation can result in restoration of the tumor.

of tumor cells undergoes differentiation into seemingly normal cells but actually exhibit evidence of tumor dormancy (Boxer et al. 2004; Shachaf et al. 2004). Whether these variations reflect programs unique to specific cell types or are a consequence of differences in the genetic events associated with each type of cancer is not known.

BRIEF OR PARTIAL SUPPRESSION OF MYC CAN REVERSE TUMORIGENESIS

A brief 2-day or partial (twofold decrease) suppression of MYC can result in sustained tumor regression. Brief suppression of MYC is associated with an irreversible change in the cellular program; in some contexts the tumors cannot be restored on MYC reactivation (Jain et al. 2002). Similarly, a twofold decrease in oncogenic levels of MYC was sufficient to induce tumor regression (Shachaf and Felsher 2005). This is tumor type specific, because lymphoma and osteosarcoma exhibit this phenotype (Jain et al. 2002; Giuriato et al. 2006), whereas epithelial

tumors such as hepatocellular or breast carcinoma do not (Boxer et al. 2004; Shachaf et al. 2004).

In osteogenic sarcoma MYC suppression results in terminal cellular differentiation from osteoblasts into differentiated osteocytes (which are associated with bone formation in vivo) (Jain et al. 2002). The reactivation of MYC not only fails to restore the cancer but either has no consequence or is associated with apoptosis. Microarray analysis revealed that MYC suppression is associated with irreversible changes in gene expression as a result of the inability of MYC to bind to the promoters of many of these genes. In particular, MYC suppression results in the permanent shutdown of genes related to ribosome biosynthesis and protein synthesis (Wu et al. 2008; van Riggelen et al. 2010b).

Partial suppression of MYC can also result in sustained tumor regression. Notably, in this case the levels of MYC were below that of human tumor-derived cell lines and above that of proliferating normal human cells or Epstein–Barr virus–transformed lymphocytes (Shachaf et al. 2008). Thus, there appears to be a thresh-

Cite this article as *Cold Spring Harb Perspect Med* 2014;4:a014241

old level of MYC that is required to sustain a malignant phenotype (Shachaf et al. 2008). Protein and gene expression analysis identified many specific changes, but notably, ribosomal gene products were suppressed. Collectively, these results suggest that a global shift in protein biogenesis is an important feature of how MYC suppression results in tumor regression (Ruggero and Pandolfi 2003).

MYC activation is also associated with global changes in the energy metabolism of cancer cells. These changes may make tumors particularly susceptible to the inhibition of enzymes that are essential for energy metabolism (Dang 1999, 2013; Dang et al. 2009; O'Shea and Ayer 2013). Hence, the addiction to MYC observed in many cancer cells could at least in part relate to acute changes in metabolism. The suppression of MYC may induce tumor regression by acutely disrupting the ability of tumor cells to maintain sufficient metabolism to sustain survival and/or by directly regulating death signaling (see Dang 2013; O'Shea and Ayer 2013; Morrish and Hockenbery 2014).

An important implication of these results is that it may be sufficient to partially and/or briefly suppress MYC expression in at least some tumor types to induce a sustained clinical effect on human disease. That transient inactivation of MYC is effective may be due to the dependence of MYC-associated oncogene addiction on molecular features that are dictated shortly after oncogene inactivation (Tran et al. 2011). Whether tumor inhibition is entirely cell autonomous or results from a delayed host-dependent mechanism remains to be determined. For example, the host immune system seems to be critical for tumor regression on withdrawal of MYC.

MYC ONCOGENE ADDICTION AND THE IMMUNE SYSTEM

In addition to cell-autonomous effects of ectopic MYC expression, alterations in immune surveillance mechanisms by MYC may also contribute to tumorigenesis (Rooney et al. 1985; Soucek et al. 2007; Grivennikov et al. 2010). Indeed, we found that MYC inactivation induces tumor re-gression through both tumor cell–intrinsic as well as host-dependent mechanisms (Rakhra et al. 2010). MYC inactivation in an immuno-compromised $RAG1^{-/-}$ host (deficient for B and T cells) or a $CD4^{-/-}$ host (deficient for $CD4^+$ T-helper cells) exhibited reduced kinetics of tumor regression, increased minimal residual disease, and inevitable tumor recurrence. An immunocompetent host is hence essential for tumor regression on MYC withdrawal.

In situ analysis following MYC inactivation showed that the absence of host immune effectors had little effect on the proliferative arrest or apoptosis in the tumor, but the absence of immune effectors largely abrogated cellular senescence and diminished angiogenesis. Thrombospondins were implicated as one of the critical effectors. Similarly, suppression of MYC through omoMYC induces changes in the tumor microenvironment associated with tumor regression (Eilers and Eisenman 2008; Sodir et al. 2011). These observations illustrate that the suppression of MYC mediates tumorigenesis both through direct effects on tumor cells as well as through alteration of immunity (Restifo 2010).

Thus, oncogene addiction may occur via mechanisms that operate on multiple levels. First, there is a tumor cell–intrinsic induction of proliferative arrest, senescence, and apoptosis. Second, there is a recruitment of immune effectors that is probably mediated by a non-canonical $CD4^+$ T-cell-specific mechanism. Third, there is a remodeling of the tumor microenvironment. The initial regression of a tumor is cell autonomous, but complete regression requires host-dependent mechanisms (Fig. 3).

An understanding of the role of the host immune system in the mechanism by which oncogene inactivation induces tumor regression could be important for development of cancer therapeutics. Therapies identified only through in vitro screens of isolated tumor cells are unlikely to accurately predict the consequences of oncogene suppression. Therapies that concomitantly target oncogenes but suppress the immune system may be counterproductive. A combination approach that targets oncogenes but also activates specific immune
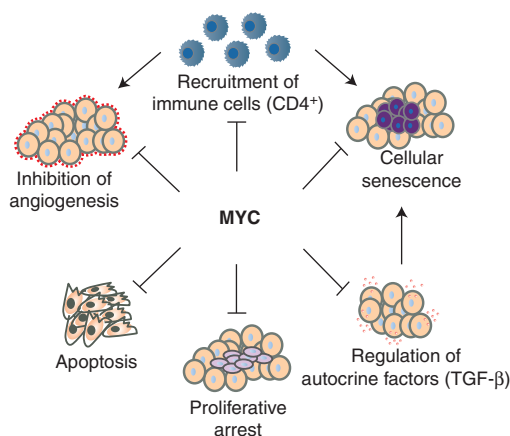
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Figure 3. MYC inactivation elicits tumor regression through both cell-autonomous and non-cell-autonomous mechanisms of tumor regression. MYC activation leads to tumorigenesis through suppression of critical safeguards such as apoptosis, proliferative arrest, differentiation, and senescence. Activation of MYC also facilitates engagement of hallmarks of tumor growth, as well as cell-extrinsic phenomena such as host immunity. TGF, transforming growth factor.

mechanisms may be complementary and most efficacious.

MODELING AND PREDICTING MYC-ASSOCIATED ONCOGENE ADDICTION

To understand the factors contributing to MYC oncogene addiction, differential changes in survival and death signals were mathematically modeled (Tran et al. 2011). Oncogene suppression could increase death signals, could suppress survival signals, or could activate or suppress both survival and death signals but with death outpacing survival. What was found through modeling was that most tumors regress because both survival and death signals dissipate on oncogene suppression, with death signals decaying at a slower rate. The specific mechanistic basis for differential decay of survival versus death signaling on MYC withdrawal is not known but may be related to differential regulation of the effectors of survival and death (Sharma et al. 2006; Tran et al. 2011), differential levels of metabolites that regulate or are required for survival or death (Wise et al. 2008;

Gao et al. 2009), and/or non-cell-autonomous mechanisms such as changes in autocrine or paracrine signaling from the host (Eilers and Eisenman 2008).

The mathematical modeling described could at least in part reconcile how the activation of MYC during tumor initiation in normal cells and the inactivation of MYC in an established tumor both can induce apoptosis. MYC activation can induce apoptosis in many cells that can serve as a barrier to tumorigenesis, unless there is at least a partial defect in programs, for example, through mutation of p53 function, accelerating tumor progression (Lowe et al. 2004). However, MYC inactivation in a tumor seemingly paradoxically results in robust apoptosis because the reduction in proliferation and survival signals occurs much more rapidly and completely than the associated attenuation of apoptotic signals. Thus, although MYC inactivation in a tumor may suppress some mechanisms that contribute to apoptotic signals, the overall effect is overwhelming tumor regression because of the concurrent complete and rapid suppression of proliferation, combined with the suppression of prosurvival signals. Even in the circumstance of attenuated apoptosis signals, in summation, the dominant effect is the overall marked increase in cell death.

CONCLUDING REMARKS

Experimental evidence supporting the occurrence of MYC addiction in animal models suggests that some human cancers could also be addicted to MYC and hence could be treated by targeting MYC. However, MYC has yet to be successfully therapeutically targeted for the treatment of cancer, as most transcription factors are generally considered "undruggable" (Verdine and Walensky 2007; Filippakopoulos et al. 2010; Delmore et al. 2011; Yan and Higgins 2013). Nevertheless, several reports suggest that small interfering RNA, short hairpin RNA, and antisense oligonucleotides could be potential strategies to target MYC (Hermeking 2003; Pastorino et al. 2004; Vita and Henriksson 2006). Therapies that briefly or even partially suppress MYC directly or indirectly may be highly effica-

cious in the reversal of neoplasia, for example, as illustrated by inhibition via statins or BRD4 inhibition (Shachaf et al. 2007; Cao et al. 2011; Delmore et al. 2011; McKeown and Bradner 2014). Alternatively, synthetic lethal screens may identify therapeutic strategies to target MYC-addicted tumors (Yang et al. 2010; Kessler et al. 2012; Toyoshima et al. 2012; Cermelli et al. 2014).

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Cite this article as *Cold Spring Harb Perspect Med* 2014;4:a014241

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MYC Activation Is a Hallmark of Cancer Initiation and Maintenance

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