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THE UPS AND DOWNS OF MYC BIOLOGY

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Summary

The basic helix-loop-helix protein Myc is a renowned transcription factor controlling disparate aspects of cell physiology that, together, allow efficient proliferation of somatic cells. This ability, together with the observation that its deregulated expression occurs in the majority of human cancers, suggests that Myc could be a good therapeutic target. However, several aspects of Myc biology remain elusive: what is the major difference between oncogenic and physiological Myc? How does oncogenic Myc evade the intrinsic tumor surveillance pathways provided by evolution? If Myc inhibition were even possible, what would be the consequences for the homeostasis of normal proliferating tissues versus the fate of cancer cells? Here we summarize the latest works addressing these issues.

The Myc family comprises three evolutionary conserved bHLHZip transcription factors – c-, N- and L-Myc - that coordinate diverse aspects of somatic and germ cell proliferation, including intracellular functions like cell growth, cell cycle progression, biosynthetic metabolism and apoptosis, as well as extracellular processes that coordinate cell proliferation with its adjacent somatic microenvironment, such as angiogenesis, invasion, stromal remodeling and inflammation [1]. The Myc proteins remain enigmatic for several reasons. Most notably, the repertoire of Myc target genes is very large and extremely diverse. It comprises RNA polymerase II protein coding target genes [2], RNA polymerase I and RNA polymerase III RNAs involved in translation and growth [3,4], and miRNAs likely to have key roles in cell proliferation, cancer and stem cell maintenance [5,6]. Second, the effect of Myc on individual genes is typically very modest and there appear to be few if any genes for which Myc is the sole, or even the principal, transcriptional regulator. More likely, Myc seems to generate global alterations in chromatin structure, which in turn modulate transcription [7]. Nonetheless, all studies concur that Myc function is essential for the efficient and orderly proliferation of somatic cells. Germ line deletion of either c-*myc* or N-*myc* leads to embryonic death around E11 due to widespread failures in organ and tissue growth, while fibroblasts lacking c-Myc proliferate very slowly and inefficiently. Third, the net consequences of Myc activity are highly context dependent, varying greatly with cell type and circumstance. Such extreme and contingent pleiotropy makes it meaningless to talk of any unitary Myc “function.” It also implies that Myc’s essentiality derives not from any specific sub-set of its functions but through its unique capacity to coordinate and integrate the diverse gamut of processes that, operating together, underpin somatic cell expansion.

In normal cells, Myc function is tightly regulated by developmental or mitogenic signals. Myc mRNAs and proteins are very short-lived and, in the absence of such sustained proactive signals, Myc transcription is curtailed and Myc protein levels rapidly fall, triggering growth arrest. Such exquisite and continuous dependence of Myc activity on mitogenic signals safeguards against untoward somatic cell expansion. Indeed, Myc activity is almost always deregulated in tumor cells, sometimes through mutations within Myc genes themselves but, more often, through their incessant induction by upstream oncogenic signals in pathways such as RTK-Ras, Wnt-β-catenin or Notch. Interest in Myc is focused on these two related but discrete aspects of Myc biology: its role in normal cells and in tissue homeostasis, and the role played by deregulated Myc in driving and maintaining neoplasia (Fig 1).

A consequence of Myc's pleiotropy is its widespread impact on many, diverse cell and tissue processes, both directly and indirectly through its modulation of downstream transcriptional programs. Such secondary programs not only ramify all aspects of cell and tissue biology but they also feed back in a context and cell type-specific way to modulate how Myc acts. Deconvoluting any recognizable causal Myc signature from such networks has proved vexing, and the many independent attempts at gene expression profiling Myc target genes have yielded data sets with little overlap [8]. Nonetheless, a recent meta analysis of Myc-dependent expression culled from many different cell and tissue types has successfully revealed a provocative concordance between Myc targets and an embryonic stem cell signature [9]. Furthermore, Myc is one of four transcription factors that are capable of reprogramming differentiated adult cells back to a pluripotent state [10], and it can also regulate miRNAs involved in self-renewal and repression of differentiation [6], suggesting a potential role for Myc in the genesis of the infamous cancer stem cells.

Switching Myc on

A complementary strategy for unpicking the direct and indirect consequences of Myc function is to use switchable technologies that allow for acute activation or inactivation of Myc. Cause and consequence relationships can then be deciphered by following how the response evolves over time in the affected cell or tissue. Several mature techniques exist for regulating protein or gene function *in vitro* and *in vivo*, including various tetracycline regulatable expression systems (e.g. tet off and tet on) and conditional excision of genes (e.g. cre-lox and flp-frt). Each has its own advantages with respect to reversibility and rapidity, as well as disadvantages in terms of efficiency and leakiness.

Fusing Myc to the hormone-binding domain of the estrogen receptor (ER) renders all known Myc functions dependent upon the presence of the ER ligand β-estradiol, which displaces ER from inactive association with Hsp90 and promotes translocation of Myc to the nucleus. Later enhancements make use of mutant ERs (e.g. ER^{TAM} [11] and ER^{T2} [12]) that are unresponsive to physiological estrogens yet activatable by the synthetic ligand 4-hydroxytamoxifen (4-OHT) and can therefore be used *in vivo*. ER^{TAM}-based switchable systems are somewhat limited by their continuous dependence on 4-OHT and by the known estrogenic and anti-estrogenic effects of 4-OHT. In practice, this necessitates daily bolus administration of 4-OHT or Tamoxifen base (which is metabolized by the liver to 4-OHT) and avoidance of estrogenic tissues. Nonetheless, they enjoy certain advantages over other regulatable systems: ER^{TAM} fusion proteins in tissues are synchronously activated within minutes of systemic administration of 4-OHT and such activation is fully and rapidly reversible. Expression of $MycER^{TAM}$ can be directed to any target tissue using a tissue specific promoter/enhancer and, because 4-OHT regulates activity of the $MycER^{TAM}$ fusion protein rather than its transcription, levels of the activated gene product in the target cell type are both predictable and consistent. This latter is an underappreciated advantage that is especially important in the case of Myc, where different levels of the oncoprotein elicit dramatically different biological outputs. Importantly, the rapid

switchability of MycER^{TAM} overcomes a profound limitation of classical transgenic technology wherein the active gene product of interest is ectopically expressed throughout the ontogeny of the target tissue, eliciting varying degrees of compensation and adaptation.

Activation of MycER^{TAM} is, alone, sufficient to drive proliferation in multiple adult tissues *in vivo*. For example, activation of high levels of MycER^{TAM} expressed from the *involucrin* promoter in suprabasal skin drives proliferation and disrupts differentiation of postmitotic keratinocytes, the consequent progressive accumulation of cells resulting in dramatic papillomatosis that rapidly regresses upon subsequent deactivation of MycER^{TAM} [13]. When targeted to the basal keratinocyte compartment, activated MycER^{TAM} forces cells out of the stem cell niche, generating a grossly expanded transit amplifying population that persists even after MycER^{TAM} has been deactivated [14]. Unexpectedly, the epidermal hyperplasia elicited by acute Myc activation involved not only expansion of keratinocytes but also of the adjacent dermal vasculature hyperplasia, providing the first inkling that activation of Myc in one cell elicits cooperative changes in that cell's adjacent niche. Similarly, activation of high-level MycER^{TAM} in pancreatic β cells driven from the *insulin* promoter is also alone sufficient to drive β cells into cycle. Unlike keratinocytes, however, such acute activation of Myc does not trigger net β cell expansion because of widespread apoptosis that rapidly overwhelms β cell proliferation and results in islet attrition and consequent diabetes. Myc-induced apoptosis is a prototypical example of intrinsic tumor suppression – an evolved tumor defense mechanism that, like senescence, serves to quell the oncogenic potential of most, perhaps all, dominant oncogenes [15–17]. Oncogenic Myc will also induce apoptosis in keratinocytes, but execution of the apoptotic program is suppressed in intact skin by local survival factors. In β cells, Myc induced apoptosis can be suppressed by transgenic co-expression of the anti-apoptotic protein Bcl-x_L whereupon Myc activation triggers rapid, progressive and uniform expansion of β cells turning all pancreatic islets into angiogenic and often invasive tumors [17]. Such Myc-driven β cell expansion is accompanied by rapid and synchronous β cell de-differentiation, down regulation of E-cadherin and loss of cell-cell adhesion, local invasion of β cells into adjacent exocrine and vascular compartments and (just as in skin) concomitant expansion and elaboration of the entire islet microenvironment, with proliferation of adjoining islet vasculature, influx of inflammatory cells and activation of stromal fibroblasts, and formation of angiogenic and invasive islet tumors [17]. Furthermore, subsequent Myc de-activation triggers regression of these complex neoplastic lesions. The rapidity and synchrony with which such multifarious traits appear in each islet mass, as well as their continuous dependence on Myc activity, clearly indicate that they are all instructed by Myc – either directly within each β cell, or indirectly through signals produced by β cells as a consequence of Myc activation within them. This, together with the reversible switchability of MycER^{TAM} *in vivo* provides an unparalleled opportunity for constructing the cause and effect sequence of processes that link Myc activation with the complex phenotypes it elicits.

Kinetic expression array analysis following acute activation, and subsequent deactivation, of MycER^{TAM} in β cells confirmed that Myc regulates multiple genes involved in cell cycle regulation, growth and metabolism. Unexpectedly, however, a significant proportion of the genes Myc was found to regulate are cell type specific [18]. In addition, a limited repertoire of candidate tumor maintenance genes could be identified on the basis that they are inversely regulated during Myc activation-induced tumor progression versus Myc deactivation-induced tumor regression [18]. The same kinetic analysis also demonstrated a direct instructive role for Myc in driving angiogenesis and the tumor microenvironment: acute Myc activation in β-cells of pancreatic islets rapidly induces expression of the pro-inflammatory cytokine interleukin 1β beta, which triggers release of sequestered VEGF from the islet extracellular matrix whereupon it homes to the endothelial compartment, and induces endothelial cell proliferation and islet angiogenesis [19]. Myc activation also induces expression of a cluster of chemokines implicated in the recruitment of mast cells, macrophages and neutrophils. Subsequently, mast

cells were shown to have an essential causal role in the expansion and maintenance of the islet tumor vasculature [20]. Both these studies proved the crucial role of Myc in governing intracellular and extracellular aspects of tumorigenesis.

These observations in the pancreatic islet MycER^{TAM} model confirm the important notion that Myc coordinates both the intracellular programs required for cell proliferation and also the many, and tissue type-specific, extracellular processes that proliferating cells require for their expansion within the somatic milieu. However, the requirement for co-expression of Bcl-x_L in the same model also underscores the potency of Myc-induced apoptosis as a mechanism to suppress untoward proliferation. This raises an important problem: since Myc is required to integrate the proliferative programs of all normal cells, how is Myc-induced apoptosis confined only to tumor, and not normal, cells? Myc is deregulated and/or elevated in most human cancers (reviewed in [21]) but until recently it has been unclear whether it is deregulation or over expression that is required for Myc oncogenic activity. However, in a variant MycER^{TAM} model in which MycER^{TAM} is driven by the very weak but constitutively *Rosa26* promoter, expression of Myc is deregulated (in the presence of 4-OHT) but expressed at low, physiological levels [22]. Activation of MycER^{TAM} in tissues of such animals drives proliferation without any attendant apoptosis, demonstrating that distinct threshold levels of Myc govern its biological output *in vivo*: low levels of "deregulated" Myc induce somatic cell proliferation and, when deregulated, tumorigenesis in multiple tissues, but substantially elevated levels of Myc are required to engage tumor suppressor mechanisms – principally apoptosis and the ARF/p53 pathway [22] (Fig 1). Such observations have important and surprising implications for tumor evolution: they indicate that low-level Myc deregulation can drive indolent oncogenesis covertly in somatic tissues without alerting our evolved mechanisms for tumor surveillance and suppression. They also offer an explanation for why Myc is so frequently activated indirectly rather than through direct mutation: while indirect activation of Myc by upstream oncogenic signals deregulates Myc activity, it does not lead to significant over-expression and so fails to engage tumor suppression. This phenomenon is starkly demonstrated by the differences between indirect activation of Myc in intestinal epithelium through activation of the Wnt-β-catenin pathway, which engages only Myc's proliferative programs [23,24] versus direct transgenic activation and concomitant over expression of Myc, which triggers activation of p53-mediated tumor suppression [25].

Switching Myc off

Taken together, the data supporting the pivotal role that Myc plays as a necessary and non-redundant coordinator of the many intra and extracellular programs required for somatic cell proliferation suggest that Myc would make an excellent target for cancer therapy. Unfortunately, there are several caveats. Most notably, Myc is widely considered "undruggable" since it has no "active site" amenable to binding by conventional small drug-like molecules. Moreover, Myc is required for the proliferation of all normal cells, so the side effects of its inhibition could be as severe as those elicited by conventional chemo and radiotherapy. Myc also plays a critical role as gatekeeper of the stem cell compartment [6, 26], so even transient inhibition of Myc might cause permanent disruption of renewing tissues. Unfortunately, the embryonic lethality associated with germ line deletion of the two principal Myc family members implicated in cancer, c-Myc and N-Myc, precludes any meaningful analysis of their roles in adult tissues, so most published data regarding the impact of Myc inhibition *in vivo* has come from conditional knockouts of the c-*myc* gene using Cre mediated recombination [26–28]. While such data are useful guides as to the essentiality of c-Myc in adult tissues, the approach suffers from several confounding problems. First, they are limited to c-*myc*, but one member of the largely isofunctional *myc* gene family [26], members of which are frequently co-expressed in tissues. Second, the extents of c-*myc* deletion within the target cells of any tissue achievable by cre-lox technology are highly variable. The unpredictable

extents to which c-Myc-deleted versus c-Myc-competent cells then contribute to tissue function have led to wildly disparate conclusions concerning the necessity of c-Myc for tissue maintenance (e.g. [27] vs. [29]) Third, conditional knockouts are irreversible, making it impossible to ascertain the impact of the type of transient Myc inhibition that would be achieved with a Myc-inhibitor drug. Recently, an alternative genetic approach to modeling Myc inhibition has made use of a reversibly inducible dominant negative Myc mutant, Omomyc [20,30–32], which competitively inhibits Myc-dependent gene transactivation by blocking the obligate dimerization of all three Myc proteins with their obligate partner Max. Omomyc inhibits binding of Myc to its consensus E-box CACGTG DNA elements and so blocks Myc-dependent transactivation of its target genes. Of note, Omomyc does not inhibit, and may even augment, Myc-dependent transrepression [30,31]. By directing transgenic Omomyc expression ubiquitously under the control of a tetracycline-responsive promoter element, Soucek *et al.* could systemically and reversibly shut down Myc trans-activation activity in mice by administration of doxycyclin [20]. Such mice were then crossed with the well-established *LSL–Kras*^{G12D} murine model of non-small cell lung cancer [33] to study both the therapeutic impact and the side effects of systemic Myc inhibition. In *LSL–Kras*^{G12D} mice, irreversible activation of oncogenic KRas^{G12D} driven from the endogenous *kras* promoter is initiated in mice by inhalation of adenovirus expressing Cre recombinase. Multifocal lung tumorigenesis then ensues and by 18 weeks each lung harbors multiple independent tumors at all stages of evolution through to adenocarcinoma [33]. Remarkably, induction of Omomyc expression for as little as 3 days triggers profound tumor shrinkage and, after 28 days of sustained Omomyc expression, animals are overtly tumor free [20]. Surprisingly, such extended systemic inhibition of Myc elicits only mild and well tolerated side effects in normal proliferating tissues. Mice exhibit no signs of distress, maintain their weight, hydration and normal blood chemistry and, while proliferating tissues such as intestine, bone marrow, skin and testis exhibit varying degrees of attrition, cell death does not occur in any adult tissue, all of which maintain structural integrity [20]. Moreover, all effects of Myc inhibition on normal tissue are fully and rapidly reversed upon restoration of endogenous Myc function.

These surprising observations lead to two unexpected conclusions. First, endogenous Myc is required not only for the proliferation of Ras-driven lung tumors but also for their survival. Second, such dependency on endogenous Myc for cell survival is specific to tumor cells and absent from all normal proliferating somatic cells (Fig 1). Together, these two observations explain the remarkable therapeutic index enjoyed by systemic Myc inhibition and strongly support rekindling interest in Myc as a therapeutic cancer target.

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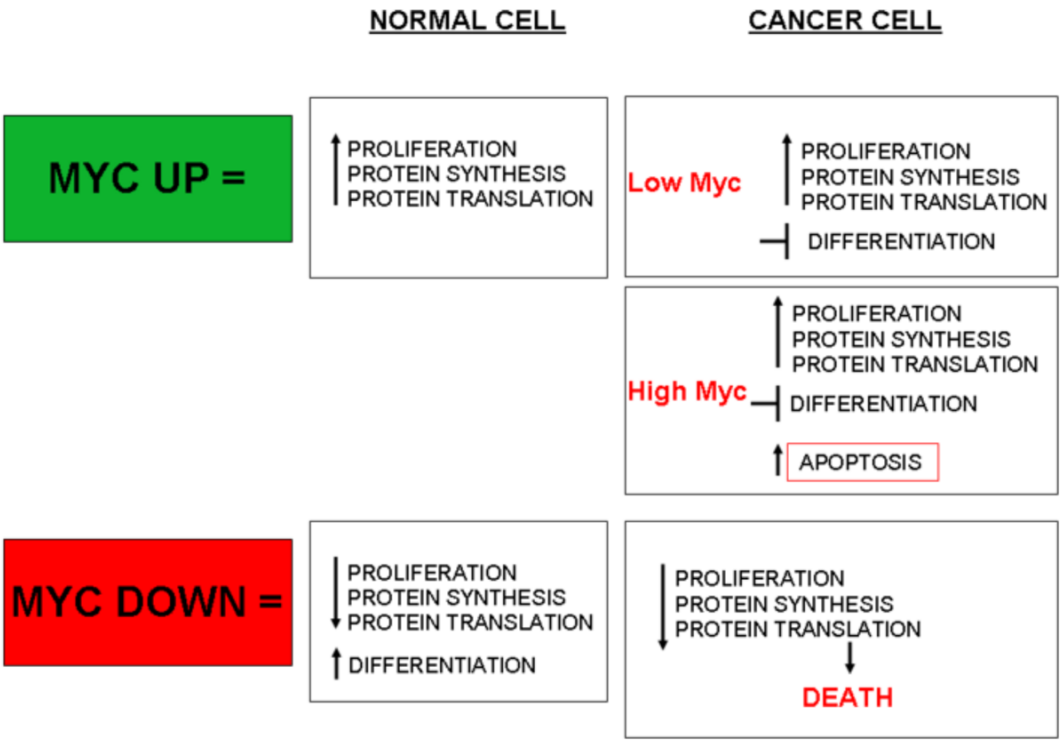

Figure 1.