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# Can't kick that oncogene habit

**One of the most exciting developments in recent cancer treatment has been the move away from crude cytotoxic agents toward drugs that inhibit specific targets in specific cellular pathways. One assumption of this strategy is that maintenance of human cancers is dependent upon a limited cadre of therapeutically tractable oncogenic lesions. In this issue of *Cancer Cell*, an intriguing paper from Sharma et al. endorses this approach by showing that evolution appears to be working for us. They show that an innate asymmetry in the dynamics of intracellular signaling biases pathway inhibition in favor of cell death. This bias may significantly potentiate targeted cancer therapies.**

Intrinsic tumor suppression pathways are innate, self-defeating programs that evolution has attached to those engines of cell expansion whose unbridled activities would otherwise constitute severe neoplastic risk (Lowe et al., 2004). Early examples included the unexpected propensity for activated RAS to induce growth arrest and the equally paradoxical proclivity of MYC to drive apoptosis. Such observations are now understood as examples of how the mitogenic actions of individual oncoproteins can be exploited by the cell only when their inherent growth-inhibitory properties are quelled by collateral signals. In the classical paradigm of oncogene cooperation, such obligate collateral signals are provided by the collaborating oncogene: hence, each oncogenic lesion is dependent on the properties of the other for its oncogenic potential to be manifest. Thus, the tumor phenotype is an emergent property of oncogenic lesions acting in concert (Evan and Littlewood, 1998)—something a geneticist might term "synthetic viability" (Figure 1A).

Such observations offered the earliest clue that tumor cells might be preternaturally dependent for their survival upon the aberrant signaling networks that drive them, by suggesting that cutting individual oncogenic cords within the tumor ensemble can expose the latent intrinsic tumor suppression pathways directed by any remaining oncogenic lesions. On the other hand, since oncogenes harbor the seeds of their own destruction, such ideas also raised the disturbing counter-possibility that inactivation of individual oncogenes might actually accentuate tumor growth by staunching the associated intrinsic tumor suppressor pathway. Only with the advent of reversibly switchable transgenic mouse cancer models, in which the activities of a specific oncogene targeted to a specific tissue can be toggled on and off at will, could the net consequences of acute oncogene ablation be directly tested in vivo. Such animals are, in essence, genetic surrogates for targeted drugs, which can be used to establish the extent to which maintenance of experimental tumors remains dependent upon the oncogenic mutations that drove their evolution, and what the nature of that dependency might be. Such in vivo studies indicated that deactivation of pivotal oncogenic mutations typically triggered profound tumor apoptosis that would frequently (Chin et al., 1999; Felsher and Bishop, 1999; Fisher et al., 2001; Pelengaris et al., 1999, 2002), but not always (Boxer et al., 2004), lead to marked tumor regression. Even though such regression was often superseded by the emergence of resistant clones, such studies confirmed, in principle, the idea that tumor cells acquire de novo a dependence upon the lesions that drive and maintain them. With the advent of targeted cancer therapies, it has finally become possible to explore this idea in human cancers in vivo, and the successful treatment of CML with Gleevec is the poster child for the notion that acquired dependency on oncogenic mutations holds for spontaneously occurring human cancers. Naysayers may point to the fact that resistant clones eventually cause relapse of Gleevec-treated patients. However, even here the news is good: the great majority of relapses involve resistant mutations in the ABL kinase rather than wholesale replacement of ABL by a newly evolved oncogenic edifice (Shah and Sawyers, 2003). This suggests that dependence upon ABL is, indeed, profound and that, notwithstanding the genomic instability that characterizes the accelerated phase of CML, room for evolutionary maneuver by surviving tumor cells is extremely constrained.

Why should tumor cells acquire a dependence upon their oncogenic mutations? The answer seems fairly straightforward in situations where an oncogenic mutation confers survival properties on the cell—for example, overexpression of BCL-2/BCL-$x_L$, or constitutive signaling through survival factors receptors and their intracellular transducers. In such cases, removal of the constitutive survival signal exposes the targeted tumor cell to the full onslaught of preexisting proapoptotic flux rife in cancers—hypoxic and nutrient-poor microenvironments, internal havoc wrought of genotoxic injuries and aberrant protein folding, and the continuous pumping of apoptotic pathways by proproliferative mutations like activated MYC and E2F or loss of RB. By contrast, the dependence that tumor cells exhibit for

oncogenic mutations that drive their proliferation is more unexpected and nuanced since, intuitively, inhibition of such lesions might be expected to elicit mere tumor stasis rather than regression—a less happy therapeutic outcome. In part, the dependence of tumor cells on their mitogenic lesions appears to be due to the fact that, in addition to driving tumor cell proliferation, most such lesions also exert protean influences on multiple aspects of tumor maintenance. Thus, mutations that drive ineluctable cell proliferation typically suppress differentiation. Consequently, pulling the proliferative plug can often reengage spontaneous resumption of that cell's terminal differentiation program, thus permanently expelling that tumor cell from the proliferative compartment. In addition, prototypical mitogenic oncogenes like RAS and MYC have been shown to buttress many diverse attributes required for maintenance of established tumors. In addition to driving the cell cycle, they promote cell growth, nutrient utilization, metabolism, angiogenesis, motility, and invasion. Consequently, their deactivation triggers widespread collapse of both cancer cell infrastructure and tumor tissue superstructure (Figure 1B).

Nonetheless, such dependencies cannot be the whole explanation because oncogene dependence is also observed in vitro, where nutrients, oxygen, mitogens, and survival factors are all abundant, and any impact of stromal cells is moot. Hence the importance of an enthralling paper by Settleman and colleagues (Sharma et al., 2006, this issue of *Cancer Cell*), which suggests that acquired oncogene dependence arises, at least at the intracellular level, from an inherent asymmetry in attenuation of intracellular signal pathways. In so doing, they have conflated the ostensibly disparate phenomena of oncogene addiction and intrinsic tumor suppression, and also added a subtle twist that could have important implications for the timing and delivery of targeted anticancer therapies. Oncogenic tyrosine kinases, like other dominant oncogenes such as RAS and MYC, sit at the apex of multiple downstream signaling pathways that exert various biological effects depending upon cell type and context. While some of these efferent signals are mitogenic, others engage intrinsic tumor suppression pathways that curb oncogenic potential, in part by promoting apoptosis. Using several independent in vitro tumor cell models, driven variously by BCR-ABL, EGFR, and SRC tyrosine kinases, Sharma et al. show that abrupt oncokinase deactivation/inhibition triggers rapid attenuation of signals passing through the downstream prosurvival effectors AKT, STAT5, and ERK1/2, abruptly pulling the plug on apoptosis protection. By contrast, attenuation of collateral proapoptotic MAPK signals generated by the same oncogenic kinases is far slower, an innate asymmetry in signal persistence that appears to be a consequence of the differential rates at which the antagonistic actions of oncogenic kinases and okadaic acid-sensitive phosphatases attack their targets. The net effect of this innate asymmetry in signal attenuation is that acute inhibition of oncokinases transiently exposes the affected cell to the unmitigated force of intrinsic apoptotic tumor suppression. The fact that this asymmetry is conserved among three very different tyrosine kinases intimates that it may represent a generally applicable affectation that evolution favors as a means to rein in the oncogenic potential of signaling molecules. Indeed, concurrent activation of both pro- and antiapoptotic signals through differing downstream effector pathways has been previously observed with activated RAS (Kauffmann-Zeh et al., 1997), and it is quite possible that the potent proapoptotic signals elicited by MYC and E2Fs share similar temporal dominance over their mitogenic siblings.

The proapoptotic signal that Sharma et al. identify arises from differential decay rates of signals following acute oncokinase inhibition. By nature, this is short lived. Does this mean that drugs, too, will only exert their therapeutic effect during a small window after delivery? It seems unlikely that such a transient burst of apoptosis would be alone sufficient to eradicate an established tumor, given that tumor cell apoptosis is likely to be modified by other, antiapoptotic lesions within the tumor cell, and drug penetration of solid tumors may be quite slow. As already discussed, however, asymmetry in signal

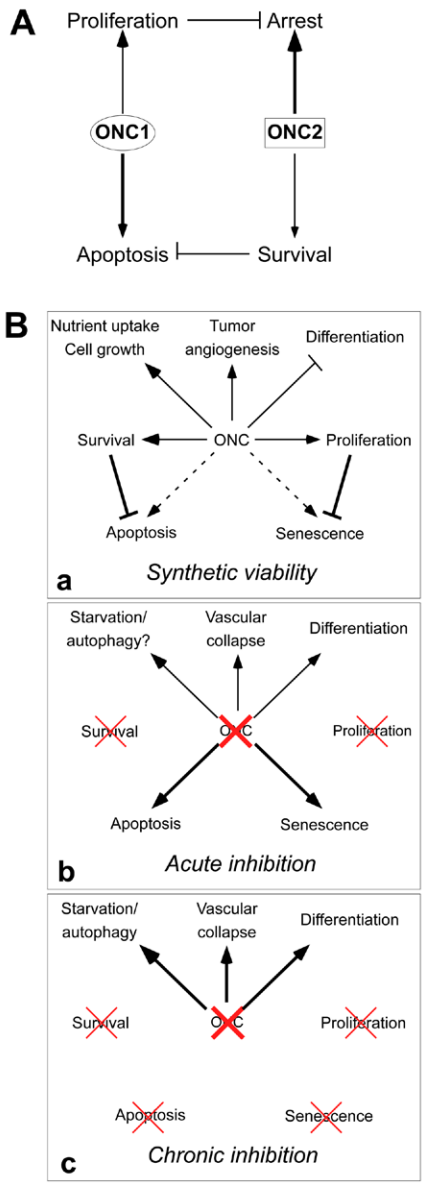


**Figure 1.** The anatomy of acquired oncogene dependence

**A:** Simplified scheme for oncogene interdependence. Interdependence of two oncogenic mutations arises because each counteracts the intrinsic tumor suppressive property of the other. In this example, the intrinsic apoptotic program of ONC1 is mitigated by the antiapoptotic actions of ONC2, while the cytostatic activity of ONC2 is overcome by the mitogenic actions of ONC1. An example of this particular class of oncogene interdependence is the cooperation between Myc and Bcl-2.

**B:** Immediate and delayed effects of oncokinase inhibition. **Ba:** Maintenance of the established tumor requires continuous oncogene activity to sustain both tumor superstructure (e.g., tumor blood supply and stromal interactions) and tumor cell infrastructure (e.g., belaying terminal differentiation, sustaining nutrient use, curbing intrinsic tumor suppressor pathways leading to death or senescence). The mechanisms shown are intended to be illustrative, not prescriptive or proscriptive. **Bb:** Acute oncogene inhibition leads to attenuation of all of these programs. However, the greater persistence of intrinsic tumor suppression pathways (apoptosis and, perhaps, senescence) means that these dominate the early stage of targeted therapy. **Bc:** At later times, these intrinsic tumor suppressor programs have also attenuated. However, collapse of tumor vasculature, failure of nutrient flux and onset of tumor cell differentiation maintains the process of tumor regression. At this point, residual tumor cells might escape therapeutic extinction by a variety of mechanisms, including evolution of alternative angiogenic mechanisms, failure to differentiate, activation of nutrient uptake, or autophagy.

decay is not the only mechanism underlying acquired oncogene dependence, and engaging these other mechanisms may require longer-term drug exposure (Figure 1Bc). Hence, it remains to be seen whether a "short, sharp shock" or "staying the course" proves the best strategy for drug delivery.

More generally, the important and fascinating observations of Sharma et al. underscore once again (as if this were even necessary) the critical importance of identifying which of the legion of mutations in human cancers is responsible for maintenance of the established tumor. Tumors accumulate much mutational clutter—bottlenecks that once passed are thenceforth irrelevant for further tumor maintenance, collateral havoc borne of telomere erosion, background noise that clones out with the tumor, bystanders swept up by neighboring amplifications or deletions, and weakly advantageous traits contingent upon the platform of oncogenic engines that buttress tumor maintenance. The real trick is to work out who is pulling the levers and pressing the buttons that keep the established tumor going and not get sidetracked into endless cataloging of epiphenomena. Sharma et al. show that evolution has handed us a great gift for cancer treatment—so long as we stay on target.

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# mILC-ing the mouse mammary gland: A model for invasive lobular carcinoma

**Mouse models that faithfully recapitulate human cancers are indispensable tools for studying the molecular mechanisms of tumorigenesis and testing potential anticancer therapies. In this issue of *Cancer Cell*, Derksen et al. describe a new mouse model that mimics multiple features of invasive lobular carcinoma of the breast (ILC), a histological subtype of human breast cancer for which no mouse model currently exists. This model further reveals an important causal link between E-cadherin loss and tumor initiation and metastasis and, in doing so, provides a valuable entrée into the tumor-suppressive functions of E-cadherin as well as the molecular underpinnings of ILC.**

Over the past two decades, the development of improved mouse models for human cancers has made important contributions to our understanding of this set of diseases. By engineering mice to contain specific genetic lesions found in human cancers, it has been possible to address the causal relationship between individual genes and the disease phenotype. Furthermore, mice that develop malignancies that faithfully recapitulate their human counterparts provide—at least in theory—more appropriate physiological systems in which to test candidate antineoplastic drugs. Indeed, an array of mouse models now exists in which the modulation of one or more genes altered in a particular human cancer gives rise to a malignancy in mice that resembles that cancer at both the histological and molecular levels (Holland, 2004). Moreover, as a first step toward fulfilling their promise, these models are now being utilized for the validation and testing of therapies (Sharpless and Depinho, 2006).

Given the success of genetically engineered mouse models to date, an important next step will be the creation of refined models that accurately reflect the diverse pathologies of human cancers. In breast cancer, for instance, the majority of patients present with invasive ductal carcinoma (IDC), whereas ~10% of patients present with a histologically distinct form of the disease, termed invasive lobular carcinoma (ILC). Beyond their morphologic distinctions, these tumor types also differ at the molecular level. One particularly prominent difference is that ILCs typically lose expression of the cell adhesion molecule E-cadherin, whereas IDCs retain its expression. ILC and IDC also exhibit differences in their biological behavior, including their patterns of metastatic spread. To date, however, there has been no mouse model that recapitulates the unique features of ILC, a fact that has impeded research into this disease.

A study by Derksen et al. in this issue now addresses this shortcom-