Oncogene Addiction versus Oncogene Amnesia: Perhaps More than Just a Bad Habit?

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Abstract

Cancer is a multistep process whereby genetic events that result in the activation of proto-oncogenes or the inactivation of tumor suppressor genes usurp physiologic programs mandating relentless proliferation and growth. Experimental evidence surprisingly illustrates that the inactivation of even a single oncogene can be sufficient to induce sustained tumor regression. These observations suggest the hypothesis that tumors become irrevocably addicted to the oncogenes that initiated tumorigenesis. The proposed explanation for this phenomenon is that activated oncogenes result in a signaling state in which the sudden abatement of oncogene activity balances towards proliferative arrest and apoptosis. Indeed, substantial evidence supports this hypothesis. Here, we propose an alternative, although not necessarily mutually exclusive, explanation for how oncogenes initiate and sustain tumorigenesis. We suggest that oncogene activation initiates tumorigenesis precisely because it directly overrides physiologic programs inducing a state of cellular amnesia, not only inducing relentless cellular proliferation, but also bypassing checkpoint mechanisms that are essential for cellular mortality, self-renewal, and genomic integrity. Because no single oncogenic lesion is sufficient to overcome all of these physiologic barriers, oncogenes are restrained from inducing tumorigenesis. Correspondingly, in a tumor that has acquired the complete complement of oncogenic lesions required to overcome all of these safety mechanisms, the inactivation of a single oncogene can restore some of these pathways resulting in proliferative arrest, differentiation, cellular senescence, and/or apoptosis. Thus, oncogenes induce cancer because they induce a cellular state of enforced oncogenic amnesia in which, only upon oncogene inactivation, the tumor becomes aware of its transgression. [Cancer Res 2008;68(9):3081–6]

The Rise and Fall of Cancer through Oncogene Inactivation

Cancer is generally thought of as a multistep genetic disorder (1). Pathopneumonic genetic lesions are associated with the perturbation of the function of specific proto-oncogenes that are the hallmarks of unique cancers. Hence, it seemed reasonable to presume that the repair or inactivation of these mutant gene products could reverse the process of tumorigenesis. However, because cancers are thought to be quite genetically complicated, it was not necessarily the case that fixing any specific mutant gene products would be sufficient to influence neoplasia. A priori, several possible outcomes were likely from the inactivation of a single oncogene: no effect, complete regression, or a partial loss of neoplastic features (Fig. 1).

Perhaps the most compelling evidence that cancer can be reversed through oncogene inactivation came from studies performed using conditional mouse models (2–4). Using different methods, several studies dramatically illustrated that a cancer initiated by a specific oncogene underwent sustained tumor regression upon the inactivation of that oncogene (5–14). Hence, it was concluded that, at least in these somewhat experimentally contrived circumstances, cancer is a reversible process.

From work in transgenic mouse models, several general principles emerged, as we have summarized previously (Fig. 2; refs. 15–19). The suppression of oncogene overexpression is sufficient to induce tumor regression, thus it is not necessary to inactivate the physiologic function of the corresponding proto-oncogene to induce tumor regression. The consequences of oncogene activation for the initiation of tumorigenesis and the consequences of oncogene inactivation for the reversal of tumorigenesis depend on the type of tumor and the cellular and genetic context. Thus, inactivation of an oncogene variously induces proliferative arrest, differentiation, apoptosis, and/or senescence. In some cases, brief oncogene inactivation is sufficient to induce sustained tumor regression, but in other cases, resumption of oncogene activity restores neoplasia. Hence, upon oncogene inactivation, cancer could be “revoked” permanently, or in other cases, cancer cells could become “dormant.” Cancers can escape dependence on oncogenes by acquiring other genetic events. Collectively, these observations suggested that there was reason for optimism and that it would be possible to define specific rules by which oncogenic activation initiates and maintains tumorigenesis.

Then, the discovery of Gleevec made it convincingly apparent that the targeted inactivation of oncogenes was also likely to be a successful therapeutic approach for at least some human cancers. Gleevec targets several tyrosine kinases, including BCR-ABL and c-kit, and was shown to be able to successfully therapeutically treat patients with chronic myelogenous leukemia and gastrointestinal stromal tumors (20). When tumors recurred after prolonged treatment with Gleevec, it was shown that there were specific mutations in the ABL that prevented the inactivation of its kinase activity (21). Thus, there was evidence that fixing a broken oncogene could reverse a human cancer. Hence, we entered an era of targeted therapeutics in which genetic principles may guide us towards the development of effective therapies for cancer.

From these results in experimental models and observations in patients, should we be so optimistic that cancers could generally be treated through targeted therapies? Although it seems that shutting down oncogenes has a dramatic phenotypic outcome, the mechanism by which this works, or why in some cases it fails to work, remains obscure. To date, targeted therapies, even when initially effective, eventually generally fail. Indeed, we are consumed by an interest in targeting specific gene products for...
the treatment of cancer without any clear insight into when or why this is a valid approach. Although one could argue that the mechanism is of less importance than the outcome, as has been generally presumed now by academia and industry, an understanding of the mechanisms by which oncogene inactivation induces tumor regression would seem important not just as an intellectual exercise, but also as a practical necessity for developing rationale cures for cancer.

**Oncogene Addiction: A New Insight into Tumorigenesis**

When we and others first described that MYC inactivation “reversed” tumorigenesis, our explanation was somewhat prosaic not because we did not have an idea of the possible mechanisms, of which we proposed several, but we were aware that, at the time, it was hard enough to be certain of the observation. We simply pointed out that when a gene was broken, and that it caused a cancer, then fixing that gene would restore the tumor cell back to its previous physiologic state which, in many cases, would result in arrest, differentiation, and/or apoptosis. Hence, cancer could literally be reversed.

However, even at that time, we were very aware that our results were thus far actually in discordance with some of our own findings, and that this discordance actually implicated a possible unifying mechanism that I will explain. Most pointedly, we had just described that MYC could induce cancer through a hit and run mechanism through the induction of genomic damage (22). A wealth of additional observations even more convincingly illustrated that many oncogenes are likely to contribute to tumorigenesis by inducing various types of genomic damage including polyploidy, aneuploidy, endoreduplication, DNA breaks, and translocations (23–25). Oncogenes have been shown to induce genomic damage by several mechanisms including the direct disruption of checkpoints that regulate DNA replication and DNA double-strand break repair (22–27). Oncogene activation has also been observed to induce genomic instability in vivo in murine models (28), and even more importantly, in human tissues (29). Thus, our observation that shutting off MYC casually resulted in sustained and complete tumor regression was initially a surprise. However, we recognized that perhaps oncogene inactivation was inducing tumor regression precisely because tumors could now recognize that they are damaged (27).

Then, the first general conceptual insight for the mechanism of reversal of cancer following oncogene inactivation was provided by Weinstein, who argued that tumors were addicted to oncogenes. In this model, oncogenes would necessarily induce a distinct and complex signaling state which would result in the activation of physiologic programs that would attempt to counteract the effects of the oncogene on proliferation and apoptosis (30, 31). Hence, when the oncogene was inhibited, these signaling programs would be unopposed resulting in synthetic lethality, and tumors would die because they had been addicted to the oncogene that initiated their pathologic state.

Oncogene addiction provides a satisfying explanation for much of what has been observed experimentally. The term is intellectually
very appealing and thus many investigators, certainly including me, have embraced this concept in broad scientific forums. In particular, oncogene addiction seems to precisely explain the general observation that oncogene inactivation particularly results in the death of tumor cells as opposed to normal cells. However, the model provides a vague explanation for the observation that the consequences of oncogene inactivation are different for different tumors and different oncogenes. Also, the model, in particular, does not seem to address the notion that “self-renewal” has emerged as one of the most fundamental epigenetic characteristics of a cancer, and a property that is not necessarily maintained by all of the cells within a tumor (32–35). The converse of self-renewal is “cellular senescence” and new evidence from my group hints that oncogene inactivation of tumors may generally induce cellular senescence (36). Therefore, pathways that regulate self-renewal, immortality, and senescence are particularly important features associated with oncogene activation and the initiation of tumorigenesis, the mechanisms that restrain tumor initiation, and the phenomena of tumor maintenance. Although cellular senescence may be an outcome of oncogene addiction, there seem to be more direct explanations for why oncogene inactivation results in the arrest, apoptosis, and senescence of tumor cells. In addition, oncogene addiction does not account for non-cell autonomous host mechanisms that contribute to tumor regression. Lastly, oncogene addiction does not address how mechanisms of tumor regression following oncogene inactivation may be more directly related to the mechanisms by which oncogene initiate and are restrained from causing tumorigenesis.

Oncogenic Amnesia: the Dr. Jekyll and Mr. Hyde Model of Cancer

We propose, as a possible unifying explanation for how oncogenes initiate and are restrained from causing tumorigenesis, and why oncogene inactivation induces tumor regression, that this is a direct consequence of the fact that specific oncogenes play a direct role in the regulation of physiologic safety switches that regulate mortality/self-renewal, differentiation, and/or DNA repair. Our model can also accommodate the notion that cell autonomous host mechanisms play a role in the mechanisms by which oncogenes initiate and sustain tumorigenesis.

It is axiomatic that many oncogenes contribute to tumorigenesis by inducing unrestrained cellular proliferation and growth, and by overcoming physiologic controls or safety switches. Analogously, oncogene activation has been shown to be restrained from causing tumorigenesis because this results in genotoxic stress—actual genomic damage—and that this stress activates cellular mechanisms that restrain any individual oncogene from causing tumorigenesis by activating cellular programs that induce proliferative arrest, cellular senescence, and apoptosis (37). Hence, cancer is postulated to arise only after these physiologic barriers have been

Figure 2. Oncogene inactivation has been observed to have different outcomes in different types of tumors including proliferative arrest, differentiation, apoptosis, and/or cellular senescence. Although the consequences are different for each type of tumor, cellular senescence seems to be a convergent common mechanism.
Indeed, one of the most characteristic features of cancer is that they not only exhibit autonomous proliferation and growth but exhibit genomic instability, suggesting that they have lost control of regulatory mechanisms that maintain genomic integrity.

As previously mentioned, oncogenes have been shown to contribute to genomic damage precisely because they override physiologic checkpoints that regulate DNA replication and repair. Yet despite these pervasive genomic disruptions that in normal cells would prompt an aggressive response inducing proliferative arrest, senescence, and/or apoptosis, tumors seem to be oblivious or amnesic to their genomic disruption. For a tumor to arise, these physiologic safety switches must be shut off, and no single oncogenic lesion is sufficient to do this. Thus, when an individual oncogene is activated, this does block some of the safety switches and this indeed can cause genotoxic stress, which we think is actually DNA damage, and this activates the other safety switches and the cells arrest, die, or undergo senescence.

Thus, for cancer to arise, other "genetic events" must occur to block enough of the other safety switches to correspondingly block the arrest/senescence/apoptosis response. Then, it may be presumed that by inactivating one of the oncogenes, you would necessarily restore at least some of these safety switches that had been "epigenetically" blocked by the "genetic" oncogenic event, awakening from their slumber the relevant physiologic programs. Indeed, upon oncogene inactivation, tumors exhibit a restoration of physiologic programs that is analogous to a physiologic response to DNA damage: proliferative arrest, differentiation, apoptosis, and/or senescence. At first glance, this seemed a paradox, for if cell cycle arrest, apoptosis, and cellular senescence are the barriers to oncogene initiation of tumorigenesis, then shouldn’t these pathways be abrogated in an established tumor, and hence, oncogene inactivation should not result in arrest, apoptosis, or senescence? However, the explanation could be that oncogene inactivation may induce tumorigenesis precisely because these gene products often play a direct role in the regulation of physiologic programs that govern not only cell cycle checkpoint mechanisms but also self-renewal/mortality and senescence programs.

Figure 3. Oncogenic amnesia: the Dr. Jeckyll and Mr. Hyde model of cancer. Cancers exhibit autonomous behavior resulting in immortality, self-renewal, and proliferation. Cancers influence the microenvironment to support tumorigenesis. Oncogene inactivation restores physiologic safety switches and results in proliferative arrest, differentiation, apoptosis, and cellular senescence, as well as the restoration of a physiologic microenvironment including the suppression of angiogenesis.
Oncogene Addiction versus Oncogene Amnesia

The important discriminating point of oncogenic amnesia and the oncogene addiction models is that tumor regression following oncogene inactivation in the former is a direct consequence of the restoration of physiologic pathways. Thus, tumorigenesis is “restrained” because oncogenes block only some but not all of the safety switches which results in DNA damage and a physiologic response. Cancer is reversed because oncogene inactivation restores the programs that were blocked by that particular oncogene. Importantly, this model recognizes that the complete inactivation of an oncogene is not required to induce tumor regression, but simply the restoration of the oncogene to physiologic levels so that physiologic programs are resumed. The consequences of oncogene inactivation would be predicted to be different depending on the particular oncogene and the particular genetic and epigenetic features of a tumor. Tumors that were defective for other reasons in apoptosis pathways would be more likely to differentiate or senesce. Tumors defective in genes that are involved in mediating many pathways would exhibit greatly impaired or transient tumor regression.

Oncogene Addiction/Amnesia Cancer Stem Cells and the Microenvironment

No single model will account for all observations and there is unlikely to be any one explanation for how oncogenes initiate or sustain tumorigenesis. However, considering cancer to be a consequence of “oncogenic amnesia” may provide a context for understanding why self-renewal/immortality/senescence seems to be some of the most important cellular programs involved in the initiation, restraint, and reversal of tumorigenesis. In addition, it is important to recognize that host-dependent tumor extrinsic mechanisms are likely to play a fundamental role in the mechanisms by which cancers arise, are prevented, and regress. How does this model accommodate the “cancer stem cell hypothesis”? The term cancer stem cell is widely agreed to be a somewhat misleading description of a phenomena which does not necessarily imply that the cells are stem cells, but rather, that only a portion of the tumor cells are immortal and self-renew indefinitely. Many of the tumor cells spontaneously lose the capacity for endless replication/self-renewal. My proposed model would account for the phenomena of cancer stem cells by suggesting that in these cells the programs that oppose self-renewal, such as cellular senescence are intrinsically turned off, most likely via epigenetic mechanisms.

Many different possible mechanisms are likely to operate. Some oncogenic lesions are likely to be more intimately related to self-renewal programs, which seems to be the likely case for MYC (38). It remains to be seen if other oncogenes also maintain tumorigenesis through the regulation of self-renewal and senescence. We have reported evidence that this is true for MYC and RAS, as well as in lymphoma, hepatocellular carcinoma, and osteosarcoma (36). The molecular basis for the “safety switches” that are being blocked by MYC and other oncogenes will have to be identified. We have found evidence suggesting that p15, p16, RB, and p53 are logical candidates (36). However, it will be important to more broadly substantiate whether oncogene inactivation induces tumor regression both in other model systems and in human tumors.

Importantly, any model of tumor regression must incorporate the idea that oncogene inactivation is likely to induce tumor regression not only from tumor cell intrinsic mechanisms, but also through host mechanisms of tumor suppression (Fig. 3). Many different mechanisms are likely, but we have recently noted that oncogene inactivation results in tumor regression both through tumor cell intrinsic and host-dependent mechanisms including angiogenesis (39). Hence, oncogene inactivation in the tumor may not only be achieved by reawakening the tumor’s normal cellular physiologic programs, but it seems to cause the tumor to send the correct cues to the host to restore the physiologic microenvironment.

As a final point, whether oncogene addiction or amnesia best defines the fate of cancers upon oncogene inactivation, it would be wise to dissect the molecular pathways that define the phenotypic consequences of oncogene inactivation. By looking at different oncogenes and seeing to what extent these pathways are similar or different, it should become manifest if there are discrete programs associated with particular oncogenes, which epigenetic variables are most important, and/or the constellation of genetic events that define a tumor. By understanding these mechanisms, it will more likely be possible to utilize targeted therapeutics more generally as an effective therapy for cancer. Only with such insights will targeted therapies realize their full potential to be more effective over existing empiric therapies.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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References

We appreciate the thoughtful article by Dr. Dean Felsher. Indeed, his seminal studies on conditional expression of oncogenes in mouse models played an important role in our formulation of the concept of oncogene addiction. We agree with him that multiple mechanisms may explain the phenomenon of oncogene addiction, depending on the particular system being studied. This is not surprising in view of the diverse functions of individual oncogenes, the coexistence in cancer cells of abnormalities in multiple oncogenes and tumor suppressor genes, and the context of the tissue in which the tumor developed. His suggestion that inactivation of specific oncogenes can restore checkpoint mechanisms (“safety switches”), that are essential for cellular mortality, self-renewal, and genomic integrity is provocative. However, except for DNA damage responses, at the present time, the biochemical mechanisms that mediate these checkpoint points are not well defined. Thus, his term “oncogene amnesia” is vague because it is not clear what was forgotten. Moreover, restoration or resumption of these physiologic programs implies that the original pathways which regulate cellular differentiation, senescence, and apoptosis are intact. This does not appear to be consistent with the bizarre circuitry, genomic instability, and aneuploidy that progressively develop during multistage carcinogenesis. Nevertheless, his hypothesis should stimulate further research on these checkpoints and their relevance to oncogene addiction.

We agree with Dr. Felsher’s emphasis on the importance of changes in both self-renewal mechanisms and cellular senescence in the response of cancer cells to oncogene inactivation. His recent studies indicating that “oncogene inactivation results in tumor regression both through tumor cell intrinsic and host-dependent mechanisms including angiogenesis” also provide new insights into the phenomenon of oncogene addiction. Hopefully, further studies on the mechanisms by which oncogene addiction affects tumor-host interactions will also reveal more effective methods for molecular targeted cancer therapy.

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