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Tumor Dormancy, Oncogene Addiction, Cellular Senescence and Self-Renewal Programs

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Abstract

Cancers are frequently sensitive to restoration of oncogenic lesions to normal physiologic regulation, which can elicit dramatic reversal of their neoplastic properties through the phenomena of oncogene addiction. In some cases, this is associated with the complete elimination of a tumor. However, in other cases the tumor undergoes conversion to differentiated and/or non-self-replicating cells; alternatively, some of the tumor cells are converted to dormant latent tumor cells that can regain the ability to self-renew upon oncogene reactivation. The ability to predict when oncogene inactivation will elicit complete and sustained tumor elimination *versus* tumor dormancy would have important implications for cancer therapies. One potentially important mechanistic insight into tumor dormancy is that oncogene addiction involves both tumor cell-intrinsic, cell-autonomous mechanisms and host-dependent, tumor cell-non-autonomous programs that both converge upon the regulation of a decision between self-renewal and cellular senescence. Another insight is that the tumor microenvironment, known to be critical during tumor initiation, prevention, and progression, also appears to dictate when oncogene inactivation will elicit the permanent loss of self-renewal through cellular senescence. Thus, oncogene addiction may be best modeled as a consequence of the interplay amongst cell-autonomous and host-dependent programs that converge upon the regulation of self-renewal programs that define when a therapy will result in tumor dormancy.

Keywords

Oncogene Addiction; MYC; Tumor Dormancy; Cellular Senescence; Self-Renewal; Transgenic Models

Introduction

Cancers are frequently sensitive to restoration of oncogenic lesions to normal physiologic regulation, which can elicit dramatic reversal of their neoplastic properties through the phenomena of oncogene addiction [1]. In some cases, this is associated with the complete elimination of a tumor. However, in other cases the tumor undergoes conversion to differentiated and/or non-self-replicating cells; alternatively, some of the tumor cells are converted to dormant latent tumor cells that can regain the ability to self-renew upon oncogene reactivation. The ability to predict when oncogene inactivation will elicit complete and sustained tumor elimination *versus* tumor dormancy would have important implications for cancer therapies. One potentially important mechanistic insight into tumor dormancy is that oncogene addiction involves both tumor cell-intrinsic, cell-autonomous mechanisms and host-dependent, tumor cell-non-autonomous programs that both converge upon the

regulation of a decision between self-renewal and cellular senescence [2-5]. Another insight is that the tumor microenvironment, known to be critical during tumor initiation [6, 7], prevention [8], and progression [9], also appears to dictate when oncogene inactivation will elicit the permanent loss of self-renewal through cellular senescence [10-12]. Thus, oncogene addiction may be best modeled as a consequence of the interplay amongst cell-autonomous and host-dependent programs that converge upon the regulation of self-renewal programs that define when a therapy will result in tumor dormancy.

Oncogene Addiction: A Mechanism of Tumor Regression

Oncogene addiction is the phenomenon by which tumor cells, through the consequence of a multitude of genetic and epigenetic changes, remain exquisitely dependent upon a single oncogenic lesion for the persistence of their neoplastic phenotype (Figure 1, 2) [13, 14]. The first suggestion that tumors cells could be addicted to tumor cells came from *in vitro* observations that tumor-derived cell lines sometimes exhibited proliferative arrest and/or apoptosis upon the suppression of an oncogene or the restoration of expression of a tumor suppressor [15]. These observations first hinted that therapeutic agents targeting the repair or suppression of these mutant gene products could be generally effective for the treatment of cancer.

Later, the development of transgenic mice that can conditionally express oncogenes enabled the direct *in situ* interrogation of the role of specific oncogenes in the initiation and maintenance of tumorigenesis. Many mouse models have been generated to explore the tumor-specific consequences of the suppression of oncogenes including *MYC*, *RAS*, *BRAF*, and *BCR-ABL* (Table 1) [2-4, 16-19]. In these models, the particular consequences of oncogene inactivation include proliferative arrest, apoptosis [2], differentiation [3, 4], and senescence [5], as well as the inhibition of angiogenesis [20, 21]. These observations implied that many cancers are addicted to a single oncogene.

Further studies established that the specific consequences of oncogene inactivation are highly dependent upon the tissue or origin from which the cancer was initiated. Even upon brief inactivation of an oncogene, the diversity of these outcomes is evidenced by the induction of a permanent loss of the neoplastic phenotype in osteosarcoma and lymphoma (Figure 1) [2, 3]. In marked contrast, oncogene suppression in hepatocellular carcinoma and breast carcinoma [4, 19] induced regression of tumors, but restoration of oncogene activity restored their neoplastic features, suggesting a state of tumor dormancy (Figure 1). In yet other cases, the inactivation of the oncogene failed to cause significant tumor regression, such as in a murine model of *MYC*-induced lung adenocarcinoma [22]. The instances in which inactivation of a specific oncogene that initiated tumorigenesis is sufficient to reverse tumorigenesis thus depends upon both cellular and genetic context.

Importantly, the clinical relevance of oncogene addiction was established through the development of several, effective targeted therapeutics [23, 24]. The identification of potent agents such as imatinib for chronic myelogenous leukemia and gastrointestinal stromal tumors [25], trastuzumab for the treatment of breast cancer [26], and vemurafenib for the treatment of melanoma [27], amongst other drugs [28], support the paradigm of exploiting oncogene addiction for the therapy of cancer. Moreover, these successes underscore how elucidating the underlying principles of oncogene addiction may be generally exploited as a strategy to treat a broad spectrum of cancers.

Oncogene addiction had been presumed to be largely a consequence of cell-autonomous mechanisms that occur through processes intrinsic and exclusively dependent upon biological programs including proliferation and apoptosis that are governed within a tumor cell (Figure 2). Several mechanisms have been proposed for oncogene addiction including

the notion of abnormal tumor cell genetic circuitry [1], reversibility of tumorigenesis [29], oncogenic shock [30], and synthetic lethality [31]. Even more recently, the host microenvironment has been shown to play a critical role in how oncogenes initiate as well as maintain tumorigenesis (Figure 2) [32-35].

Oncogene Addiction, Tumor Dormancy, Senescence, and Self-Renewal Programs

Even brief inactivation of an oncogene may result in tumor regression [2]. However, in some instances, although oncogene inactivation appears to result in the complete loss of the neoplastic properties of a tumor, the reactivation of the oncogene results in the rapid restoration of neoplastic properties [4]. Tumors that are not fully eliminated may also recur due to resistance to the targeted therapy conferred by mutation(s) in either the targeted gene or a downstream pathway [36-38]. This tumor dormancy, or the persistence of a state of minimal residual disease, therefore represents an immense hurdle to tumor elimination and ultimately patient survival [39].

One convergent feature of oncogene addiction appears to be the rapid and sustained proliferative arrest of tumor cells associated with the loss of self-renewal (Figure 1, 2) [40-43]. The importance of limitless self-renewal as the essential feature of cancer cells has been appreciated for decades [44]. More recently, it has been dramatically illustrated that only a subpopulation of tumor cells retain this limitless lifespan potential and thus are deemed cancer stem cells (CSCs) [45-50]. The self-renewal of CSCs involves complex regulation of multiple signaling pathways and transcription factors, including *MYC* [50-53]. Therefore, dramatic regression of tumors following oncogene inactivation is anticipated to involve loss of this self-renewal capacity.

At least in some cases, the loss of self-renewal of cancer cells has been associated with molecular and morphological features that have been described as cellular senescence [41]. Senescence is a cellular program that was first described as a barrier to limitless proliferation of normal cells grown *in vitro* [54, 55], and subsequently has been shown to be a conserved response to many types of cellular stress including telomere shortening [56, 57], DNA damage [58, 59], chemotherapy treatment [60-62], and oncogene activation [63-66]. Cellular senescence is associated with permanent changes in gene expression, chromatin condensation, induction of cell cycle arrest programs that involve p15(INK4b), p16(INK4a) and/or p53, and is correlated with an increase in acidic beta-galactosidase enzymatic activity [67-71].

Oncogene addiction may elicit cellular senescence through at least four different mechanisms: first, through induction of expression of cell cycle arrest proteins including p15(INK4b), p16(INK4a) and p21(CIP1) [5]; second, through the restoration of autocrine programs that induce cellular senescence, such as TGF-beta (TGF- β) signaling [72, 73]; third, through unopposed MAPK signaling [74, 75]; fourth, via immune mechanisms that appear to be mediated through secreted cytokines such as TSP-1 [76, 77].

Thus, oncogene addiction can be modeled as a consequence of the balance between self-renewal and cellular senescence programs (Figure 2). Cellular senescence is defined by its irreversibility. The ability of oncogene inactivation to elicit cellular senescence, and hence prohibit self-renewal of cancer cells, would be a mechanism to permanently suppress the tumor phenotype. Thus, cellular senescence appears to be a likely mechanism that would dictate tumor dormancy. Hence, whether oncogene inactivation induces tumor elimination or tumor dormancy also appears to depend upon the balance between self-renewal and cellular senescence programs.

Oncogene Addiction, Tumor Dormancy, and the Tumor Microenvironment

Tumor cells evolve in a host with an intact immune system [78]. Co-evolution of incipient tumors cells with host cells is integral to each step of tumorigenesis, including tumor initiation [6, 7], prevention [8], and progression [9]. Tumors appear to undergo immune editing, which is important to both their generation and therapeutic destruction [79, 80]. Thus, tumorigenesis is a consequence of interactions between incipient neoplastic cells and host stromal cells [32] that interact to regulate tumorigenesis [81].

Specific immune effectors and secreted factors have been implicated in the initiation of tumorigenesis [6, 7] as well as tumor growth, survival, and metastasis [81]. Immune effectors, including macrophages, T-cells, and B-cells, have been shown to either have a role in promoting [82-84] or inhibiting [73, 85-87] tumorigenesis. For example, NK (natural killer) cells [88] can inhibit metastasis whereas CD4⁺ T-cells [89] and macrophages [90] have been shown to promote metastasis. Similarly, in human patients, autoimmune stimulation or inflammation can be associated with increased tumorigenesis [78, 91-93]. Immune-compromised hosts exhibit a magnitudes increased incidence of certain tumors [79]. Consequently, the presence or absence of immune effectors, such as CD4⁺ T-cells is associated with a favorable [94] or a non-favorable prognosis [95] depending on tissue type, thereby indicating the complexity of the interaction between the host immune system and the evolving tumor. Indeed, immune cells and cytokines are important to the pathogenesis of tumorigenesis.

Oncogene activation can directly influence the immune response [96-100]. The *RET* oncogene in normal human thymocytes induces an inflammatory response leading to tumor tissue remodeling, angiogenesis and metastasis [101]. *RAS* up-regulates expression of the cytokines IL-6 [102] and IL-8 [103], which contribute to tumorigenesis. *MYC* can suppress CD4⁺ T-cells to maintain the angiogenic tumor microenvironment in multiple tumor models [76, 104]. However, *MYC* activation of macrophages is also associated with tumor suppression [73]. Hence, oncogene activation and inactivation can have dramatic consequences on both the tumor cells and the host tumor microenvironment (see Table 1).

The host immune system also is important to the efficacy of therapeutics [10-12]. Patients with impaired host immunity have decreased overall and progression-free survival in a variety of solid and hematologic malignancies [105, 106]. In colorectal carcinomas, the type, density, and intratumoral location of the T-cell infiltrate has proven a more robust predictor of patient outcome than the TNM or Duke's classification [11]. More generally, the host immune status influences the efficacy of conventional chemotherapy and radiation therapies [106].

In mouse models, the immune system can be directly interrogated mechanistically to define its role in therapeutic response [11]. For example, in mouse models of hepatocellular carcinoma, pancreatic tumor, and B-cell lymphoma innate immune components such as mast cells [107] and macrophages [73] have been implicated as barriers to tumor growth and facilitators of tumor regression. In models of colon and breast adenocarcinomas, chemotherapeutic agents and radiation therapies have been shown to elicit immunogenic apoptosis of cancer cells [108].

Multiple mechanisms of the immune contribution to the therapeutic response have been suggested, including both innate and adaptive immune effectors as well as specific cytokines [10-12]. Recently, it has been proposed that restoration in tumor cells of the "find me" and "eat me" immune stimulatory signals could potentially be used therapeutically to treat cancer [108, 109]. Hence, the promotion of both the adaptive and innate arms of host immunity may be highly useful towards the complete elimination of tumor cells [108, 109].

Immune Effectors and Tumor Dormancy *versus* Elimination

Specific cellular and cytokine-mediated immune effectors may define the consequences of oncogene inactivation. Experimentally, CD4⁺ T-cells appear to be essential to the mechanism of tumor regression upon oncogene inactivation in mouse models of *MYC*- or *BCR-ABL*-induced hematopoietic tumorigenesis (Figure 3, Table 1) [76]. Oncogene inactivation in *MYC*-induced tumors in CD4⁺ T-cell immunodeficient mice resulted in significantly delayed kinetics of tumor regression and failed to completely eradicate tumor cells, leaving up to 1000-fold more minimal residual disease (MRD) than in wildtype hosts [76]. Other effectors are also recruited to the tumor site suggesting their possible contribution [110].

CD4⁺ T-cells contribute to sustained tumor regression at least by two mechanisms: enforcing both the induction of cellular senescence and the suppression of angiogenesis (Figure 3, Table 1) [76]. Of import, both of these processes previously have been characterized as hallmarks of oncogene addiction (Figure 2, 3). CD4⁺ T-cells may mediate their influence on the tumor and tumor microenvironment directly or indirectly through the expression of many cytokines [111-114].

Thrombospondin-1 (TSP-1) was found to be a critical mediator of CD4⁺ T-cell-mediated sustained tumor regression upon *MYC* inactivation (Figure 3). TSP-1 may play a role in contributing to remodeling of the tumor microenvironment upon oncogene inactivation [76, 115]. TSP-1 is a potent anti-angiogenic and immune-modulatory cytokine that can induce apoptosis of endothelial cells and regulate T-cell chemotaxis [116]. TSP-1 also may mediate its effects through the regulation of TGF- β [117]. TGF- β can play a tumor-suppressive role in the tumor microenvironment [118, 119]. In particular, TGF- β can contribute to both the restraint of tumor onset as well as oncogene addiction through the regulation of cellular senescence upon *MYC* activation and inactivation [72, 73].

Additional cytokines and effectors that may be involved in CD4⁺ T-cell-mediated oncogene addiction. Cytokines that appear to play a role include: eotaxin-1, IL-5, IFN- γ and TNF- α , as well as the down-regulation of “pro-tumor” cytokines such as VEGF, IL-1, and MCP-1 upon *MYC* inactivation [76]. Whether any of these cytokines contribute more generally to the phenomenon of oncogene addiction remains to be seen.

CD4⁺ T-cells coordinate multiple components of both the innate and adaptive immune system [120], suggesting the contribution of other immune effectors is likely. Indeed, in oncogene-induced hepatocellular carcinoma, pancreatic tumor, and B-cell lymphoma, innate immune cell types such as mast cells [107] and macrophages [73] have been implicated as barriers to tumor growth and facilitators of tumor regression.

Notably, the restoration of the p53 tumor suppressor has been shown previously to induce tumor senescence, elicit chemokine expression, and induce the activation and recruitment of innate immune cells that contribute to tumor clearance [77]. Thus, the restoration of normal cellular function of a single tumor suppressor or oncogene can elicit oncogene addiction through changes in the tumor microenvironment dependent upon various host immune effectors.

Both cellular and cytokine-associated immune mechanisms are essential components of oncogene addiction. They define the kinetics, extent, and durability of tumor elimination (Figure 3). In the absence of an immune system, upon oncogene inactivation tumor cells persist, in a dormant state, whereas in the presence of a fully intact immune system there is complete elimination of tumor cells.

Therapeutic Implications: Tumor Dormancy *versus* Elimination

For maximal clinical efficacy, ideally a therapeutic for cancer would either completely eliminate a tumor or induce a permanent state of dormancy. Since both tumor cell-intrinsic and host-dependent programs appear to be required to elicit oncogene addiction, it would seem that in designing a therapeutic that is most efficacious it would be critical to consider both the tumor and the host. Therapies that target programs in cancer cells but suppress the immune system, or those that stimulate the immune system but have no effect on the biology of a tumor cell, may not be as effective as therapies that modulate both processes in concert. In particular, therapies that target the tumor but suppress the immune system could blunt their overall efficacy. Many existing anti-cancer therapies cause immunosuppression and lymphodepletion that may undermine their efficacy [10].

To best identify anti-cancer therapies, it would be critical to perform pre-clinical evaluation in host model systems that have an intact immune system and recapitulate a tumor microenvironment. *In vitro* or animal models in which a host is immuno-compromised would not correctly identify the best therapeutic agents precisely because the kinetics of tumor cell elimination, the degree of tumor elimination, the ablation of minimal residual disease (MRD), and the duration of a clinical response could all be dictated by mechanisms related to the host.

The ability to identify whether a therapy will induce dormancy *versus* elimination would be critical to evaluating potential therapeutics. The regulation of self-renewal *versus* cellular senescence appears to be the key determinant of the fate of a tumor. The ability to interrogate self-renewal may be intrinsic to evaluating and predicting therapeutic activity. The direct targeting of self-renewal/cellular senescence programs through the inactivation of particular oncogenes or other gene products may therefore be a particularly effective strategy for treating cancer. This critical decision in cell fate appears to be tightly coupled to interactions between tumor cells, host cells, and cytokines and appear to define whether a tumor expands, regresses, or becomes dormant (Figure 3) [39]. Hence, therapeutics that target self-renewal and/or activate cellular senescence could be very effective, including, for example, the induction of p53 or the modulation of genes that regulate the cell cycle machinery [41]. Therapeutic strategies that modulate the tumor microenvironment also may be useful adjuncts, including drugs that target angiogenesis [121]. A combination of approaches is likely to be most effective for tumor elimination.

Finally, the appreciation that immune mechanisms can dictate the balance between self-renewal and senescence suggests that the therapeutic manipulation of host immune system and secreted cytokines may be an important treatment strategy. Specific host immune effectors and chemokines profoundly influence the consequences of therapeutic oncogene inactivation, radiation therapy, and chemotherapy [11]. The integration of targeted- and immune-therapy may be the most efficacious strategy in treating cancer [122].

Modeling and Predicting Tumor Dormancy *versus* Elimination

Through mechanistic understanding of oncogene addiction it should be possible to predict therapeutic efficacy. Oncogene addiction involves both tumor cell-intrinsic and host-dependent programs that regulate self-renewal and cellular senescence. Thus, it should be possible to generate models that predict oncogene addiction, incorporating these cellular outcomes [30, 123]. One such possible approach would be to presume that cancer cells behave stochastically and can exist in three states: proliferating, apoptotic, or quiescent/dormant. Then, the acquisition of even very simple measurements of proliferation and apoptosis combined with assessments of tumor size could be used to mathematically predict oncogene addiction [123].

Such modeling has revealed some possible insights into the mechanism of oncogene addiction and tumor regression following oncogene inactivation [123]. A simple differential decay between pro-survival and pro-death signals is sufficient to explain the majority of what occurs upon oncogene inactivation. A decay of both pro-survival and pro-death signals follows targeted oncogene inactivation. Although, the final level of the pro-death signal is comparable to the pro-survival signal, it is precisely because the death signals induced by the oncogene are extinguished more slowly after oncogene inactivation than the survival signals that tumors regress. These results support the oncogenic shock hypothesis, first suggested by both Settleman and Kaelin [30, 31].

Mathematical modeling of the response to targeted therapy indicates that simple measurements of tumors before and after initiation of a therapeutic may be useful to predict therapeutic outcome [124]. A variety of different computational approaches could be used and this could potentially be very useful in enabling the more rapid identification of therapeutics as well as the more rapid discontinuation of therapies that are not effective (Figure 4). This approach would exploit existing as well as emerging imaging techniques to rapidly and reliably assess tumor cell proliferation and apoptosis *ex vivo* [125-129].

Even simple models may be able to predict oncogene addiction with measurement of proliferation and apoptosis alone [123]. However, the inclusion of additional parameters such as immune cell infiltration, onset of cellular senescence, loss of self-renewal, and suppression of angiogenesis would likely improve the modeling. New molecular imaging approaches as well as proteomic technologies may enable the measurement of such parameters (Figure 4). Then, the application of both mechanistic and predictive modeling may further enable the goal of predicting when targeted inactivation of a gene product or combination of products would elicit tumor elimination or tumor dormancy.

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Figure 1. Oncogene addiction elicits tissue-specific effects

Oncogene inactivation has been observed to have different outcomes depending upon the tissue origin of tumors, including proliferative arrest, differentiation, apoptosis, and/or cellular senescence. The specific consequences of oncogene addition have a dramatic impact on whether targeted therapies will result in tumor dormancy, as in the case of MYC-induced hepatocellular carcinoma, or tumor elimination, as shown for MYC-induced lymphoma.

Figure 2. Oncogene addiction comprises both cancer cell-autonomous and non-cell-autonomous mechanisms of tumor regression

Oncogene inactivation reverses many of the hallmarks of cancer to lead to tumor regression through reinstatement of cell-intrinsic programs such as proliferative arrest, apoptosis, and differentiation, as well as host-dependent phenomena including immune system activation and destruction of the tumor vasculature. Notably, cellular senescence is both a tumor cell-intrinsic and a host-regulated consequence of oncogene addiction; however, it is likely only in an immune intact host that targeted therapy will result in complete tumor elimination.

Figure 3. Tumor dormancy *versus* tumor elimination is regulated by an intact host immune system

Oncogene inactivation results in tumor regression regardless of host immune status due to proliferative arrest, apoptosis, and/or differentiation. In an intact host, the immune system is subsequently activated to facilitate elimination of the residual tumor cells via induction of cellular senescence and destruction of the tumor vasculature. However, in the absence of an immune system, tumors establish a state of dormancy, due to lack of inhibition of self-renewal and angiogenesis, followed by eventual escape from therapy and tumor recurrence.

Figure 4. Modeling and predicting when oncogene inactivation will result in tumor dormancy versus tumor elimination

A combinatorial, iterative approach can be utilized to model the consequences of oncogene addition, thereby allowing for prediction of response to targeted therapy in patients. Continuing progress in molecular imaging and biomarker discovery will be crucial for the validation of mathematical models of oncogene addition in primary animal models of cancer. In parallel, the advent of new molecular imaging tools in the clinic will allow for incorporation of discoveries in these pre-clinical models into assessment of human cancer patient response to therapy.

Table 1
Examples of immune system-mediated oncogene addiction

Murine models of *MYC* and *BCR-ABL* inactivation as well as *P53* restoration directly implicate immune involvement in implementing the consequences of oncogene addiction. Below, oncogenes whose tumorigenicity relies heavily on immune evasion and/or pro-tumor inflammation highlight the potentially broad generalizability of the concept of immune system-mediated oncogene addiction.

	Oncogene	Tumor Type	Immune Compartment	Immune-Mediated Mechanism	Refs
Adaptive Immunity	MYC	T cell acute lymphoblastic lymphoma	CD4 ⁺ T cells	Induction of senescence and suppression of angiogenesis	[76]
	BCR-ABL	Pro-B cell acute lymphocytic leukemia	CD4 ⁺ T cells	Induction of senescence and suppression of angiogenesis	[76]
	PML	Acute promyelocytic leukemia; prostate carcinoma	CD8 ⁺ T cells	Influencing MHC class I antigen presentation	[97, 98]
	BRAF	Melanoma	Dendritic cells, CTLs	Inhibition of antigen presentation and induction of IL-10, IL-6	[99, 130]
Innate Immunity	MYC	B cell lymphoma; pancreatic islet cell tumor	Macrophages, Mast cells	Macrophage induction of senescence; mast cell promotion of angiogenesis	[73, 107]
	P53	Hepatocellular carcinoma	Neutrophils, Macrophages, NK cells	Tumor clearance	[77]
	RAS	Cervical cancer; renal cell carcinoma	Neutrophils	Promotion of angiogenesis and tumor growth due to IL6 and IL8	[102, 103]