Published in final edited form as:

Curr Opin Immunol. 2013 April ; 25(2): 246–258. doi:10.1016/j.coi.2013.02.003.

Noncanonical Roles of the Immune System in Eliciting Oncogene Addiction

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Summary

Cancer is highly complex. The magnitude of this complexity makes it highly surprising that even the brief suppression of an oncogene can sometimes result in rapid and sustained tumor regression illustrating that cancers can be “oncogene addicted” [1-10]. The essential implication is that oncogenes may not only fuel the initiation of tumorigenesis, but in some cases necessarily their surfeit of activation is paramount to maintain a neoplastic state [11]. Oncogene suppression acutely restores normal physiological programs that effectively overrides secondary genetic events and a cancer collapses [12,13]. Oncogene addiction is mediated both through both tumor intrinsic cell-autonomous mechanisms including proliferative arrest, apoptosis, differentiation and cellular senescence [1,2,4,12] but also host-dependent mechanisms that interact with these tumor intrinsic programs [14,15]. Notably, oncogene inactivation elicits a host immune response that involves specific immune effectors and cytokines that facilitate a remodeling of the tumor microenvironment including the shut down of angiogenesis and the induction of cellular senescence of tumor cells [16]. Hence, immune effectors are critically involved in tumor initiation and prevention [17-19] and progression [20], but also appear to be essential to tumor regression upon oncogene inactivation [21-23]. The understanding how the inactivation of an oncogene elicits a systemic signal in the host that prompts a deconstruction of a tumor could have important implications. The combination of oncogene-targeted therapy together with immunomodulatory therapy may be ideal for the development of both a robust tumor intrinsic as well as immunological effectively leading to sustained tumor regression.

Introduction: Oncogene Addiction as a Mechanism of Targeted Therapies

Oncogene addiction is a description of the dramatic and sustained regression of some cancers upon the specific inactivation of a single oncogene [24]. Cancer can be defined by the acquisition of specific hallmark phenotype features [25]; correspondingly, oncogene addiction is characterized as the complete and sustained reversal of a tumor associated with the restoration of oncogene disrupted programs back to a physiologic state [Figure 1]. A key feature that is that whereas in normal cells the suppression of a normal proto-oncogene does not appear to be associated with the acute destruction of the associated normal cellular tissue, the consequences are excessively disastrous for the cancer. Hence, oncogene

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Competing interests statement: The authors declare no competing financial interests.

addiction has been associated with the en masse proliferative arrest, cell death, cellular senescence, and/or permanent differentiation of cancer cells [26].

The precise mechanism by which oncogene addiction occurs is obscure. The simple brief reduction of oncogene expression can be sufficient to have dramatic consequences [1,4]. The suppression of an oncogene to levels that are still significantly elevated above a normal cell can be sufficient [11]. The inhibition of many different oncogenes has been associated with oncogene addiction and thus is not unique [27] [Table 1]. The particular consequences of suppression of an oncogene appear to be influenced by both genetic and cellular context that blunt the phenotypic consequences of oncogene addiction [27].

Notably, addiction to some oncogenes, such as MYC, appears to be absolute, impossible to bypass even through other oncogenic events [28]. Whether this will generalize is unclear. In the specific case of MYC, there appear to be a multitude of ways a cancer cell will attempt to configure the ability to restore MYC expression [28]. Whether the mechanisms of oncogene addiction are the same for different oncogenes and in different tumors remains to be defined. Clinically, the targeted inactivation of an oncogene is associated in many cases with tumor regression, albeit in most cases tumors eventually recur [29-31]. Thus, although oncogene addiction appears to be relevant to the treatment of human patients, as yet, no combination of therapies has proven a panacea.

Several non-mutually exclusive possibilities have been articulated for the mechanism of oncogene addiction. Oncogene inactivation may restore the function of normal physiological programs that regulate proliferative arrest, differentiation, apoptosis and cellular senescence [15]. Cancers may become rewired such that they necessarily depend upon particular oncogenes to maintain their survival, and oncogene inactivation uncovers synthetic lethal interactions [13]. The suppression of an oncogene may result in changes in survival and death signaling that necessarily are kinetically differentially regulated upon oncogene inactivation [32]. These possibilities are not mutually exclusive and may depend upon context.

There are several important considerations in applying oncogene addiction as a therapeutic paradigm. First, there is an increasing appreciation that the best therapeutic targets may be essential driver mutations that are important for the molecular scaffolding for maintaining a cancer phenotype [33,34]. The acknowledgement that cancers may be addicted not only to particular mutant oncogenes themselves, but to the fundamental physiologic programs they regulate, including key signaling, metabolism and checkpoints, illustrates that targeting what had been thought to be “house-keeping” or non-oncogene addiction associated genes may be the ultimate culprit of oncogene addiction [25]. The emerging role of epigenetic programs in globally regulating cancer phenotype heralds the notion that oncogene inactivation may elicit a domino-like action on the transcriptome that accounts for the resulting obliteration of a cancer [35]. The incorporation of a multi-scale and/or systems analysis suggests that only through the modeling survival and death signaling alone it may be possible to infer fundamental decision points that can be used to predict oncogene addiction [32]. Regardless of the precise mechanisms that account for oncogene addiction, the essential implication is that cancer cells, despite their genetic and epigenetic complexity, are often highly dependent upon a single mutant gene product for a sustained neoplastic phenotype [13,36].

The clinical relevance of oncogene addiction is suggested by many observations. The earliest appreciation that the suppression of an oncogene, or the restoration of a tumor suppressor, could lead to loss of neoplastic features of human cancer cells was demonstrated in vitro [37]. A multitude of anti-cancer drugs have been developed based upon these observations, albeit without a mechanistic explanation for why suppression of an oncogene

results in tumor regression. Anti-cancer drugs targeting oncoproteins such as BCR-ABL, c-kit, Her2-NEU, EGFR, and PML-RAR α have all shown to be effective in the clinic in specific patient populations [38-40]. Most recently, vemurafenib was FDA-approved for treatment of BRAF V600E mutation-positive metastatic melanoma [41]. Similarly, small molecules have been developed and are in clinical trials to target other oncogenes including: ALK, JAK2, Mdm-2, and PI3 Kinase [42]. Other oncogenes, such as K-Ras and MYC, are highly desirable drug targets, but have yet to be successfully targeted, have been considered not yet “druggable”.

Many investigators have examined the effects of suppressing oncogenes back to physiological state using in vivo conditional transgenic models, including: MYC, RAS, BCR-ABL, BCL2, MET and BRAF [1,2,4,5,8,43,44]. The inactivation of an oncogene in mouse models is associated with proliferative arrest, apoptosis [4], differentiation [1,2], senescence [12], and the inhibition of angiogenesis [45,46]. The specific consequences are dependent both upon the tumor cell type and genetic context. Even a brief inactivation of an oncogene in osteosarcoma and lymphoma results in a permanent loss of the neoplastic phenotype [1,4]. In contrast, in epithelial associated tumors such as hepatocellular carcinoma, breast carcinoma [2,44], and lung adenocarcinoma [47], brief oncogene inactivation is not necessarily associated with sustained tumor regression. Hence, the precise consequences of the suppression of a driving oncogene to reverse tumorigenesis are influenced by the specific type of tumor.

The clinical relevance of oncogene addiction has been dramatized through the successful validation of targeted therapeutics for human cancer [48,49]. Examples of successful anti-cancer drugs include imatinib for chronic myelogenous leukemia and gastrointestinal stromal tumors [50], trastuzumab for the treatment of HER2-NEU positive breast cancer [51], and vemurafenib for melanoma [52]. The mechanism of oncogene addiction operates has long been presumed to be cell autonomous; inactivation of the driving oncogene inhibits proliferation, increases apoptosis and senescence, and leads to tumor regression. Several cell-autonomous mechanisms have been proposed, such as abnormal cancer cell genetic circuitry [26], reversibility of tumorigenesis [53], oncogenic shock [54], and synthetic lethality [55]. However, the host microenvironment is well known to play an important role in the process by which oncogenes initiate and sustain tumorigenesis [25,56-58], which implies that host factors may also play an imperative role in oncogene addiction.

Oncogene Addiction and the Host Immune System

The relationship between host immune cells and the restraint and emergence of tumor growth was suggested more than a century ago by Rudolf Virchow [59]. The acceptance that the immune system is integral to tumorigenesis has been only more recently become axiomatic [60]. What appears to be agreed is that both the innate and adaptive immune system actively participate in tumorigenesis, including during tumor initiation [18,19], prevention [17], and progression [20].

An elegant way of encapsulating the dynamic nature of the interaction between host and tumor is the concept of immune editing, which has provided a unifying paradigm for understanding how the immune system may restrain tumorigenesis as well as be modulated as a therapeutic maneuver for the treatment of tumors [61,62]. Tumorigenesis occurs as an evolution with continuous adaptive interactions between incipient neoplastic cells and a host immune environment that include innate and adaptive effectors, endothelial cells, and stromal fibroblasts and extracellular matrix components and secreted factors [56].

In addition to immune editing, the immune system has been shown to play a role in regulating the tumor microenvironment through programs of inflammation and/or wound

healing [60,63,64]. Immune effectors have been shown to be integral to both the initiation and restraint of tumorigenesis [65]. Innate and adaptive immune programs, via cell and cytokine mediated mechanisms have been illustrated to evoke tumorigenesis [18,19], facilitate tumor growth, amplify survival, impede apoptosis and promote metastasis [65] through observations both in mouse models as well as human patients.

Many different host immune cells have been implicated in the pathogenesis of cancer. Macrophages, CD8⁺ cytotoxic T cells, and B cells have been shown to have roles promoting [66-68] or inhibiting [69-72] tumor growth, depending on the particular tumor type. Other immune cells, such as natural killer (NK) cells [73] can impede metastasis, whereas CD4⁺ T-helper cells [74] and macrophages [75] have been shown to support metastasis. Similarly, the presence or absence of immune effectors, such as CD4⁺ T cells, in a particular tumor microenvironment, can have either an advantageous [76] or non-advantageous outcome [77]. In human patients, immune cells have been also suggested to both promote as well as suppress tumorigenesis, depending on context [78-80]. Lymphocytes that mediate immune surveillance are thought to antigenically recognize and clear newly transformed tumor cells [61]. Suppressive lymphocytes [81] and macrophages [82] can lead to a dampening of the anti-tumor response and consequently, disease progression. However, noncanonical immune mechanisms are likely also involved, as described further below.

Provocatively, in several cases, oncogenes have been shown to directly influence the host immune response [83-87]. For example, the activation of the *RET* oncogene in normal human thymocytes leads to an inflammatory response, resulting in tumor tissue remodeling, angiogenesis, and metastasis, which assist in the maintenance of the transformed state of the tumor [88]. Mutant *RAS* elicits the expression of the cytokines IL-6 [89] and IL-8 [90], contributing to inflammation associated tumor initiation. *MYC*-induced B cell lymphomagenesis is restrained through the production of TGF- β expression associated with innate immune infiltration of macrophages [71]. Many oncogenes, including *MYC*, can activate the angiogenic switch [91].

Cancer and the Immune System

The suggestion that the immune system contributes to the mechanism of action of tumor therapy is supported by many observations. Tumor infiltration by T cells has been found to have a positive predictive impact on local advanced breast cancer treated with neoadjuvant chemotherapy, and that these immune infiltrates of the primary tumors, as well as of metastases, are not only independent prognostic biomarkers but can also constitute predictive factors, implying that the pre-treatment immune response can predict the efficacy of conventional anti-cancer drugs.

Tumor-associated T cell infiltrates and prolonged survival have been delineated in ovarian [92], colon [22,93,94], renal cell [95], non-small cell lung carcinomas [96], and follicular lymphomas [23]. The immune system may contribute to the therapeutic response via both innate and adaptive immune effectors, as well as specific cytokines [21-23]. It has also been suggested that restoring the “eat me” and “find me” immune stimulatory signals within tumor cells could be used therapeutically to treat cancer [97,98]. Consequently, the promotion of both the adaptive and innate arms of host immunity may be highly useful towards the complete clearance of tumor cells [97,98]

Additionally, accumulating evidence elaborates that chemotherapy can stimulate anti-cancer immune responses together with an increased intratumoral lymphocyte infiltration, which correlates with smaller tumors and patient survival [99]. Others have found that the host immune response is crucial for maximal efficacy of many cancer therapeutics [21-23]. Patients with a dampened immune system appear to have decreased overall and progression-

free survival in several different solid and hematologic malignancies [100,101]. Thus, results from both the bench and the clinic demonstrate that host immunity boosts the response to anti-cancer treatments.

In experimental mouse models of cancer, some recent observations suggest a complex role for the immune system in influencing the therapeutic response. Mouse models of hepatocellular carcinoma, pancreatic tumor and B cell lymphoma have illustrated that innate immune members including mast cells [102] and macrophages [71], may function as a hindrance to tumor growth and may facilitate tumor regression. Taken together, these findings indicate that the host immune response may be of underestimated importance in determining the possible outcome of anti-cancer therapies.

Mechanisms by which Oncogene Addiction Collaborates with the Immune Response

Recent results point to the importance of the immune system to the efficacy of targeted therapies for cancer. For example, the co-administration of IL-12 with mouse anti-HER2/neu mAb (4D5) enhances the FcR-dependent immune mechanisms that contribute to its antitumor activity against murine colon adenocarcinoma [106]. Combination therapy was associated with increased circulating levels of IFN- γ and RANTES. Experiments with IFN- γ -deficient mice established that this cytokine was necessary for the antitumor effects of IL-12 plus mouse anti-HER2/neu [106]. Immune cell depletion experiments showed that NK cells mediated the antitumor effects. Taken together, these findings suggest that tumor regression in response to targeted therapy (in this case, trastuzumab) may be mediated through NK cell IFN- γ production and provide a rationale for the co-administration of NK cell-activating cytokines with therapeutic mAbs [106]. Thus, there is increasing rationale to consider that targeted therapies mediate their clinical effects in concert with specific immune mechanisms.

Therapeutic antibodies that modulate the immune response have emerged as an important strategy to potentially amplify the immune response to maximize the activity of cancer therapies. For example, the discovery of the importance of CD137 has suggested a novel avenue of attack of cancer [107-109]. After interacting with trastuzumab-coated, HER2-overexpressing breast cancer cells, natural killer cells become activated and express the costimulatory receptor CD137. CD137 activation, which is dependent on NK cell expression of the Fc γ RIII receptor, occurs both in vitro and in the blood of patients with HER2-expressing breast cancer following trastuzumab treatment. Stimulation of trastuzumab-activated human NK cells with an agonistic mAb specific for CD137 killed breast cancer cells more efficiently both in vitro and in vivo. Thus, combining a tumor-targeting antibody with a second antibody activating the host innate immune system may improve the therapeutic effects of antibodies against surface oncoproteins such as HER2/neu [110]. Furthermore, breast cancer patients treated with trastuzumab develop a CD4⁺ T-helper cell response [111]. Thus, there appear to be potentially provocative clinical applications of therapies that target CD137.

Therapeutic antibodies are likely to mediate their clinical efficacy in concert with immune mechanisms. Thus, the therapeutic efficacy of HER2-neu targeted treatment in experimental animal models requires Fc receptors and CD8⁺ T cells; animals treated with these antibodies generated tumor-specific T cells more robustly than did controls [112]. Similarly, in patients who received trastuzumab, a strong T cell response was associated with better clinical outcomes [113]. Thus, the most robust response to trastuzumab may be generated either by induction of an immune response and/or combination with immunotherapeutics.

Targeted therapeutics may require an intact immune response for optimal efficacy. The clinical activity of combination therapy of imatinib plus IL-2 is completely abolished in mice treated with a neutralizing tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) antibody, implying that TRAIL plays a crucial role in imatinib-induced cytotoxic activity [114]. Patients who responded to imatinib (versus those that developed resistance) developed a proportionally larger number of CD20⁺/IgM⁺/CD5⁺ B-1 lymphocytes; the “natural” antibody secreted by these cells was also found to be tumor-specific [115]. Furthermore, imatinib does not appear to diminish the proliferation of patient T cells or the production of immunomodulatory cytokines, such as IFN- γ and TNF- α [116], a finding that suggests that combining immunomodulatory therapies together with imatinib may be successful. More generally, the mechanism of therapeutic activity of oncogene inactivation may rely on changes in the tumor microenvironment.

Specific Immune Populations May Be Required to Elicit Oncogene Addiction

Recent findings suggest a surprising and potentially crucial role for CD4⁺ T cells in the mechanism of tumor regression upon oncogene inactivation in mouse models of MYC- or BCR-ABL-induced hematopoietic tumorigenesis [16]. Experiments performed in immunocompromised animals indicate that without an intact immune system, oncogene inactivation in MYC or BCR-ABL-driven tumors leads to a delay in the kinetics of tumor regression and tumor cells are incompletely eradicated, with up to 1000-fold more minimal residual disease (MRD) than in immune-competent animals [16].

It was unexpected that CD4⁺ T cells, and not the traditionally anti-tumor cytotoxic CD8⁺ T cells, were found to be key immune effectors of sustained tumor regression following MYC inactivation. CD4⁺ T cells homed to the tumor as early as four days after MYC or BCR-ABL inactivation, and they remained for up to three weeks; it is important to note that other effectors also home to the tumor, suggesting that they may also contribute to lasting regression [14]. CD4⁺ T cells coordinate multiple factors in both the innate and adaptive immune system [117]. Consequently, it is likely that other immune effectors contribute to the mechanisms of oncogene addiction. Finally, it is likely that the novel role of CD4⁺ T cells in tumor regression (and subsequent senescence and shutdown of angiogenesis) occurs following inactivation of many disparate tumor-driving oncogenes, as this phenotype was observed in both tumors driven by MYC and tumors driven by BCR-ABL [16].

CD4⁺ T cells appear to contribute to oncogene addiction through the regulation of cellular senescence and the suppression of angiogenesis [16]. Both of these programs have been characterized as hallmarks of oncogene addiction [12,27,118], but neither program has been generally thought to be regulated by adaptive immune cells. The most likely mechanism of action of the CD4⁺ T cells is that they directly express and/or elicit the recruitment of other immune effectors that express specific cytokines that regulate senescence and angiogenesis, [119-122]. However, there are other possible mechanisms, including the direct cellular interactions between CD4⁺ T-cells and the tumor cells or stromal cells in the tumor microenvironment.

Thrombospondin-1 (TSP-1) was found to be at least one of the critical molecules of CD4⁺ T cell-mediated tumor regression following oncogene inactivation. TSP-1 is produced by a wide variety of cells [16,123] and is a strong anti-angiogenic and immunomodulatory cytokine that can lead to apoptosis of endothelial cells and T cell chemotaxis [124]. Importantly, TSP-1 can activate dormant TGF- β [125]; TGF- β can be tumor suppressive [126,127]. TGF- β has been found to regulate the onset of cellular senescence upon MYC activation and inactivation [71,128]. TSP-1, as well as other cytokines (such as eotaxin-1,

IL-5, IFN- γ and TNF- α) likely plays a role in tumor regression; it is also likely that the downregulation of “pro-tumor” cytokines (such as VEGF, IL-1 β , and MCP-1) upon *MYC* inactivation [16] assists in tumor-free survival. However, to date, therapeutic use of TSP-1 molecules has not been found to be clinically useful [129]. One possibility is that TSP-1 will only be useful in the context of the appropriate targeted inactivation of an oncogene.

Importantly, not only is oncogene inactivation associated with immune mediated destruction of a tumor. The restoration of the p53 tumor suppressor has been demonstrated to induce senescence of tumor cells, chemokine expression, and the activation and recruitment of innate immune cells that assist in tumor clearance [130]. Thus, the restoration of normal function of a single tumor suppressor or oncogene results in anti-tumor consequences through both tumor cell-specific and tumor microenvironment changes. Thus, the immune system is likely to play a pivotal role in the pathogenesis of cancer associated with many different oncogenes or tumor suppressor genes.

A particularly important emerging principle is that to gauge the effectiveness of targeted oncogene inactivation, it may be critical to consider that the biology of a tumor will be greatly influenced by the size of the tumor [103]. Indeed, most mouse models of cancer examine relatively small tumors, especially when considering that in human patients cancers are frequently diagnosed only after a considerable cancer burden.

In this mouse model of relatively large tumors, “immunogenic cell death” (discussed more later in this review) was observed following oncogene inactivation. However, not all mice remained tumor-free following regression in the presence of normal host T cells; factors that may influence tumor cell clearance and minimal residual disease may include immunogenic cell death, the time before oncogene inactivation to ensure a particular amount of time of antigen exposure, and the size of the tumor due to both the stroma and the likelihood of more genetic variants. In contrast, relatively small tumors completely regressed and never reoccurred [104]. In this model, the CD8⁺ effector cells appear to be responsible for the elimination of tumor through the shut down of angiogenesis that helps eliminate even the rare tumor cells that may escape dependence upon a particular oncogene through the mechanism of “bystander elimination” [103]. In addition, tumor cells could be cleared via cross-presentation of other tumor-associated antigens [105].

Clearly, a multitude of immune effectors may contribute to the response of targeted therapies likely dictated by genetic and cellular context of a tumor. Importantly, observations in other mouse models of oncogene-induced tumors have implicated innate immune members such as mast cells [102] and macrophages [71] as barriers to tumor growth and facilitators of tumor regression. The combination of various strategies of immune therapy could complement in maximizing the clinical benefit of oncogene addiction. Some examples include enhancing NK activity [131], engineering T-cell response to cytokine signaling [132], adoptive transfer of T memory stem cells [133] [134], engineering other specific cytotoxic and T-helper cells [135][136] [137], NK cells [138-142], gamma delta cells [143], dendritic cells [144], antibodies and/or B-cells [145,146] and Cytokines [147]. Key will be to define which immune therapies will best complement particular targeted therapies.

Clinical Evidence that Immune Mechanisms Contribute to the Response to Targeted Therapies

Increasingly, it has been appreciated that the host immune response is required for the best response to therapeutics. For example, in gastrointestinal stromal tumors (GIST) treated with imatinib, progression-free survival has been found to correlate with IFN- γ secretion by NK

cells in the peripheral blood [148]. The host immune system is required for the therapeutic effect of imatinib in gastrointestinal stromal tumor (GIST) [149]. In a mouse model of spontaneous GIST, imatinib treatment activated CD8⁺ T cells and lead to regulatory T cell apoptosis within the tumor; CD8⁺ T cells were required for optimal imatinib results, and this was modulated by a reduction in expression of the immunosuppressive enzyme indoleamine 2,3-dioxygenase (Ido) within the tumor cells. Furthermore, adding immunotherapy (anti-CTLA4 therapy) to imatinib improved the efficacy of the targeted therapy, suggesting that the best clinical outcomes may be seen when combining targeted therapy with immunological-based therapies.

Other therapeutics that target oncoproteins show synergy when combined with immunotherapeutic agents; vemurafenib is one such targeted therapy that is used against BRAF V600E mutant melanoma. The inhibition of BRAF appears to result in immune response alongside the tumor cell response [150]. Immunomodulatory treatment alongside a BRAF inhibitor may lead to a synergistic response [151]; inhibition of BRAF actually increased the tumor infiltration of adoptively transferred T cells [152]. New findings also suggest that following BRAF inhibitor treatment, there is an infiltration of CD4⁺ and CD8⁺ T cells in Stage III and Stage IV melanomas [150]. Increased intratumoral CD8⁺ T cell expression was correlated with a reduction in tumor size and an increase in necrosis within the tumor. An increase in tumor-infiltrating lymphocytes induced by BRAF inhibitor is associated with superior clinical outcomes [150]. Lastly, targeting BRAFV600E appears to diminish the expression of immunosuppressive cytokines and chemokines, such as IL-10, VEGF, and IL-6 [86].

Vemurafenib has been found to preserve the viability and function of lymphocytes [153], suggesting that rational combination therapy should be investigated further. The preserved viability and function of lymphocytes exposed to high concentrations of Vemurafenib suggest that this agent could be a potential candidate for combining with immunotherapy strategies for the treatment of patients with BRAF V600E mutant melanoma. A phase I/II trial combining ipilimumab and vemurafenib has recently begun accruing patients [154] and may provide lasting tumor-free survival.

Targeted Oncogene Inactivation May Activate the Immune System

Precisely how targeted therapies recruit an immune response is not known. However, it is well known that tumor cell death can result in the general activation and recruitment of the immune system [155-157]. Hence, cytotoxic cancer therapies can actually turn the dying tumor cell into a therapeutic vaccine; in mouse models of colon and breast adenocarcinomas, chemotherapeutic agents and radiation therapies have both been found to induce immunogenic cell death [98].

Some chemotherapeutics induce immunogenic cell death [158]. Chemotherapeutics including anthracyclines and oxaliplatin induce immunogenic cell death [159]; furthermore, immunogenic cell death has been observed in mouse models of oncogene inactivation [103]. Cardiac glycosides have been identified as efficient inducers of immunogenic cell death and have intensified the anti-cancer effects of DNA-damaging agents in immune competent, but not immunodeficient, mice [159].

Immunogenic tumor cell death is characterized by the pre-apoptotic exposure of calreticulin (CRT) on the cell surface [97], post-apoptotic secretion of the chromatin-binding protein high mobility group B1 (HMGB1) [160], and release of ATP [161]. CRT, HMGB1, and ATP interact with CD91, TLR4, and purinergic P2RX7 receptors, respectively, which are found on the surface of dendritic cells (DCs). CD91, TLR4, and P2RX7 encourage engulfment of dying tumor cells [162,163], presentation of tumor-associated antigens [164],

and production of interleukin-1 β (IL-1 β), respectively [161,165]. It also appears that autophagy is necessary for optimal ATP release but is not necessary for the generation of other immunogenic signals; autophagy-deficient tumor cells fail to induce a therapeutic immune response [158]. It is possible that for sustained regression, oncogene-targeted therapies must induce immunogenic tumor cell death, or oncogene-targeted therapies might be enhanced through combination with apyrase inhibitors, which enhance local ATP concentrations [158]. Hence, the manipulation of these programs could be important for increasing the efficacy of therapeutics.

Noncanonical Immune Mechanism and Oncogene Addiction

How oncogene inactivation and/or targeted therapy activates the immune system and how this response may be coupled to the subsequent response by specific immune effectors remain to be identified. Understanding these mechanisms could enhance the efficacy of targeted therapeutic strategies. It will be very important to consider that the immune system may be contributing through noncanonical mechanisms such as through the regulation of tumor microenvironment and angiogenesis and the regulation of the programs of cellular senescence. Identifying the specific immune effectors and chemokines may provide novel targets for both therapeutic intervention but also may predict the therapeutic response. For optimal clinical efficacy, the influence of a therapeutic on the host immune status would be critical, particularly since many anti-cancer therapies cause immunosuppression [21]. Combining targeted therapy with immune modulating therapy may have the best possible synergy towards sustained tumor regression [169], leading to increased response rates and longer tumor-free survival [154]. Immunotherapy may further boost the host response to eliminate remaining and potentially therapy-resistant tumor [144,170].

The host immune system appears to contribute to oncogene addiction through influences on tumor intrinsic programs and the general remodeling of the tumor microenvironment. This appears to occur through many mechanisms including specific immune cell effectors such as CD4⁺ T cells and CD8⁺ T cells, particular secreted cytokines such as TSP-1, and particular physiological programs of cellular senescence and host programs of angiogenesis [Figure 1]. However, many questions remain: What is the mechanism of activation of the immune response? The inactivation of an oncogene may cause a tumor cell to express molecules that recruit an immune response. Alternatively, tumor cell death may result in the general activation of the immune response and surveillance [166].

How does the immune system specifically influence cellular senescence and angiogenesis? Direct cellular interactions and/or secreted factors could contribute. The initial cell autonomous senescence of tumor cells may result in the expression of secreted factors that mediate a feedback signaling that elicits a host immune response. For example, factors that modulate senescence can also negatively regulate the differentiation of some types of tumors through the epithelial-mesenchymal-transition (EMT). Regulators of EMT can negatively regulate senescence, creating a “dual negative feedback loop” [168]. Cells that undergo EMT can express a variety of cytokines and other secreted factors that can shut down the immune response, which permits cells that have undergone EMT to evade immunosurveillance [168]. Thus, complex evolving interactions between the tumor and host ultimately dictate the clinical response.

Is the immune contribution to oncogene addiction antigen-driven? Although the initial response appears to be nonspecific, in some cases, it appears at least that an antigen-specific response develops. What are the critical cellular and cytokine factors and are they unique to particular targeted therapies and/or types of cancer? Whether there are general mechanisms or they are unique to each context is not known. Can modulation of specific immune

effectors maximize the response to targeted therapies? Ongoing clinical studies are examining this, but without specific mechanistic insights, it is hard to know what combinations make sense. Finally, wouldn't existing "non-targeted" cancer therapies such as cytotoxic chemotherapy, radiation therapy, and hormonal therapy interfere with the therapeutic response by impeding immune dependent host mechanisms? Indeed, couldn't targeted oncogene therapies have the untoward effects of suppressing the immune response? The combination of therapies could have contradictory consequences. The dissection of the mechanistic contribution to the immune system to oncogene addiction should enable the prediction of the most efficacious therapeutic combinations.

Acknowledgments

The authors acknowledge current and former members of the Felsher laboratory for insightful discussion and for the characterizing the laboratory's many models of oncogene addiction. Within the Felsher laboratory, research has been funded by the Burroughs Wellcome Fund Career Award, the Damon Runyon Foundation Lilly Clinical Investigator Award, NIH RO1 grant number CA 089305, 105102, 170378 PQ22, National Cancer Institute's In-vivo Cellular and Molecular Imaging Center grant number CA 114747, Integrative Cancer Biology Program grant number CA 112973, NIH/NCI PO1 grant number CA034233, the Leukemia and Lymphoma Society Translational Research grant number R6223-07 (D.W.F.). S.C.C. is currently supported by the Stanford University Cellular and Molecular Immunobiology Training Grant (NIH, 5 T32 AI07290).

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Highlights

- Cancers are often oncogene addicted.
- Oncogene addiction is mediated by tumor intrinsic and immune-dependent mechanisms.
- Tumor intrinsic mechanisms include proliferative arrest, apoptosis, and differentiation.
- Immune-dependent programs include CD4⁺ T cells and cytokines
- Combining immune and targeted therapy may be a more effective cancer therapy.

Figure 1.

The interaction between tumor-intrinsic and host-dependent mechanisms in the therapeutic response to oncogene inactivation. The host immune system is required for sustained tumor regression following oncogene inactivation. Immediately after oncogene inactivation, tumor regression occurs in both immune competent and immunodeficient hosts; this is mediated via proliferative arrest, apoptosis, induction of senescence, and the shutdown of angiogenesis. The host immune system, however, plays a crucial role in sustained tumor regression and tumor-free survival through the presence of both CD4⁺ and CD8⁺ T cells, NK cells, and signaling molecules and cytokines released both by local immune mediators and dying tumor cells.

Table 1

Multiple roles for the role immune system in oncogene addiction.

	Oncogene	Tumor Type	Immune Compartment	Immune-Mediated Mechanism	Refs
Adaptive Immunity	<i>MYC</i>	T cell acute lymphoblastic lymphoma	CD4 ⁺ T cells	Induction of senescence and suppression of angiogenesis	[16]
	<i>BCR-ABL</i>	Pro-B cell acute lymphocytic leukemia	CD4 ⁺ T cells	Induction of senescence and suppression of angiogenesis	[16]
	<i>BRAF</i>	Melanoma	Dendritic cells, CTLs	Inhibition of antigen presentation and induction of IL-10, IL-6	[86,171]
	<i>HER-2/NEU</i>	Breast Cancer	CD4 ⁺ , CD8 ⁺ T cells	Antitumor immunity, tumor clearance	[112,113, 172]
	<i>PML</i>	Acute promyelocytic leukemia; prostate carcinoma	CD8 ⁺ T cells	Influencing MHC class I antigen presentation	[84,85]
Innate Immunity	<i>MYC</i>	B cell lymphoma; pancreatic islet cell tumor	Macrophages, Mast cells	Macrophage induction of senescence; mast cell promotion of angiogenesis	[71,102]
	<i>BCR-ABL</i>	Chronic myeloid leukemia	NK Cells	Tumor clearance	[142]
	<i>HER-2/NEU</i>	Breast cancer	NK cells	Cytotoxicity, IFN- γ secretion	[106,110, 112,139]
	<i>P53</i>	Hepatocellular carcinoma	Neutrophils, Macrophages, NK cells	Tumor clearance	[130], [114]
	<i>RAS</i>	Cervical cancer; renal cell carcinoma	Neutrophils	Promotion of angiogenesis and tumor growth due to IL-6 and IL-8	[89,90]
	<i>SRC</i>	Chronic myeloid leukemia	NK cells	Tumor clearance	[141,142]
	<i>MET</i>	Papillary thyroid carcinoma	Macrophages, Mast cells	Induction of inflammatory program, Increases tumor invasion/metastasis	[83,88]