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Review

Exploiting the balance between life and death: Targeted cancer therapy and "oncogenic shock"

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ABSTRACT

Rational approaches to targeted cancer therapy have begun to predominate the pipelines of oncology drug development. Our rapidly increasing understanding of the "wiring" of tumor cells and the vulnerabilities of such cells that can potentially be exploited through targeted treatments has opened up enormous opportunities for improved therapies. Accumulating evidence suggests that many of these vulnerabilities reflect states of dependency or "addiction" that are unique to cancer cells (versus normal cells). Such addiction can arise due to a strict dependency on a single activated oncogene, a cell lineage-specific factor, or even to a non-oncogene, and identifying these "Achilles' heels" within individual tumors remains an important challenge to the development of targeted therapies. Recent technology advances that facilitate high-throughput genomic analysis of tumor specimens and genome-wide RNA interference screening in cancer cell lines are key among the newly developed tools that are beginning to reveal novel context-dependent therapeutic targets, and the rapidly increasing application of these technologies by a large number of laboratories will undoubtedly lead to more effective cancer therapies in the near future. Here, we review the various forms of cancer cell addiction and their relevance to the discovery of novel therapeutic targets.

Contents

1. Introduction

1.1. Balance between life and death: a recurrent theme in biological systems

Maintaining the delicate balance between life and death is one of the most important pre-requisites of a sustainable and healthy ecosystem. Perturbation in this balance leads to predominance of a

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species and, depending on the resilience of the ecosystem, can result, ultimately, in the collapse of the ecosystem. Similarly, this balance is also crucial for the health and survival of each member within this ecosystem and is particularly important for multi-cellular organisms, including humans. It is estimated that the average adult human body generates anywhere from 60 to 300 billion new cells daily. It thus stands to reason that a similar number of cells must die if we are to maintain our size. Thus keeping a balance between life and death is a vital part of normal existence for all multi-cellular organisms. This truism, at the organismal level, also extends to the tissues that comprise the organism and ultimately the cells that comprise the tissues. For tissues to maintain a normal size, generation of new cells has to be finely balanced with elimination of old ones, so that the net gain in cell numbers is close to zero. However, this system also has to be flexible such that, under conditions that require growth of the tissue (e.g., liver regeneration), the balance is tipped in favor of new cell generation, whereas conditions that require the elimination of cells (e.g., during T-cell maturation or during certain stages of development) the balance is tipped in favor of cell death. Extending the analogy to individual cells, normal cellular homeostasis is maintained by establishing a fine balance between signaling pathways that trigger cell survival and those that activate cell death pathways. Thus, the balance between life and death signals is an overarching theme that is at the heart of the optimal functioning of all biological systems. The precise orchestration of both survival and death pathways and the intricate control they exert over each other is essential for a variety of normal biological processes such as growth, development, morphogenesis, tissue injury and repair. Imbalances or disruption of this delicate balance leads to a variety of pathological conditions, including cancer.

1.2. Signals regulating the life and death balance in normal cells

At the molecular level, cell growth, as well as cell death, is stringently controlled by signal transduction pathways. While a plethora of extra-cellular signals triggered by growth factors and cytokines promote cell survival through their action on cell surface receptors, most of these inputs quickly converge on a relatively small number of key survival "nodes", including among others, PI3K/AKT (reviewed in [1]), RAS/RAF/ERK (reviewed in [2]), STAT (reviewed in [3,4]) and PKC (reviewed in [5,6]). The signal transducers that comprise these pathways function as relays (consisting of "nodes" and "amplifiers"), propelling the signal from the cell surface to critical intracellular "effectors" by a variety of post-translational modifications, including protein-protein interactions and phosphorylations. Besides these key pro-survival pathways, there are also a few key anti-apoptotic (hence pro-survival) transducers of the Bcl-1 family, such as Bcl2, Bcl-xL, Bcl-w, Mcl1 and A1 (reviewed in [7,8]), that play important roles in determining the balance between life and death of the cell (Fig. 1). Likewise, an equally large number of signals can also lead to the demise of the mammalian cell, primarily through a complex form of programmed cell death, apoptosis, which is classified into four basic types: (i) extrinsic or receptor mediated (ii) intrinsic or mitochondria-mediated (iii) caspase-dependent (iv) caspase-

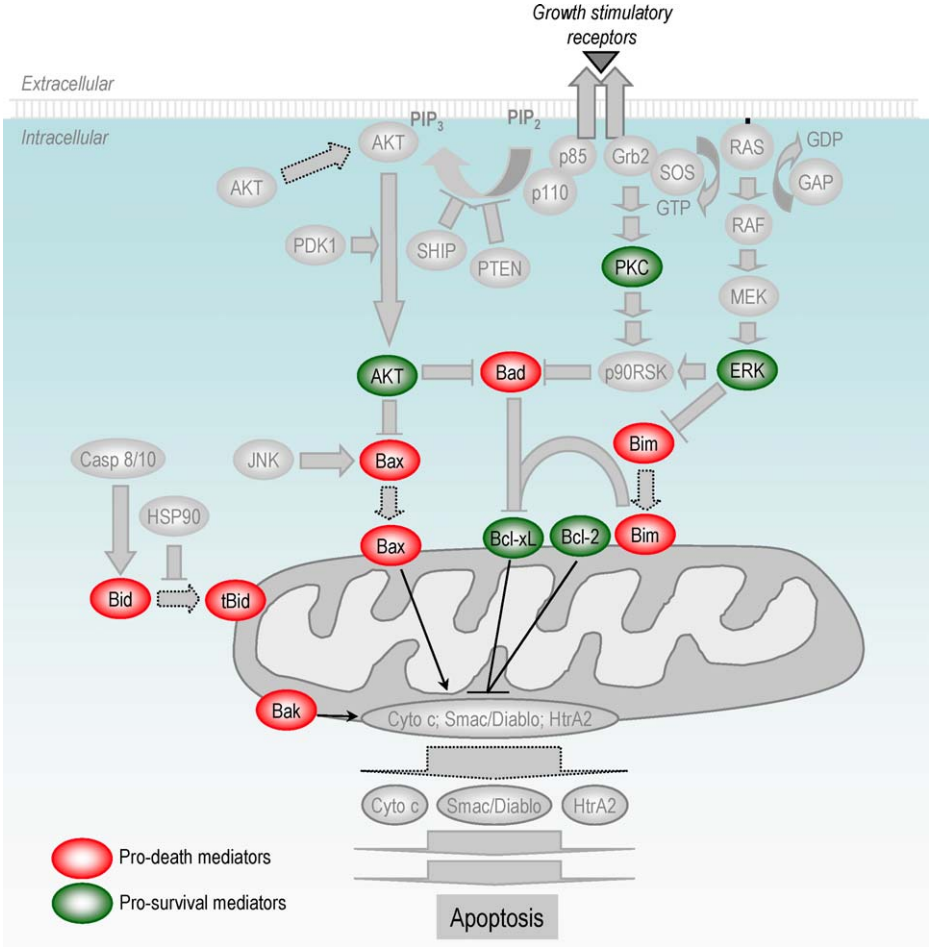


Fig. 1. Balance between pro-survival and pro-death mediators. Three important cell survival pathways (mediated by AKT, ERK and PKC kinases) that operate downstream of activated transmembrane receptor tyrosine kinases along with some of the key constituent signaling molecules are illustrated. Key pro-survival mediators are shown in green and key pro-death mediators are shown in red. Dashed arrows indicate change in subcellular localization.

independent or perforin/granzyme A-mediated (reviewed in [9]). Apoptotic cell death is facilitated by a variety of pro-apoptotic mediators that include, members of the Bax subfamily (Bax, Bak and Mtd/Bok) as well as members of the BH3-only subfamily (Bik, Hrk, Bim, Blk, Bad, Bid, and BNIP3) and Bcl-xS (reviewed in [7,8]) that need to be held in check by pro-survival mediators in order to maintain cell viability (Fig. 1). Extending the analogy to ecosystems, apoptosis is not cell death resulting from an overwhelming system-wide failure of the cell but a highly regulated "decision" by the cell to self-destruct.

Cells can also die by a variety of non-apoptotic mechanisms such as necrosis, mitotic catastrophe and autophagy (reviewed in [10,11]). Given that cancer cells actively suppress apoptotic pathways, it has been proposed that activation of these alternative cell death pathways may be a powerful way to kill cancer cells. However, the mechanisms that drive these pathways are relatively poorly understood and hence exploiting these pathways to our advantage in treating cancer remains challenging. Be that as it may, the basic fact is that in a viable cell, the pro-survival mediators counterpoise the pro-death signal transducers, often in complex regulatory networks, thereby negating their lethal effects, and the net result is therefore cell viability (Fig. 1). In this context, it is important to note that a normal cell has the capacity to receive and process, simultaneously, a multitude of growth stimulatory signals (in the form of survival factors, growth factors, cytokines, etc.) that engage a large number of cell surface receptors and activate pro-survival pathways to maintain cell viability. Therefore, the inhibition of any single growth stimulatory signal in a normal cell may go unheeded, given the large numbers of alternative signals that are operational in activating pro-survival pathways and maintaining cell viability. This is one of the key differences between normal and cancer cells and, if appropriately exploited, offers a rare opportunity to selectively target the cancer cell.

1.3. Balance between life and death in cancer cells: oncogenes at the fulcrum

Studies conducted over the past 50 years have resulted in a deeper understanding of the inner workings of the normal cell and an intimate knowledge of pathways that are deregulated in various pathological conditions, such as cancer. One of the fundamental discoveries to emerge from these studies is the realization that cancer-causing oncogenes are in fact mutated versions of cellular genes, known as proto-oncogenes (reviewed in [12,13]). Subsequent biochemical analyses have unequivocally shown that activated/mutated oncogenes are enzymatically similar, albeit much more potent and unregulated versions of proto-oncogenes (reviewed in [14]), and in many cases hyperactivate cell survival pathways while simultaneously suppressing cell death pathways [15–17]. As discussed in the preceding section, a normal cell is maintained by a variety of pro-survival signals. The introduction of an activated oncogene, one that drives one particular growth stimulatory signal, into a normal cell milieu has two important consequences. First and foremost, given its potent nature, it often becomes the predominant growth stimulatory signal-generating molecule in the cell, and in a sense, hijacks the cell survival apparatus. Second, over time, all other growth stimulatory pathways of the cell may become insignificant or redundant, perhaps through disuse, and the cancer cell is now said to be "addicted" to the oncogene, with its survival being strictly dependent on the presence of the oncoprotein. Thus, through the action of the activated oncogene, a normal cell becomes a rogue cancer cell that has a growth advantage due in part to its resistance to apoptotic stimuli.

1.4. Exploiting the balance between life and death in cancer cells; targeting mutated oncogenes as an anti-cancer strategy

Beginning in the middle of the 20th century, cancer has been treated with cytotoxic agents, many of which constitute the mainstay of anti-cancer chemotherapeutic strategy, even today (reviewed in [18]). The realization that mutated oncogenes were the drivers of cancer shifted the focus away from non-specific poisons and led to major efforts aimed at the discovery and development of a new generation of targeted therapeutics that focused on components of the signal transduction pathways that are altered in cancer cells. This approach was based on the initially simplistic assumption that since oncogenes represented hyperactive forms of proto-oncogenes, inhibitors of the enzymatic activity of these proteins might prove useful in controlling the cellular activity of oncoproteins, and by extension, the cancer cell. Of the signal transduction mediators, protein kinases, due to their importance in the etiology of cancer (reviewed in [19]), quickly emerged as front-runners, and selective kinase inhibitors have gained pre-eminence as important anti-cancer agents (reviewed in [20]). Table 1 presents several such small-molecule inhibitors, the

Table 1
Examples of kinase-targeted therapeutics, the kinases they target and their clinical development stage.

Agent	Target kinase	Development stage
Imatinib (STI-571, CGP-57148, Gleevec)	ABL, PDGFR-β, C-KIT	Licensed: GIST, CML, Phase I/II/III
Nilotinib (AMN-107, Tasigna)	ABL, PDGFR-β, C-KIT	Licensed: CML, Phase III (GIST), Phase I/II
Dasatinib (BMS-354825, Sprycel)	ABL, SRC	Licensed: CML, ALL; Phase I/II/III
Gefitinib (ZD-1839, Iressa)	EGFR	Licensed: 2d- or 3rd line NSCLC (Asia)
Erlotinib (OSI-774, Tarceva)	EGFR	Licensed: 2d- or 3rd line NSCLC (Asia and US), advanced pancreatic cancer
Lapitinib (GW-572016, Tykerb)	EGFR, HER-2	Licensed: breast, Phase I/II/III
Sunitinib (SU11248, Sutent)	VEGFR, PDGFR, C-KIT, FLT-3	Licensed: RCC, imatinib-resistant/-intolerant GIST
Sorafenib (BAY43-9006, Naxavar)	VEGFR, PDGFR; C-RAF-1, B-RAF	Licensed: advanced RCC, HCC, Phase I/II/III
Lestaurtinib (CEP-701)	FLT-3, TRK-A, JAK-2	Phase III (AML), Phase I/II
Seliciclib (R-roscovitine, CYC-202)	CDKs	Phase II (NSCLC, MM, lymphoid leukemia, mast cell leukemia), Phase I
PD-0332991	CDK4, CDK6	Phase II (multiple myeloma), Phase I
Enzastaurin (LY-317-615)	PKC-β, GSK-3, AKT	Phase III (glioma, non-Hodgkin lymphoma), Phase I/II
Leflunomide (SU101, Arava)	PDGFR, EGFR, FGFR	Phase II/III (prostate cancer, GBM)
NVP-AEW-541 (AEW-541)	IGF-1R	Phase I
MLN-8054	Aurora kinase	Phase I

Abbreviations: GIST, gastrointestinal stromal tumors; CML, chronic myelogenous leukemia; ALL, acute lymphoblastic leukemia; NSCLC, non-small cell lung carcinoma; RCC, renal cell carcinoma; HCC, hepatocellular carcinoma; AML, acute myeloid leukemia; MM, multiple myeloma; ABL, abelson oncogene; PDGFR, platelet derived growth factor receptor; KIT, KIT oncogene; SRC, sarcoma oncogene; EGFR, epidermal growth factor receptor; HER-2, human epidermal growth factor receptor-2; VEGFR, vascular endothelial growth factor receptor; FLT, FMS-like tyrosine kinase; IGF-1R, insulin-like growth factor 1 receptor; FGFR, fibroblast growth factor receptor; GSK, glycogensynthase kinase; PKC, protein kinase C; CDK, cyclin-dependent kinase; JAK, janus kinase; TRK, neurotrophictyrosinekinase.

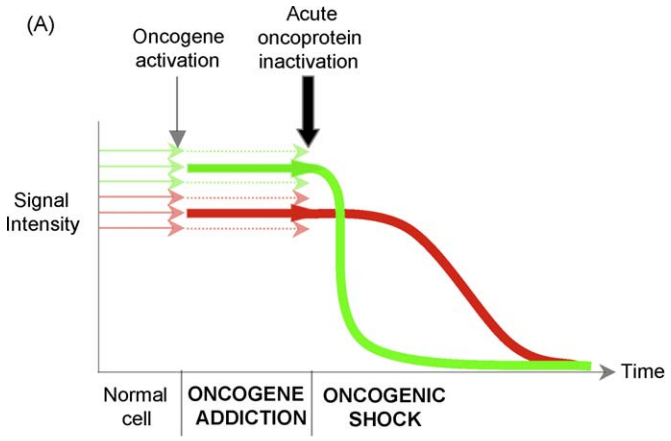
kinases that they target, and their current status in the drug development process.

The now classic example in this arena is imatinib, a small molecule inhibitor that targets the Bcr-Abl oncogenic tyrosine kinase in Chronic Myelogenous Leukemia (reviewed in [21–23]. However, the clinical deployment of many of these agents revealed very quickly that, except in rare cases, only a small subset of patients respond to these inhibitors, quickly dampening the enthusiasm surrounding these agents. The silver lining around this dark cloud was the fact that the small fraction of tumors that did respond were largely characterized by massive apoptosis of the tumor cells, with surprisingly limited effects on normal tissues. This unexpected stroke of serendipity was all the more remarkable considering that many of these inhibitors target kinases that are, in most cases, ubiquitously expressed. The reason for the differential sensitivity observed in normal versus cancer cells upon kinase inhibition remains an enigma that is the subject of much investigation. In recent years however, a concept known as "oncogene addiction" has emerged that may provide clues to explain the dramatic clinical responses to many kinase-targeted therapeutics in tumors with mutationally activated kinases—and possibly extends to other classes of therapeutics.

1.5. Oncogene addiction

The oncogene addiction hypothesis was first proposed by Dr. Bernard Weinstein, who suggested that, "because of their bizarre circuitry, cancer cells suffer from 'gene addiction' and 'gene hypersensitivity' disorders that might be exploited in both cancer prevention and chemotherapy" [24–26]. Evidence for addiction to a large number of dominant-oncogenes as well as addiction to the lack of tumor suppressor genes (a.k.a. "tumor suppressor hypersensitivity") has emerged from a variety of sources such as human cancer-derived cell lines as well as mouse models. In the case of dominant oncogenes, acute inactivation of the oncogene was achieved by a variety of methods such as RNA interference, inducible expression systems, small-molecule inhibitors, antibodies and dominant-negative interference. Demonstration of tumor suppressor hypersensitivity involved reintroduction of the wild type form of the tumor suppressor, stabilizing the wild-type protein, or even converting the mutant version of the tumor suppressor protein to a functioning form. Such studies have been extensively reviewed elsewhere [27].

Among the oncogenes most clearly implicated in the oncogene addiction phenomenon are those that encode protein kinases. While the mechanistic details of oncogene addiction remain to be elucidated, one fact that has emerged from numerous lines of investigation is that mutationally activated kinases appear to transduce excessive survival signals through signal transduction pathways controlled by pivotal proteins such as AKT, ERK and STAT (not itself a kinase), and suppressing these signals with kinase-inhibitory drugs causes a cessation of proliferation, specifically of the cancer cells, but not of normal cells by a variety of mechanisms such as growth arrest, differentiation, senescence or apoptosis (reviewed in [28]). This observation then begs the question as to why mutationally activated kinases are such good drug targets and why does their attenuation have anti-proliferative effects specifically in cancer cells? While it was known for some time that oncogenic kinases produce very strong pro-survival signals, more recent studies have uncovered a less intuitive fact, that they also produce potent pro-apoptotic signals (Fig. 2B). Thus, in the context of an oncogene-addicted cancer cell, the driving oncogene plays a pivotal role in the survival of the cancer cell by finely balancing life and death signals within the cell. While it is fair to say that many instances of tumor regression following anti-cancer therapy are attributable to oncogene addiction, the molecular underpinnings that drive this crucial process are not understood. Gaining a better understanding of oncogene addiction is key to more effectively deploying anti-cancer therapeutics. Below are some of the current models that have been put forth in an attempt to form a molecular framework for oncogene addiction.



(B)

ONCOGENE	REFERENCE
Oncogenic Transcription factors	
MYC	[68-69]; [79]
E2F1	[80-82]
JUN	[83-85]
FOS	[86-87]
MYB (p75 splice variant)	[88]
Tumor Suppressors	
RB	[89]
P53	[90-92]
Oncogenic Kinases	
RAF	[93-95]
SRC	[96-97]; [66]
ABL	[98]; [66]
EGFR	[66]
ALK	[99]
MET	[100]
RET	[101]
Oncogenic G-proteins	
KRAS	[102]
HRAS	[103-106]
RRAS	[109]
Viral oncogenes	
E1A	[107]
papillomavirus E7	[108]

Fig. 2. (A) Relationship between oncogene addiction and oncogenic shock. In normal cells, pro-survival signals (thin green arrows) predominate and keep the various pro-apoptotic stimuli (thin red arrows) in check, thus leading to normal cell homeostasis. In cancer cells, the activation of an oncogene can yield an oncogene addicted cancer cell. In oncogene addicted cancer cells, the pre-eminence of an oncoprotein may result in the "atrophy" of other survival (dashed green arrows) and death (dashed red arrows) signals and the dominance of oncoprotein-dependent survival (thick green arrow) and death (thick red arrow) outputs. Even in this oncogene-addicted state, the survival outputs from the actively signaling oncoprotein predominate, thereby keeping potential oncoprotein-induced death signal in check. Upon acute inactivation of the oncoprotein, "oncogenic shock" arises due to differential signal attenuation. Thus, cancer cells experience a signal imbalance associated with the rapid attenuation of oncoprotein-generated pro-survival signals, while the oncoprotein-induced pro-apoptotic signals linger sufficiently long such that the cell becomes committed to an apoptotic death. (B) Examples of oncogenes demonstrating pro-apoptotic capabilities in addition to their oncogenic activity.

1.6. Models for oncogene addiction: synthetic lethality

In an effort to explain the curious observation that attenuation of mutated oncogenes in cancer cells leads specifically to the demise of the cancer cell, a concept known as synthetic lethality was put forward (reviewed in [29]). The concept of synthetic lethality, originally discovered in model organisms such as yeast and flies, proposes that two genes are said to be synthetic lethal if mutation of either one of the two genes is compatible with viability but mutation of both genes results in cell lethality [30–32]. Thus, in a cancer cell driven by a mutated oncogene (first mutated gene in the synthetic lethal pair), synthetic lethality would predict that there are other genes (second genes which are in synthetic lethal relationship with the mutated oncogene) whose attenuation would specifically kill the cancer cell but leave other normal cells (without the mutated oncogene) unaffected (reviewed in [33,34]). One of the most striking proofs-of-concept for this approach is exemplified by the extreme sensitivity of breast cancers deficient in the tumor suppressors BRCA1 or BRCA2 to inhibitors of poly(ADP-ribose) polymerase-1 (PARP1) and the translation of this concept to the clinic [35–37].

Using unbiased genome-wide screens (with chemicals or siRNA) investigators have attempted to uncover new genes engaged in synthetic lethal interactions with known oncogenes such as mutant K-RAS, revealing genes such as voltage-dependent anion channels [38–40], STK33 and TBK1 [41,42] and polo-like kinase PLK1 [43]. Similarly, other studies have shown that renal cell carcinoma cells lacking von Hippel-Lindau tumor suppressor protein (pVHL) show extreme sensitivity to mTOR (mammalian target of rapamycin) inhibitors [44]. Thus, synthetic lethality screens have the ability to identify crucial genes whose inactivation can potentially lead to the specific demise of the cancer cell. The next challenge will be to validate these targets in cancer patients to ensure that the lessons learnt from *in vitro* synthetic lethal screens will find application in the development of novel strategies for targeted anti-cancer therapy.

1.7. Expanding the target range for targeted anti-cancer therapy: "non-oncogene addiction"

In recent years the term "non-oncogene addiction" has been proposed and refers to the fact that cancer cells might harbor potential therapeutic targets that do not correspond to oncogenes *per se* but constitute proteins to which the cancer cell is similarly addicted [45]. Thus, these might serve as additional targets whose attenuation might enable the selective elimination of cancer cells. According to this model, potential targets that might confer non-oncogene addiction are those that are hyperactive in cancer cells and are believed to be engaged in specifically supporting the growth of cancer cells i.e., pathways involved in stress (mitotic, proteotoxic, metabolic, oxidative, DNA replication, etc.), angiogenesis and stromal signaling, to name a few [46]. Thus, by this definition, any effective anti-cancer agent that does not specifically target an oncogene-encoded protein is believed to be acting by disrupting non-oncogene addiction. In some sense, non-oncogene addiction is very much related to synthetic lethality, in that non-oncogene addiction presumably reflects a vulnerability of cancer cells that is context-dependent. Examples of agents that potentially target a state of non-oncogene addiction would include most conventional chemotherapy agents as well as inhibitors such as geldanamycin (targets hsp90), AP12009 (targets TGFβ2), AZD2281 (targets PARP1), bevacuzimab (targets VEGF), botrezomib (targets the proteasome), celecoxib (targets cyclooxygenase 2), mapatumumab (targets TRAIL receptor), PF-00477736 (targets chk1), and rapalogs (target mTOR) [46]. Recent studies have extended the range of potential non-oncogene targets to include the molecular chaperone HSP70 [47,48]. However, using inhibition of molecular chaperones to argue for non-oncogene addiction must be interpreted with caution since many of these chaperones play a direct or indirect role in the conformational maturation of oncoproteins, and the lines between oncogene and non-oncogene addiction can therefore become blurred. It could also be argued that the recent discovery of the preferential expression of the M2 isoform of pyruvate kinase in cancer cells [49] or mutations in isocitrate dehydrogenase that lead to overexpression of 2-hydroxyglutarate in low-grade glioblastomas [50] are additional examples of non-oncogene addiction. Be that as it may, if this principle can be extended to the clinical setting, it should vastly expand out repertoire of potential targets that can be used in anti-cancer intervention strategies.

1.8. "Lineage addiction"

The oncogene addiction model recently gave rise to a related hypothesis known as "lineage addiction", which attempts to explain the strict requirement for certain lineage specific genes in tumorigenesis [51,52]. Using high-resolution genome maps of the NCI60 collection of tumor-derived cell lines, these studies identified the microphthalmia-associated transcription factor (MITF) and surmised that it confers lineage dependency and enables the survival of cells specifically of the melanocyte lineage [53,54]. Consistent with this hypothesis, MITF is amplified in a subset of melanomas and functions in concert with oncogenic BRAF to regulate melanoma proliferation [55]. That MITF confers melanocyte lineage addiction, specifically in melanomas, was based on the rationale that, whereas over-expression of MITF in primary melanocytes induces cell cycle arrest [56], proliferating melanoma cells over-express this protein. Thus MITF appears to confer cell cycle arrest (in normal melanocytes) or proliferation (in melanomas) in a context dependent manner, suggesting that the cancerous melanoma cells have uncoupled the pro-survival effects of MITF from its growth-inhibitory effects, and suggest a tumor lineage-specific (melanoma) dependency for MITF. Consistent with such dependency, melanoma cell proliferation is inhibited by simultaneous inhibition of MITF and BRAF [57]. In general, lineage dependency genes appear to induce proliferation in the tumor cells from a particular cell lineage, but differentiation (consequent cessation of proliferation) in their normal cellular counterparts. Other examples of genes that engender lineage dependency include cyclin D1 in breast cancer [58]; FLT3 in acute leukemia [59]; androgen receptor in prostate cancer [60]; TITF1 in lung cancer [61,62] and perhaps CDX1 in intestinal cancer [63,64] and ETS-1 in breast cancer [65]. The majority of the lineage dependency genes identified thus far correspond to lineage restricted transcription factors (reviewed in [51]). Unfortunately, this class of proteins is not readily "druggable", and it remains to be seen whether the identification of additional lineage addiction genes will yield clinically useful cancer therapeutics.

1.9. Molecular basis for targeted therapeutics: oncogene addiction and oncogenic shock

As stated earlier, the oncogene addiction hypothesis postulates that disruption of an oncogene in an oncogene addicted tumor cell results in cessation of proliferation of the tumor cell by as yet unexplained mechanisms. However, in most cases of targeted therapy that induce "tumor shrinkage" the response is primarily apoptotic. In such cases, it is not clear whether pro-apoptotic signals from oncogenic kinases actively kill drug-treated tumor cells or whether death resulted merely as a consequence of elimination of the survival signals upon attenuation of the oncoprotein by a targeted therapeutic. To distinguish between these two possibilities, as well as to gain a better understanding of the molecular

underpinnings of oncogene addiction, a variety of *in vitro* systems associated with oncogene addiction, such as BCR-ABL-, EGFR- and SRC-transformed cells were examined. In all of these systems, it was observed that, upon acute inactivation of the oncogenic kinases, pro-survival and pro-apoptotic signals decayed at different rates, with the survival signals decaying much more rapidly than the apoptotic signals [66]. Based on these studies, a concept known as "oncogenic shock" was proposed which, together with the "oncogene addiction" model, provides a molecular hypothesis to explain the response to many targeted therapeutics (reviewed in [27]).

It is important to consider that oncogene addiction refers to the state of the cancer cell before exposure to the therapeutic, and oncogenic shock refers to the apoptotic effects resulting from treatment of the addicted cancer cell. In this regard, the two concepts (oncogene addiction and oncogenic shock) go hand-in-hand and are not mutually exclusive. As shown in Fig. 2A, in normal cells a variety of pro-survival signals (shown in green) emanating from numerous signaling kinases keep pro-death signals (shown in red) in check. Upon the introduction of a dominant oncogene into the cell, the pro-survival (as well as the pro-apoptotic) signals become focused on this oncogene, and over time, perhaps due to the potent nature of the dominant oncogene, other pro-survival and pro-death signals gradually disappear and the cancer cell becomes solely dependent upon the oncogene for its survival, and is said to be in an "oncogene addicted" state. Upon acute inactivation of the oncoprotein (either by a small molecule drug, an antibody directed against the oncoprotein or a variety of other means) the pro-survival signals, such as activated AKT, ERK1/2 and STAT-3/5 decay very rapidly (within minutes), whereas pro-apoptotic signals decay much more slowly (in the time-scale of hours) [66]. The resulting imbalance leads to a brief period during which pro-apoptotic signals exceed pro-survival signals within the cell, resulting in "oncogenic shock".

Notably, the term oncogenic shock is primarily restricted to targeted therapeutics (i.e., therapeutics that cause tumor cell apoptosis) and does not explain other outcomes of oncogene inactivation in oncogene addicted cancer cells, such as cessation of cell proliferation due to growth arrest, differentiation or senescence [26]. Implications of the oncogenic shock model for anti-cancer therapeutics are numerous. First, this model suggests that the death of the "addicted" cancer cell upon acute oncogene inactivation is an active process as opposed to a passive process whereby the cell simply dies by the removal of pro-survival signals; i.e., pro-death signals from the activated oncoprotein are actively killing the cell. Second, this model can explain why mutationally activated or amplified oncogenes are such good targets for anti-cancer drugs. Hyperactive oncogenes transduce not only excessive pro-survival signals but also deliver a potent pro-apoptotic punch. Third, it highlights the importance of identifying additional activating kinase mutations in human tumors since they could serve as novel therapeutic targets. Fourth, acute transient inhibition ought to be as effective as continuous inhibition of the target and argues for pulsatile dosing as opposed to the continuous dosing that is commonly employed currently. Stated another way, this point argues in favor of potent inhibitors with short half-lives as opposed to weaker inhibitors with a longer half-life. This last point has undergone some clinical validation in the context of chronic myeloid leukemia patients, wherein it was demonstrated that transient potent BCR-ABL inhibition is equivalent to prolonged target inhibition in committing tumor cells irreversibly to apoptosis [67].

1.10. The apoptotic function of oncogenes: the dark side of the force

One of the important tenets of the Oncogenic Shock model is the requirement that oncogenes transduce pro-apoptotic signals. While the pro-survival role of oncogenes is a well-established function, the counter-intuitive pro-apoptotic activity of oncogenes was first identified for the MYC oncogene [68–70]. These studies collectively showed that oncogenic MYC induced apoptosis only in the absence of other serum survival factors, which, in all likelihood, probably promoted addiction of the cells to the MYC oncogene by eliminating all other growth stimulatory inputs. Thus, under appropriate conditions, it was possible to uncover the pro-apoptotic function of oncogenes. MYC-induced cell death is mediated by the pro-apoptotic BAX, since BAX disruption appears to abrogate this process [71]. Similarly, over-expression of BCL-2 blocks MYC-induced apoptosis both *in vitro* [72] and *in vivo* [73]. Thus, cell survival or death in the context of the MYC oncogene involves an intricate interplay between pro-survival and pro-death signals. The pro-apoptotic function of the MYC oncogene has also been studied extensively in mouse models using inducible systems to turn on or off the oncogene at will [74,75]. Since the initial reports of this functional duality (i.e., both pro-survival as well as pro-apoptotic) in the case of the MYC oncogene, similar findings have now been documented for a large number of oncogenes (Fig. 2B) and it would not be surprising to discover that all oncogenes as well as tumor suppressor genes would be eventually found to exhibit this duality of function, under appropriate conditions. Thus, the emerging picture is one in which the cancer cell is operating at its maximal proliferative capacity, delicately balancing cell-survival with cell-death but teetering on the brink of an apoptotic event. Consequently, it becomes critical to determine exactly how to "pull the trigger" that sets this apoptotic cascade into motion, specifically in these oncogene-addicted cancer cells.

1.11. Modeling oncogene addiction in cultured cells to uncover genotype-associated drug sensitivity

Significantly, all the studies leading to the proposal of the oncogenic shock model were conducted *in vitro*, utilizing cell lines derived from human tumors, suggesting that human tumor cell lines are robust models of oncogene addiction. That this phenomenon persists at all in human tumor derived cell lines growing in culture was somewhat surprising given the genetic drift that is such an integral part of cancer and when considering the growth of these cell lines under non-physiological conditions (i.e., on plastic, in semi-synthetic medium) often for decades, passing through different laboratories and different hands. The persistence of oncogene addiction under such artificial circumstances suggested that the phenomenon was probably strongly selected for preservation because of its usefulness to the survival of the cell. In addition, the demonstration of oncogene addiction and oncogenic shock in cell lines suggested that this phenomenon is cell autonomous and is a direct response to acute oncogene inactivation, and that this is largely independent of external factors such as tumor–stromal interactions, etc. This therefore provided a rationale for using human cancer cell lines in high throughput screens to analyze the genetic basis of oncogene addiction and genotype-associated drug sensitivity in cancer cells. Such an analysis is ongoing at the Center for Molecular Therapeutics at the Massachusetts General Hospital Cancer Center and the strategy that is employed is to profile a large panel of human cancer cell lines with molecularly targeted agents to identify subsets of oncogene addicted and treatment-sensitive lines. The goal is to identify genotypes correlated with treatment sensitivity to guide clinical testing and therapy decisions. These studies have revealed that, at least for the selective kinase inhibitors, it is possible to employ this strategy broadly to reveal genotype-associated drug sensitivities that recapitulate clinical findings (reviewed in [76]). This is best exemplified by the demonstration that NSCLC lines with greatest erlotinib sensitivity are enriched for EGFR mutations [77] and ALK translocations are associated with sensitivity to ALK inhibitors in NSCLC [78].

The substantial genomic heterogeneity among human cancers—even those of similar histology—is becoming increasingly apparent, and cell line studies, such as those described above, have highlighted the strong association between underlying genomic features of tumors and their response to various molecularly targeted therapies. Taken together with the clinical findings in studies of many such agents, which often demonstrate activity limited to a subset of treated patients, such observations have begun to reveal the critical role of patient stratification prior to treatment in order to maximize the clinical benefit of these agents. As investigators continue to develop a better understanding of tumor genomics and their relationship to states of addiction, the prospects for the development of more effective cancer therapies will undoubtedly improve.

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