Chapter

Targeting Oncogene Addiction for Cancer Therapy

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Abstract

Oncogene addiction, a term first coined by Bernard Weinstein in 2000, refers to a condition where a tumor cell, despite harboring a multitude of genetic alterations, depends on a single oncogenic pathway or oncoprotein for sustained proliferation and survival. Several lines of evidence from mammalian cell culture models, genetically modified mice models, and human intervention trials of targeted drugs have revealed that many tumors, if not all, rely on oncogene addiction for sustained proliferation and survival. Oncogene addiction strongly impacts the therapeutic response of tumors to acute oncoprotein inhibition. An important implication of oncogene addiction is that inhibiting this critical pathway, on which cancer cells become dependent, can cause selective and specific cell death in cancer cells while sparing normal surrounding cells that are not oncogene addicted. However, the mechanism by which cancer cells become dependent on a single pathway or activated oncoprotein is not precisely understood in most cases. Thus, a better understanding of oncogene addiction may provide a rationale for improving current cancer therapies and help develop novel therapeutic strategies for the management of cancer.

Keywords: oncogene, oncogene addiction, cancer, targeted drugs, therapy

1. Introduction

Many cellular programs and signaling pathways that are normally used during development are reactivated and modified by cancer cells to acquire sustained proliferative characteristics. During embryogenesis and tissue homeostasis, these programs regulate coordinated actions, such as cell proliferation, cell polarity, migration, differentiation, and apoptosis. Cancer evolves with random mutations and epigenetic modifications in these pathways, followed by clonal selection of genetically altered cells that can survive and reproduce in conditions that would ordinarily be harmful [1]. Although several oncogenes (such as PI3K and RAS) and tumor suppressors (such as p53, PTEN, Rb, and p16INK4a) are typically altered in cancer cells, there appears to be a huge number of low-frequency genetic alterations that can contribute to tumorigenesis. Indeed, evidence from tumor sequencing initiatives reveals a staggering range of mutations in cancers [2]. The malignant phenotype of cancer cells depends significantly on the rewiring of metabolic pathways and survival pathways. As a result, identifying important functional nodes in the oncogenic signaling network whose blockage would result in system failure, that is, the end of the tumorigenic state via apoptosis, necrosis, senescence, or

differentiation, is critical to successful therapy [3]. Furthermore, therapeutic drugs targeting these nodes must have a big enough therapeutic window to destroy tumor cells while sparing normal surrounding cells from damage. Many tumors are highly dependent on a single oncogenic pathway for sustained proliferation and survival, a condition known as oncogene addiction. The term "oncogene addiction" was first described by Bernard Weinstein to describe the dependence of certain tumor cells on a single activated oncoprotein or signaling pathway, despite harboring multiple gain-of-function mutations and loss-of-function mutations that contribute to the malignant phenotype, to maintain their malignant behavior [4]. Various xenograft models and genetically engineered mice models have revealed that many oncogene-driven tumors, if not all, undergo tumor regression, growth arrest, differentiation, and/or apoptosis in response to acute inhibition of oncoprotein function [5]. The process of oncogene addiction, irrespective of mechanistic basis, contributes significantly to the clinical activity of various drugs that have recently been observed following treatment with so-called "rationally-targeted" agents. The purpose of cancer therapeutics is to specifically target the mutations that initiate and maintain the proliferation and survival of cancer cells. Although the majority of cancers are known to possess multiple oncogenic mutations, many cancers are sensitive to targeted inhibition of a single oncogene, a phenomenon known as oncogene addiction [6]. Oncogene addiction supports the growth of cancer cells, signifying the role of oncogene-targeted therapies in cancer management. However, in many cases, resistance to oncogene-targeted therapies develops which limits the therapeutic targeting of oncogene addiction in clinical settings. Luckily, oncogene addiction offers several opportunities that can be utilized for achieving therapeutically useful outcomes [7]. Oncogene addiction is seen in several cancers. An important example is chronic myelogenous leukemia (CML), a disease driven by the BCR-ABL mutant oncogene. The mutant BCR-ABL fusion gene encodes for a type of enzyme known as tyrosine kinase which stimulates uncontrolled growth of leukemic cells. The addiction of CML to BCR-ABL is apparent from the profound clinical response of patients to imatinib, a drug that targets BCR-ABL. This addiction of CML to BCR-ABL is also noticeable from the reactivation of BCR-ABL kinase activity which imparts drug resistance to CML [8]. Observations of this type furnish proof for the concept of oncogene-targeted cancer therapy. It may appear insignificant that a tumor cell can be dependent on a single protein that contributed to the malignant phenotype at some time in its history. Somatic deletion of the KRAS oncogene in human colorectal cancer cells with a KRAS mutation causes reversion of the transformed phenotype and eliminates the capacity of these cells to develop tumors in nude mice [9]. Drugs targeting the appropriate proto-oncogene should be effective in treating cancers lacking the tumor suppressor in circumstances where a tumor suppressor negatively regulates the activity of a proto-oncogene. PI3K inhibitors are expected to be responsive in cancers that have lost the tumor suppressor and lipid phosphatase (PTEN), which acts to prevent PI3K activation [10]. Loss of Rb, p16, p21, or p27, for example, causes an increase in cyclin-dependent kinase (CDK) activity, which stimulates cell-cycle entrance. In theory, cancers arising from these genetic alterations may be more susceptible to CDK inhibitors. The fact that inactivating the normal counterpart of such oncogenic proteins in normal tissues is frequently tolerated with no apparent consequences underscores the distinct state of addiction that appears to occur in cancer. Switching off this critical pathway, on which cancer cells have become reliant, should have fatal consequences for cancer cells while protecting normal cells that are not similarly reliant. Of course, any effective cancer therapy requires this discriminating activity. There is no obvious positive signaling pathway to target in cases where the tumor suppressors p53 or ARF are lost, thus alternative therapeutic techniques must be investigated [11, 12].

2. Oncogene addiction

It is a process in which cancer cells become dependent on a single activated malignant gene or protein or pathway to maintain their malignant behavior [13]. Cancer cells have multiple genetic and epigenetic abnormalities. Besides this, they may depend on the single activated malignant gene for their sustained growth and proliferation. The concept of oncogene addiction emphasizes that the inactivation of this single gene or protein can provide a rationale for molecular targeted therapy [14]. The phenomenon of oncogene addiction is widely recognized as one of the major factors contributing to the impressive clinical activity observed after treatment with "rationally-targeted" agents [15, 16]. Oncogene addiction has been largely explained by three molecular models at the molecular level.

2.1 Genetic streamlining

This theory postulates that non-essential pathways are inactivated during tumor evolution so that the dominant or addictive pathways are not substituted by any compensatory signals. Therefore, when dominant signals are abrogated, there is a collapse in the whole cellular architecture of cancer cells and undergo cell cycle arrest and apoptosis [17].

2.2 Oncogenic shock model

In the "oncogenic shock" model, addictive oncoproteins (e.g., RTKs) trigger at the same time pro-survival and pro-apoptotic signals. Under normal conditions, the pro-survival signals dominate over the pro-apoptotic signals. Thus, subsequent to blockade of the addictive receptor or oncoprotein, the rapid decline in the activity of survival pathways subverts this balance in favor of death-inducing signals which tend to last longer and eventually lead to apoptotic death [17].

2.3 Synthetic lethality

Two genes are considered to be in a synthetic lethal relationship when loss of one or the other is still compatible with survival but the loss of both is fatal [17]. A majority of drugs used in cancer cure are targeted at genes and pathways that are mutated which limits the range of drugs that can be used for cancer treatment. Synthetic lethality exploits the fact that the presence of a mutation in a cancer gene is often associated with a new vulnerability that can be targeted therapeutically, thus considerably expanding the range of potential drug targets.

3. Activated kinases—The "Achilles' heel" of many cancers

Chronic oncogenic signaling may result in the inactivation of signaling pathways in cancer cells as a result of genetic drift at the biochemical and transcriptional levels. Indeed, a degree of reactive adaptation, such as activation of compensatory pathways and positive or negative feedback loops, is expected to offset the persistent activity of dominant oncogenes [18]. For example, the presence of "sensitive" and "indifferent" pathways addicted to the mesenchymal–epithelial transition factor (MET) oncogene can be observed in several cell lines. This protooncogene encodes the tyrosine kinase receptor for a hepatocyte growth factor (HGF) and is often used as a model addicting oncoprotein to explore potential and pitfalls stemming from the implementation of anticancer strategies

targeting oncogene addiction [7]. Once activated, the MET receptor stimulates phosphatidylinositol 3-kinase (PI3K/AKT) and mitogen-activated protein kinase (ERK/MAPK) pathways, RAS, and STAT3. In these circumstances, MET or EGFR suppression causes a selective reduction of RAS- and PI3K-dependent cascades, whereas many other signals known to affect MET and EGFR-driven proliferation in non-addicted cells, such as JNK, p38, STATs, and NF-kB, remain active or show only minor responses [6]. In terms of genetic streamlining, this finding supports the idea that cancer cells have a significant number of inactive and functionally neutral pathways, as well as a small number of functionally active, self-sufficient transducers. The absence of buffering circuits and the existence of only a small number of functioning signaling nodes highlight the susceptibility of oncogene addiction state [8].

3.1 Molecular mechanism of oncogene addiction

The genetic streamlining hypothesis is derived from the well-established concept of natural selection, in which cancer cells undergo constant genetic drift as a result of the selective pressure exerted by the tumor microenvironment during the tumorigenic process [13, 19]. As a result, cancer cells may lose certain functions, which are unnecessary for cell survival or genome organization [20]. More precisely, at the molecular level, the tumor microenvironment may exert selective pressure over non-essential genes and may induce epigenetic modifications and have little effect on cell growth dynamics [13, 17].

Bernard Weinstein had proposed the synthetic lethal relationship concept of oncogene addiction, which states that two genes will be in a synthetically lethal relationship if one of either genes gets inactivated, rather than both, but still is compatible for cell survival [14]. Therefore, in these types of cancer cells, both the oncogene (that is activated and inactivated one) is believed to be in a synthetic lethal relationship with one another. Thus, under these conditions the elimination of the activated oncogene will lead to the death of cancer cell, but the same would not be observed in normal cells, which does not possess a synthetic lethal relationship [20, 21]. More specifically, cancer cells are more dependent on a particular oncogene in comparison with normal cells. Since there are various inactivated genes are found in cancer cells, which make them less adaptable [22, 23]. Even it is reported from *in vitro* studies that elimination of the critical oncogene cause death in cancer cells due to differential attenuation rates in the ratio of prosurvival and proapoptotic signals, a phenomenon known as "oncogene shock" [15].

Oncogene addiction has been recently proposed as "lineage survival oncogenes". Since it is recognized for years that there is a close nexus between cell lineage and cancer phenotype, which during the development govern lineage proliferation and survival, might also underlie tumorigenic mechanisms [24]. Even many somatic genetic alterations express lineage-restricted patterns in cancer cells, which clearly indicates the genetic alteration in cancer might be conditioned by the lineage programs that exist in tumor precursor cells. There are genes termed as lineage-survival oncogenes which comprise master regulatory genes and are presumed to promote tumor progression. For example, transcription factor MITF in melanoma and androgen receptors in prostate cancer are listed as prototype lineage-survival oncogenes [25, 26].

3.2 Oncogenic shock model

Oncogenic shock model is a concept proposed by Settleman and colleagues in order to explain the death of oncogene addicted cancer cells via inhibition of the

addicted oncoprotein. *In vitro* studies revealed that there is an imbalance in the duality of pro-survival and pro-apoptotic signals overexposure to kinase inhibitor drugs [27]. MYC oncogene possesses apoptosis-inducing properties and can be inhibited by PI3K/AKT pathway activation or by the overexpression of anti-apoptotic BCL-2 protein but normally, the pro-apoptotic function of MYC is evident during the development, since it causes negative selection of T-lymphocytes upon antigen stimulation [28, 29]. It is believed that c-MYC induces cell death through distinct "death priming" and "death triggering" events in which "death priming" and mitogenic signals are well coordinated.

The oncogenic shock hypothesis relies on the experimental observation that targeted disruption of signal-generating oncoproteins results in differential kinetics of downstream signal decay: anti-apoptotic effectors (such as ERKs, AKT) display rapid diminution of activity; while death-inducing molecules (such as p38) display delayed accumulation [17, 30]. This temporal imbalance has been demonstrated in a variety of cellular systems driven by oncogenically active tyrosine kinases, including BCR-ABL, SRC, and EGFR [31]. The oncogenic shock hypothesis deserves at least two comments. First, it postulates that the apoptotic response observed following the abrogation of addictive oncoproteins is an active process of signal-mediated induction of cell death; this is in contrast to the passive occurrence of signal deprivation predicted in the genetic streamlining model. Second, the "potency" of the oncogenic signal in generating pro-survival and pro-apoptotic outputs seems to be more crucial than the temporal appearance of the dominant genetic lesion [32]. While it can be intuitive to think that an initiating oncogene will be more influential as a dominant alteration than genetic lesions occurring subsequently during tumor evolution, we can also reasonably argue that addictive oncogenes with powerful pro-apoptotic activity are likely to arise late during the tumor's natural history when at least some apoptotic safeguards have been disengaged; otherwise, cells would die, and oncogene hyperactivity would be negatively selected [9, 15].

4. Salient features of oncogene addiction

Malignant cells are thoroughly dependent on a particular protooncogene and/or tumor suppressor gene for their proliferation and survival [21]. The inhibition of addicted oncogenes via RNA interference (RNAi) or chemical inhibitors would cause apoptosis in oncogene-addicted cancer cells, but not in other cells. For example, imatinib (Gleevec, a BCR-ABL1 kinase inhibitor) and gefitinib (Iressa, an EGFR inhibitor) are typical examples of drugs successfully targeted to the appropriate molecules and are effective for the treatment of chronic myeloid leukemia (CML) and non-small cell lung cancer (NSCLC), respectively [21]. Oncogene may play a more essential and qualitatively different role in a given pathway or "module" in cancer cells compared with its role in normal cells [21]. Although with limitations, targeting oncogene addiction is clinically significant in the therapeutics of many cancers. For example, a very high percentage of anaplastic lymphoma kinase (ALK) mutated lung tumors, BRAF mutant melanomas, and EGFR mutant non-small cell lung cancers respond to drugs that selectively inhibit these mutationally activated kinases (**Table 1**) [21]. During a clinical trial investigating the efficacy of imatinib in blast-crisis CML patients, the issue of acquired resistance to targeted anticancer treatments initially surfaced. Following that, substantial rates of mutations in the BCR-ABL gene were discovered in individuals who developed insensitivity to imatinib despite initial remission [38]. T315I, commonly known as the "gatekeeper" mutation, was discovered to obstruct the insertion of the drug into the ATP-binding pocket of the ABL-kinase via steric hindrance while maintaining kinase activity,

Targeted oncogene	Cancer cell line	References
Cyclin D1	Esophagus, colon, pancreas, squamous	[33]
β-Catenin	Colon	[13]
Cyclin E	Liver	[34]
Mutant B-RAF	Melanoma	[35]
Mutant K-RAS	Pancreas	[36]
HER-2	Breast	[37]

Table 1.
Examples of oncogene addiction.

resulting in drug insensitivity [39]. Other mutations that inhibit drug binding by disrupting the conformational changes essential for appropriate interaction between the drug and the kinase active site have also been discovered [40]. Novel drugs targeting the mutant form of the protein, such as dasatinib and nilotinib are the only inhibitors that can block the activity of the T315I BCR-ABL mutation. These drugs have been developed to treat relapsed CML patients who have developed resistance to imatinib [40, 41]. The acquisition of secondary mutations that prevent drug binding to the target kinase catalytic site, which has been shown for a range of oncogene-addicted cancers, including EGFR in NSCLC, has been highlighted as a recurrent theme in the landscape of targeted therapy [42].

5. Acquired drug resistance and oncogene addiction

The primary mechanism of acquired resistance to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) is the acquisition of a secondary mutation in exon 20 of the EGFR gene which results in threonine to methionine substitution at position 790 and has been found to account for ~50% of tumors with acquired resistance to EGFR TKIs which include afatinib, dacomitinib, erlotinib, gefitinib, and osimertinib. Another mechanism of resistance found in NSCLC tumors resistant to gefitinib is an amplification of the gene encoding the MET receptor [43]. Overall, resistance mechanisms that appear to act either vertically or horizontally can bypass targeting the addictive oncoprotein in cancer cells: in the first scenario, acquired lesions at the level of the inhibited oncoprotein re-stabilize previously inactivated signaling pathways (e.g., T790M mutation within the EGFR gene), while in the latter, parallel signaling axes are active. Importantly, variability across cancer cell populations could indicate the availability of pre-existing insensitive subclones that could be selected by drug treatment, perhaps leading to acquired resistance mechanisms [44, 45].

Some combinatorial techniques that target multiple tumor vulnerabilities at the same time could be useful in preventing or delaying the formation of resistance mechanisms [46]. Indeed, apoptosis may prevail in systems driven by growth inhibitory signals that gradually shut down after specific oncogene activity is disrupted. Resistance mechanisms could emerge in systems with quick removal of pro-apoptotic signals emitted by the targeted oncoprotein, allowing escape from apoptosis and allowing time for survival signaling pathways to re-establish [47]. According to the findings, BRAF-mediated activation of the SPRY family of RTK inhibitory proteins occurs, meaning that targeted suppression of BRAF activity causes survival signaling to decay, which then reduces SPRY-mediated inhibition of RTK activity [48].

The MET signaling pathway has been discovered to have critical roles in a variety of physiological and developmental cellular processes, in addition to its involvement as an oncogene in several human cancers. Indeed, epithelial cells from a range of organs, including the kidney, liver, muscle, pancreas, prostate, and bone marrow, have been shown to express it. Under physiological conditions, the interaction between MET and its ligand HGF, which is secreted by cells of mesenchymal origin, activates the morphogenetic program known as "invasive growth" (also known as "cell scattering"), which is critical for epithelial growth, morphogenesis, and differentiation during embryogenesis, thus acting as a master developmental regulator [49, 50]. MET and its ligand are required for organ protection and regeneration after injury, recruitment in adult hematopoiesis, and regulation of bone remodeling during adulthood, in addition to their crucial involvement during organ development [51]. Regenerating hepatic skeletal muscle and infarcted myocardium are two examples of the aforementioned circumstances. Furthermore, MET has been found to play a critical function in immune system modulation [52]. The principle that some tumors rely on a single oncoprotein for continuous growth and the conclusion that this oncoprotein is the target for therapeutic intervention has emerged as a master rule in translational cancer research over the last decade, providing a rational framework for developing new targeted compounds for the treatment of various cancer types. A series of successful clinical trials demonstrating the efficacy of targeted treatments when administered correctly in selected cohorts of patients with oncogene-addicted tumors attest to this line of action [1].

5.1 BCR-ABL in chronic myeloid leukemia

It was first identified as a cytogenetic abnormality correlated with chronic myelogenous leukemia (CML) by Nowell and Hungerford in 1960. The fusion transcript of the breakpoint cluster region (BCR) and the gene coding for the Abelson tyrosine kinase (ABL) in Philadelphia (Ph) chromosome is produced many years after the chromosome translocation could actually be confirmed [53]. Several subsequent studies reported that BCR-ALB possesses a crucial role in the pathogenesis and maintenance of chronic myelogenous leukemia (CML); indeed, it was the first oncogene that could be considered addictive before the concept of oncogene addiction became popular. Then, as it should be expected, much effort was devoted to research on chemical compounds that could inhibit BCR-ABL. The results of subsequent clinical studies confirmed that almost 100% of patients experienced complete hematologic responses [54]. The magnitude and frequency of clinical responses were remarkably high even when trials were conducted on patients going through blast crisis, indicating that BCR-ABL continued to serve as causative factors in sustaining malignant proliferation throughout the disease. In approximately 90% of gastrointestinal stromal tumors (GISTs), activating mutations in the KIT gene have been identified, whereas 35% have to activate mutations in platelet-derived growth factor receptor alpha (PDGFRA) [55]. Imatinib can be effectively used in advanced solid tumors, where the functional significance of driver mutations does not yet make much sense because the late-stage disease is characterized by an increasingly demystifying landscape of driver mutations [55].

In the context of cancer treatment, imatinib represented a paradigm shift: medical oncologists had to contend with the concept that cancer is partly a genetic disease, both at the molecular level and therapeutically [56]. A small-molecule inhibitor was synthesized and characterized very thoroughly in the development of imatinib. Unlike many traditional chemotherapeutic drugs, imatinib was not discovered by chance. It was designed by collaborating academics and industrialists for years [57, 58].

The overexpression of the HER2 protein in breast cancers is a consequence of gene amplification, which is associated with a poor prognosis in 25–30% of cases. The fact that a genetically altered with a prognostic significance also plays a causal role in sustaining mammary malignant phenotypes was shown to be further evidence that HER2 amplification plays a driving role in tumors development [59, 60].

Humanized monoclonal antibodies targeting the extracellular domain of HER2 were the first agents that inhibited HER2 activity clinically. Breast cancer HER2 amplification and CML BCR-ABL translocation share the same basis (an inherited genetic defect). The characteristic of the disease that predicts response to imatinib is highly prevalent in the patients with CML: almost all patients display the mutation that predicts response to the drug, and almost all of them respond to the drug. Amplification of HER2 defines only a subset of breast cancers, and responses are found only in a fraction of cases in HER2-amplified tumors. Together, these features highlight the addictive power of HER2 amplification in breast cancer [61, 62]. The so-called "primary" or "de novo" resistance of HER2-alternative pathways dominates the hyperactivation of HER2 or blunts the detectability of HER2-dependent signals in trastuzumab-resistant tumors [63]. In addition, parallel activation of PI3K-based transduction cascades and the overexpression of EGF family ligands are examples of parallel activation of IGF1 receptor signaling. In line with these findings, a functional RNAi screen identified PTEN down-regulation as a mechanism for trastuzumab resistance. Mutations in the PIK3CA gene, loss of function of PTEN are responsible for activation of the PI3K pathway [64, 65].

The important revelation that certain EGFR kinase domain-activating mutations were strongly linked with objective response to receptor blockade was made after retrospective genetic analysis of NSCLCs in responders and non-responders. The importance of mutationally activated kinases as anti-cancer therapeutic targets was once again underscored by this association [66, 67]. The major takeaway message from this example is that targeted inhibition of tyrosine kinases is only successful in a small subset of patients in some instances, and kinase mutations are necessary predictors for patient stratification. Furthermore, the rarity of genetically characterized responsive patient subsets raises the concern that a reliable portrayal of genetic variation necessitates a far larger sample of patients within a cancer type than previously anticipated [68, 69]. This could be related to other changes in the EGFR coding sequence, such as minor exon 20 insertions or deletions, or uncommon mutations coexisting with typical activating mutations [70]. The use of crizotinib, a small molecule inhibitor of anaplastic lymphoma kinase (ALK) in NSCLC patients is the most current insight into the successful therapeutic use of the oncogene addiction principle. The fusion protein contains a constitutively active ALK and has tumorigenic potential, according to biochemical and functional tests [71, 72].

When a clinical trial of imatinib in blast-crisis CML patients revealed that some subjects developed clinical insensitivity to the drug after a dramatic but brief remission, the formation of secondary (acquired) resistance at some point during therapy became clear. According to preliminary research, the average chronic-phase patient using imatinib had a 10% chance of relapsing into blast crisis every year [73]. The BCR-ABL gene has a significant incidence of mutations, according to an analysis of BCR-ABL sequences in myeloid clones of patients with the imatinib-resistant, relapsing illness. The prototypical amino-acid change (T315I) causes a steric barrier in the ATP-binding pocket of the ATP-binding pocket of the kinase [74]. Other mutations impede imatinib binding by locking the BCR-ABL kinase domain in an active state [75].

Chemicals that can bind to this conformation should be able to achieve their full inhibitory potential in this circumstance. Dasatinib (Sprycel, Bristol-Myers Squibb)

Target	Disease	Agent	Regimen
HER-2	Breast	Trastuzumab	Combination
BCR/ABL	CML	Imatinib	Monotherapy
C-KIT	Stromal Tumor	Imatinib	Monotherapy
EGFR	NSCLC	Gefitinib Erlotinib	Monotherapy
EGFR	Pancreas	Erlotinib	Combination
VEGF	Breast Kidney	Bevacizumab	Combination

Table 2.
Clinical evidence of oncogene addiction.

and nilotinib (Tasigna, Novartis) are two compounds that have this feature and are being utilized to treat relapse, resistant CML patients [76]. Imatinib resistance is caused by amplification of the BCR-ABL gene, which results in elevated levels of the matching protein product in a minority of cases. Secondary resistance has been described for various targets and in different oncogene-addicted tumors, including mutant EGFR and EML4-ALK in NSCLCs and mutant c-KIT in GISTs, as well as the acquisition of secondary mutations that inhibit drug binding to the kinase catalytic cleft. Alternatively, other oncogenes can be genetically altered to create aberrant signaling in place of the suppressed target's pathways that are no longer maintained [77, 78]. There are several examples that provide clinical evidence for oncogene addiction and the treatment regimen may involve a single agent (monotherapy) or combination of several drug agents (combination) (**Table 2**).

Resistance-inducing mutations have also been found in relapsed patients' tumor tissue. The inactivated target is bypassed in all of these examples by compensating lesions that may act vertically or horizontally: in the former, secondary alterations within the same upstream target re-stimulate the downstream signaling flux along with the same, previously inhibited pathway; in the latter, parallel axes are activated to replace the block [79–81]. Under the selection pressure of medication exposure, genetic instability may fuel the emergence of oncogenic lesions that have been evolutionarily chosen to drive cancer survival and growth [81].

6. Non-oncogene addiction (NOA)

In addition to oncogene addiction, several other examples of non-oncogene addiction have been reported in the literature. The concept of non-oncogene addiction (NOA) is based on the idea that tumorigenicity is dependent on the activity of a wide range of genes and pathways, many of which are not inherently oncogenic [82]. These genes and pathways are essential to maintain the oncogenic phenotype of cancer cells, but not to the same extent for normal cell viability. These dependencies should yield a large number of pharmacological targets that, when inhibited, will cause synthetic lethality with the underlying tumor genotype. Anti-tumor medicines can take use of NOA genes and pathways. Tumor-intrinsic and tumor-extrinsic NOA genes are the two types of NOA genes. Tumor-intrinsic NOA genes support the tumor cell's oncogenic state in a cell-autonomous way, whereas tumor-extrinsic NOA genes function in stromal and vascular cells, providing heterotypic support for the tumor. Targeting these accessory cells has the advantage of being genetically more stable than tumor cells, which means they

are less likely to develop drug resistance. However, tumors may be able to evolve a reduced reliance on these accessory cells in some circumstances [82–84].

7. Conclusion

Oncogene addiction is a phenomenon in which tumor cells develop a dependency on a driver oncogenic product that plays a role in nurturing and fueling the malignant phenotype, laying the groundwork for the development of anticancer therapies that target single oncoproteins in specific cancer patient populations. Despite their exceptional translational impact, clinical application of molecularly targeted anticancer treatments demonstrated the establishment of similar resistance mechanisms across most tumor subtypes, which severely reduces the benefit of oncoprotein-targeted therapy. These recurring resistance mechanisms must be thoroughly investigated in order to block disease progression or at least predict the disease progression. Combinations of several drugs may provide greater therapeutic benefit and postpone the establishment of resistance mechanisms in such situations. Cancer cells' ability to quickly adapt to their surroundings and clonal heterogeneity are essential features of human malignancies. The increased ability to understand, and so forecast, cancer evolution in response to therapy in order to accompany it to the intended destination, we believe, will be a major step toward the creation of more successful anticancer therapies. In years to come, the ability of cancer cells to evolve will continue to challenge researchers. Consequently, our approach to cancer therapy will also need to evolve.

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Author contributions

RAR and ST conceived the idea. ST wrote the chapter with assistance of RAR, SKK, and MB. All authors contributed to the writing of the chapter and approved the final submitted version.

Conflict of interest

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