Oncogene Addiction in Solid Tumors

2

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Carcinogenesis is a multistep process resulting from the progressive accumulation of mutations and epigenetic abnormalities in expression of multiple genes that collectively give rise to a malignant phenotype [1, 2]. However, experimental evidence suggests that the suppression of an oncogene or the restoration of a tumor suppressor gene expression can be sufficient to inhibit the growth of cancer cells and even lead to improved survival rates [3].

The term "oncogene addiction" was coined by Weinstein in the early 2000s [3] to describe the phenomenon where the hyperactivity of a specific oncogene (or pathway) is required for cancer cells to survive and proliferate. Initially, some studies on hematological tumors have identified that cancer cells are often "addicted to" constitutive activation or overexpression of an oncogene for the maintenance of their malignant phenotype: It has been reported that acute inactivation of MYC in transgenic mice models of MYC-induced lymphoma and leukemia leads to the rapid induction of apoptosis and differentiation [4]. Since then some evidences that support the concept of oncogene addiction have been obtained in other tissues in murine models and using human cancer cell lines [5]. Nevertheless, the most convincing evidence for this concept comes from its application to the clinical setting. The clinical relevance of oncogene addiction paradigm is highlighted by a growing number of examples that demonstrate the efficacy of several therapeutic agents that target specific oncogenes in various cancer types. The clinical success of the multikinase inhibitor imatinib, which targets the oncogenic BCR/ABL protein in chronic myeloid leukemia (CML) [6] and also targets the product of the oncogene c-kit in gastro intestinal stromal tumors (GIST) [7], provides direct evidence for the phenomenon of oncogene addiction in the context of cancer therapy. Likewise, selective epidermal growth factor receptor (EGFR) tyrosine-kinase inhibitors (TKI), gefitinib, erlotinib, and afatinib have achieved positive outcomes in non-small cell lung cancer (NSCLC) [8, 9], pancreatic cancer [10], and glioblastoma [11]. Furthermore, similar results were obtained using the monoclonal antibody trastuzumab, which targets the receptor tyrosine kinase HER-2/NEU in patients with breast cancer [12]; the monoclonal antibody cetuximab, which targets the EGFR in patients with head and neck and colorectal cancer [13, 14]; bevacizumab, a monoclonal antibody to vascular endothelial growth factor (VEGF) in carcinomas of the breast, colon and kidney [15–17]; vemurafenib, a B-Raf enzyme inhibitor for the treatment of melanoma [18]; and crizo-

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Table 2.1 Clinical evidence of oncogene addiction[a]

Target	Therapeutic agent (monotherapy)	Cancer	Reference
BCR/ABL	Imatinib mesylate	CML	[6]
C-KIT	Imatinib mesylate	GIST	[7]
EGFR	Gefitinib/Erlotinib	NSCLC	[8]
			[9]
B-RAF	Vemurafenib	Melanoma	[18]
EML4-ALK	Crizotinib	NSCLC	[19]
Target	**Therapeutic agent (combination)**	**Cancer**	**Reference**
EGFR	Erlotinib	Pancreas	[10]
EGFR	Cetuximab	Head and neck	[13]
		Colorectum	[14]
HER-2/NEU	Trastuzumab	Breast	[12]
VEGF	Bevacizumab	Breast	[15]
		Colorectum	[16]
		Kidney	[17]

[a] Treatment regimen indicates therapeutic agent alone (monotherapy) or in combination with other chemotherapeutic agents (combination)

tinib, an ALK inhibitor, which targets the fusion protein EML4-ALK and has produced excellent results in clinical trials in NSCLC patients [19] (Table 2.1).

The principle that some cancers depend on one single oncoprotein for their continuous growth and the conclusion that this oncoprotein could represent the target for therapeutic treatment is confirmed in patients who develop acquired resistance to these therapeutic agents via de novo mutations on the same oncogene and not by mutations in other oncogenes. For example, the leukemic cells of individuals with CML can undergo a secondary mutation in the kinase domain of the BCR/ABL protein which blocks the inhibitory activity of imatinib [20]. Similarly, there may be cases of secondary resistance to gefitinib and erlotinib in patients with NSCLC due to *de novo* mutation on EGFR gene identified as T790M [21]. However, in other cases of acquired resistance, cancer cells may undertake an alternative or redundant survival pathway. For example, it has been reported that a subset of NSCLC patients with acquired resistance to EGFR TKIs exhibit amplification of the MET tyrosine kinase gene [22]. It is also known that the loss of the tumor suppressor gene PTEN is associated with treatment failure in glioblastoma patients, presumably due to the activation of pathways downstream of the EGFR [23].

The Molecular Basis of Oncogene Addiction

The molecular mechanisms underlying oncogene addiction have been extensively studied, and it has been demonstrated that these occur by processes intrinsic and exclusively dependent upon biological programs within a cancer cell. In particular, three models have been proposed to clarify the mechanisms of oncogene addiction: genetic streamlining, oncogenic shock and synthetic lethality. The genetic streamlining hypothesis is based on the concept that genetic instability in cancer cells causes the inactivation of some signaling pathways during tumor evolution, which are operational in a normal cell but not required for growth in the cancer cell. In this state, an initially nonessential oncoprotein may become essential through the genetic streamlining, and the cancer cell becomes predominantly dependent on the oncogene driven processes [24]. The blockade of the addictive receptor causes cell cycle arrest and/or apoptosis.

A second mechanism is based on the concept of "oncogene shock." According to this model, dominant oncogenes are able to sustain at the same time both prosurvival and proapoptotic signals. Normally, the prosurvival outputs dominate over the proapoptotic, but the inactivation of ad-

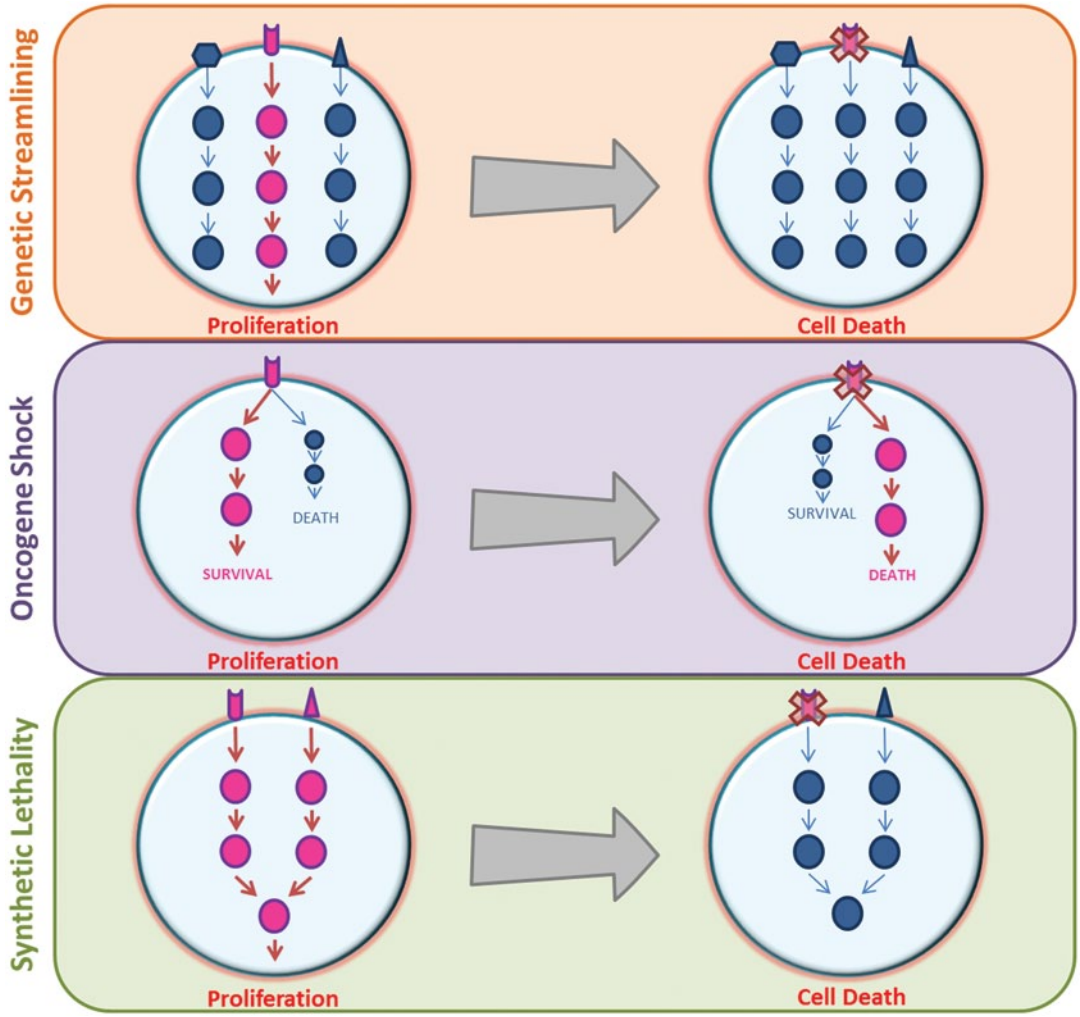


Fig 2.1 Molecular mechanisms of oncogene addiction, showing the three different hypotheses of oncogene addiction: genetic streamlining, oncogene shock and synthetic lethality

dictive receptor in cancer cells causes their death because of differential attenuation rates of pro-survival and proapoptotic signals [25].

A third hypothesis is based on the model of synthetic lethality, derived from studies in lower organisms. This theory holds that two genes are considered to be in a synthetic lethal relationship if mutation of one of the two genes is compatible with survival but mutation of both genes causes cell death [26]. This concept of synthetic lethality is rather intuitive when the two genes belong to alternative metabolic chains with a common end product, but it can also be applied to more sophisticated and integrated cellular functions, such as survival and proliferation. Furthermore, cancer cells may be more dependent on a specific oncogene with respect to normal cells as they are less adaptable because they carry several inactivated genes (Fig. 2.1).

Future Perspectives

The phenomenon of oncogene addiction has allowed novel important therapeutic opportunities through the selective elimination of tumor cells that exhibit strict dependence on a protein, providing a potential "Achilles' heel" in specific

types of human cancers. For instance, the use of small interfering ribonucleic acids (siRNAs), a class of double-stranded RNA molecules, can be useful to identify which genes are required to maintain the proliferation and survival of cancer cells and subsequently to design drugs that target the related protein [27]. Furthermore, it has been reported that a specific siRNA preparation might be administered to patients in order to knock down the expression of a critical oncogene in the tumor, thus providing a novel approach to cancer therapy [28]. In addition, oncogenes that are mutated in cancer, and not overexpressed, represent the most appropriate target for therapy because they have qualitatively different roles than oncogenes that are only overexpressed, as evidenced by the properties of mutated EGFR in NSCLC cells [29]. Today, the emerging molecular biology techniques allow us to identify different proteins and gene expression profiles between normal tissues, cancers, and subtypes of specific cancers and thus facilitate identification of specific pathways of oncogene addiction in several cancer cells. As described above, some cancers can "overcome" a given state of oncogene addiction through mutations in other genes and pathways, due to the genomic instability of cancers. Moreover, in some cases, the inactivation of the oncogene fails to cause significant tumor regression as demonstrated in a murine model of MYC-induced lung adenocarcinoma [30]. For this reason, not always the inactivation of an oncogene necessary for tumor growth and survival is sufficient to reverse tumorigenesis. In these cases, the combination therapy helps us to overcome these obstacles. It has been widely demonstrated that the efficacy of certain targeted agents can be enhanced by combining them with cytotoxic drugs, such as agents that act by inhibiting deoxyribonucleic acid (DNA) or chromosomal replication [12]. Similarly, the combination of bevacizumab or cetuximab with chemotherapy agents can improve response rates in metastatic colon and breast cancer patients, respectively [14, 15].

All these evidences support the role of oncogene addiction in the development of cancer phenotype. This phenomenon can be exploited to identify new targeted agents, which specifically target the most relevant oncogenes.

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