Oncogene Addiction

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Abstract

Cancer cells contain multiple genetic and epigenetic abnormalities. Despite this complexity, their growth and survival can often be impaired by the inactivation of a single oncogene. This phenomenon, called "oncogene addiction," provides a rationale for molecular targeted therapy. The efficacy of this strategy requires novel methods, including integrative genomics and systems biology, to identify the state of oncogene addiction (i.e., the "Achilles heel") in specific cancers. Combination therapy may also be required to prevent the escape of cancers from a given state of oncogene addiction. [Cancer Res 2008;68(9):3077–80]

Multistage Carcinogenesis and Oncogene Addiction

Human cancers usually evolve through a multistage process that can extend over a period of decades. This process is driven by the progressive accumulation of mutations and epigenetic abnormalities in expression of multiple genes that have highly diverse functions (1–4). Despite this extensive disruption of the genome of cancer cells, there are many examples in which the reversal of only one or a few of these abnormalities can profoundly inhibit the growth of cancer cells, and in some cases, lead to improvements in patient survival (refs. 5, 6; Table 1). We introduced the concept of "oncogene addiction" to emphasize this apparent dependency of some cancers on one or a few genes for the maintenance of the malignant phenotype (1, 2, 5, 6). Evidence that supports this concept has been obtained in genetically engineered mouse models of human cancer, mechanistic studies in human cancer cell lines, and clinical trials involving specific molecular targeted agents (Table 1). Thus, in a transgenic mouse model, switching on the *c-myc* oncogene in the hematopoietic cells led to the development of T-cell and myeloid leukemias. However, when this gene was subsequently switched off, the leukemia cells stopped dividing and displayed differentiation and apoptosis (7). Dependence on the continued expression of other oncogenes for the maintenance of the neoplastic state has also been seen in other tissues in murine models (Table 1).

Numerous studies using human cancer cell lines indicate that although these cells are aneuploid and carry several genetic and epigenetic abnormalities, they can also be highly dependent on the activity of a single oncogene for continued cell proliferation and survival (Table 1). The most convincing evidence for the concept of oncogene addiction comes from the increasing number of examples of the therapeutic efficacy of antibodies or drugs that target specific oncogenes in human cancers (Table 1). The earliest example is the antibody trastuzumab (Herceptin), which targets the receptor tyrosine kinase HER-2/NEU in patients with breast cancer. More recent evidence is provided by the therapeutic efficacy of drugs that target various oncogenic protein kinases. Examples include imatinib, which targets the *bcr-abl* oncogene in chronic myeloid leukemia and also targets the *c-kit* oncogene in gastrointestinal stromal tumors, and gefitinib and erlotinib, which target the epidermal growth factor receptor (EGFR) in non–small cell lung carcinoma (NSCLC), pancreatic cancer, and glioblastoma. It is of interest that the clinical responses in NSCLC are mainly confined to the subset of cancers that have mutations or amplification in the *EGFR* gene.

In a subset of patients with chronic myeloid leukemia who initially responded to imatinib but later suffered a relapse, the leukemic cells contained a *de novo* mutation in the kinase domain of the BCR/ABL protein which blocks the inhibitory activity of imatinib (8). Likewise, a secondary mutation (T790M) was identified in the EGFR in the recurrent NSCLC tumors that acquired resistance to gefitinib or erlotinib therapy (9–11). This strong selective pressure for the emergence of cells that carry *de novo* mutations in the respective oncogenes indicates the remarkable dependence of these neoplastic cells on specific oncogenes, because in principle, the cells could have become resistant by *de novo* mutations in other oncogenes. Fortunately, there are kinase inhibitors that can circumvent the acquired resistance of the mutant BCR/ABL (12) and EGFR (11) proteins. There are, however, several examples of a true escape from a given state of oncogene addiction. This has been seen in mouse models of breast cancer and seems to be due to secondary mutations in K-*ras* or *p53*, or increased expression of the transcription factor Snail (Table 1). Furthermore, although glioblastoma carrying a mutant form of the EGFR, EGFRVIII, often respond to EGFR kinase inhibitors, loss of the tumor suppressor gene *PTEN* is associated with treatment failure, presumably because of the activation of pathways downstream of the EGFR. This phenomenon has been called "context-dependent oncogene addiction" (13).

Mechanisms of Oncogene Addiction

We proposed that the phenomenon of oncogene addiction is a consequence of the fact that the multistage process of carcinogenesis is not simply a summation of the individual effects of activation of multiple oncogenes and inactivation of multiple tumor suppressor genes (5, 6). This is because the proteins encoded by these genes often have multiple roles in complex and interacting networks. Thus, the intracellular circuitry or "wiring diagram" that regulates signal transduction and gene expression in cancer cells is very different, i.e., "bizarre," when compared with that of normal cells. Therefore, in cancer cells, a given oncogene may play a more essential and qualitatively different role in a given pathway or "module" compared with its role in normal cells. The concept of "synthetic lethality," derived from studies in lower organisms, may also be relevant (14). Two genes are said to be

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Table 1. Oncogene addiction: studies in mice, studies in human cancer cell lines, and clinical evidence

Studies in mice*

Targeted oncogene	Cancer type
c-myc	T cell and acute myeloid Leukemia
Bcr-Abl	Leukemia
H-ras	Melanoma
K-ras	Lung
c-myc	Pancreatic β-cell
c-myc	Osteogenic sarcoma
Her-2/neu	Breast
c-myc	Breast
Wnt-1	Breast

Studies in human cancer cell lines †

Targeted oncogene	Cancer cell line
Her-2	Breast
Cyclin D1	Esophagus, colon, pancreatic, squamous, nasopharyngeal
K-ras^{mut}	Pancreatic
K-rasv^{12}	Pancreatic
β-Catenin	Colon
Cyclin E	Liver
Mutant β-Raf	Melanoma
MITF	Melanoma

Clinical evidence

Targeted oncogene (s)	Disease	Agent ‡
HER-2	Breast§,‖	Trastuzumab (combination)
BCR/ABL	Chronic myeloid leukemia§	Imatinib (monotherapy)
C-KIT	Gastrointestinal stromal tumor§	Imatinib (monotherapy)
EGFR	NSCLC§	Gefitinib, erlotinib§ (monotherapy)
EGFR	Head and neck, colorectal§	Cetuximab (combination)
EGFR	Pancreas§	Erlotinib (combination)
VEGF	Breast, colorectal§,‖, kidney	Bevacizumab (combination)
VEGFR, RAF	Kidney§	Sorafenib (monotherapy)

NOTE: For specific references and further details, see ref. 6.
*Switching off the indicated oncogene led to growth inhibition, differentiation, apoptosis and/or tumor regression.
† Treatment of these cell lines with an antisense oligonucleotide or a RNAi directed to the respective oncogene caused growth inhibition, and in some cases, decreased tumorigenicity and increased chemosensitivity.
‡ Treatment regimen indicates agent alone (monotherapy) or in combination with cytotoxic agents (combination).
§Food and Drug Administration–approved.
‖Phase III evidence shows improved disease-free or overall survival rates.

synthetic-lethal if mutation of one of the two genes is compatible with survival but mutation of both genes causes cell death. For example, certain cancer cells might be highly dependent on a given oncogene because during their development, they lost the function of another gene that normally performs a similar function. In a broader context, cancer cells may be more dependent on a specific oncogene compared with normal cells as they are less adaptable because they carry several inactivated genes. *In vitro* studies suggest that in some cases, inactivation of a critical oncogene in cancer cells causes their death because of differential attenuation rates of prosurvival and proapoptotic signals, a phenomenon called "oncogene shock" (15). However, other mechanisms must also play a role in oncogene addiction because inactivation of a critical oncogene in mouse models can cause the differentiation of leukemia cells (7) or inhibit angiogenesis (16). A corollary to oncogene addiction is the recently proposed concept of "lineage-survival oncogenes" in which specific types of cancer are dependent on the expression of an altered form of a gene that normally plays an essential role in the development of the cell lineage in which the cancer arose. Examples include the androgen

receptor in prostate cancer and the transcription factor MITF in melanoma (17).

Identification of the ''Achilles' Heel'' in Specific Human Cancers

Given the multiple genetic and epigenetic abnormalities in tumors and tumor heterogeneity, how can we identify the specific state of oncogene addiction, i.e., the "Achilles' heel," in specific types of human cancer so that patients can be treated with the appropriate molecular targeted agent? At the present time, there are no methods to fully assess the total circuitry that controls cell proliferation, differentiation, and apoptosis in normal or cancer cells. Advances in network theory, systems biology, and computer modeling may eventually make this possible. Currently, several empirical approaches can be used to help identify the Achilles' heel in specific types of human cancer. One approach is to use small interfering RNAs to identify which genes are required to maintain the proliferation and/or survival of specific types of cancer cells. Once such genes are identified, drugs can be designed to target the related protein(s). Oncogenes that are mutated or amplified and not simply overexpressed might be more likely targets for therapy because they reflect the "hard-wiring" of cancer cells, and the abnormality is probably present in both the stem cell population and the progeny cells of tumors. In addition, mutated oncogenes might be more likely to have qualitatively different properties, as illustrated by the mutated EGFR receptor in a subset of cases of NSCLC cells. The importance of gene amplification is illustrated by a recent study indicating that an inhibitor of the MET receptor tyrosine kinase caused extensive apoptosis in gastric cancer cell lines with MET amplification but not in cell lines without MET amplification (18). Dependence on a specific oncogene may be different in the stem cells than in the progeny cells in a given tumor because of differences in their intracellular circuitry. Optimal therapy would then require developing agents that target the critical oncogene in the stem cells of specific cancers. Further characterization of tumor stem cells should clarify this aspect of oncogene addiction. Advances in profiling patterns of gene expression, genomics, and proteomics have made it possible to compare the profiles of thousands of genes and proteins between normal tissues, cancers, and subtypes of specific cancers. An example of the power of this "integrative genomic" approach is the recent discovery of IKBKE as a frequent breast cancer oncogene which is required for the survival of breast cancer cells in which it is overexpressed, thus providing another example of oncogene addiction (19).

Combination Therapy

It should be emphasized that although the concept of oncogene addiction may apply to a given cancer at a particular time or stage, it is apparent from some of the mouse models and from clinical experience with molecular targeted agents that cancers can "escape" from a given state of oncogene addiction, through mutations in other genes and pathways, presumably because of the frequent genomic instability of cancers. For this reason, as well as tumor heterogeneity, it is unlikely that the use of a single molecular targeted agent will achieve long-lasting remissions or cures in human cancers, especially for late-stage disease. Combination therapy will therefore be required, which raises several unresolved questions. Can such combinations be rationally designed? Should the individual agents act on the same molecular target but by different mechanisms, or on different targets in the same pathway; or should each agent target a different pathway or cellular mechanism? Clinical studies indicate that the efficacy of certain molecularly targeted agents can be enhanced by combining them with cytotoxic agents, i.e., agents that often act by inhibiting DNA or chromosomal replication (Table 1). Thus, trastuzumab that targets HER-2 can improve response and survival rates if given in combination with paclitaxel to patients with metastatic breast cancer. The combination of bevacizumab or cetuximab with cytotoxic chemotherapy agents can also improve response rates in patients with metastatic breast and colon cancer, respectively. Furthermore, when bevacizumab was added to a combination chemotherapy regimen, it improved overall survival rates in patients with metastatic colon cancer. As with chemotherapy, the efficacy of targeted therapy will likely be greater in patients with minimal residual disease.

Conclusion

At the present time, the choice of the best molecular targeted agent and the appropriate combination therapy for a specific patient with cancer is largely empirical. Nevertheless, the rapid development of diverse molecular targeted agents, coupled with further mechanistic studies and advances in profiling the molecular circuitry of specific subsets of human cancer, should make it possible to further exploit the concept of oncogene addiction to achieve more effective and selective therapies for several types of human cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Response

The review by Weinstein and Joe thoughtfully describes the phenomena of oncogene addiction, which is one of the most compelling explanations for why oncogene inactivation induces tumor regression and provides a logical rationale for the development of targeted therapies for cancer. The concept has been widely adopted and provides a benchmark for our understanding of tumor biology, not only predicting why tumors regress and undergo apoptosis upon oncogene inactivation, but also explaining why tumors escape oncogene dependence and why inactivation of multiple oncogenes may be a more effective treatment for cancer.

However, some observations may not be as well-explained by the phenomena of oncogene addiction. In particular, as noted by Weinstein, although oncogene addiction does account for why oncogene inactivation induces apoptosis, it does not account for why oncogene inactivation can result in arrest, senescence and apoptosis. Nor does oncogene addiction account for the presence of "cancer stem cells" or the important role of the host microenvironment. Finally, oncogene addiction does not reconcile why oncogene activation in normal cells and oncogene inactivation in tumor cells has similar consequences. I proposed a complimentary and non-mutually exclusive model for tumorigenesis: oncogene amnesia.

Oncogene amnesia conceives of cancer as an enforced cellular state of ignorance of what is happening both within a cell and outside a cell in the host environment. Oncogene amnesia could account for the observation that oncogene activation and inactivation identically result in programs of proliferative arrest/differentiation/apoptosis and/or senescence. Precisely because oncogene activation silences critical safety switches that necessarily results in genotoxicity and/or genomic damage, cell defense mechanisms are activated that prevent any single oncogene from causing tumorigenesis by restoring cellular programs. If a cell subsequently acquires the correct compliment of genetic lesions to completely abrogate these checkpoint processes, the result is tumorigenesis. However, when the initiating oncogene is inactivated, the same safety switches that this particular oncogene was responsible for blocking are now restored, thereby, resulting in tumor regression.

Oncogene amnesia may also account for how cancers exhibit, as a fundamental feature, the stem cell property of "self-renewal." Oncogenes contribute to tumorigenesis by either coopting cells that already self-renew, or alternatively, by inducing a program of self-renewal. Finally, oncogene amnesia would be consistent with the observation that cancers do not occur autonomously but rather in the context of a permissive host microenvironment. Upon oncogene inactivation, not only the tumor cells, but the cancerous environment is also reversed back to a normal state.

A distinctive difference between the models is that in oncogene addiction, tumorigenesis is conceived as arising from a "bizarre" signaling state. In contrast, oncogene amnesia does not consider the signaling abnormal, but rather, the ability of the cell to respond to self-destructive internal cellular and external host cues. The consequences of oncogene inactivation in a tumor are a direct consequence of the regained ability of that oncogene to now normally respond. Importantly, oncogene amnesia may provide a general way of conceiving how both the initiation and maintenance of tumorigenesis are intertwined.

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