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Key Principles in Glioblastoma Therapy

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1. Introduction

Glioblastoma is the most common form of primary brain tumor. The incidence of this tumor is fairly low, with 2-3 cases per 100,000 people in Europe and North America ¹. It is one of the most aggressive forms of cancer ². Without treatment, the median survival is approximately 3 months ³. The current standard of treatment involves maximal surgical resection followed by concurrent radiation therapy and chemotherapy with the DNA alkylating agent, temozolomide ⁴. With this regimen, the median survival is approximately 14 months. For nearly all affected, the treatments available remain palliative.

The best available evidence suggests that glioblastomas originate from cells that give rise to glial cells^{5,6}. These glial derived tumors are graded by the World Health Organization (WHO) into 4 categories, termed WHO grade 1 to grade 4. The higher grade denotes histologic features of increased malignancy. WHO 4 glioma is essentially synonymous with glioblastoma⁷.

Studies carried out over the past three decades suggest that glioblastomas, like other cancers, arise secondary to the accumulation of genetic alterations. These alterations can take the form of epigenetic modifications, point mutations, translocations, amplifications or deletions and modify gene function in ways that deregulate cellular signaling pathways leading to the cancer phenotype ⁸. The exact number and nature of genetic alterations and deregulated signaling pathways required for tumorigenesis remains an issue of debate⁹, although it is now clear that CNS carcinogenesis requires multiple disruptions to the normal cellular circuitry. The genetic alteration results in either activation or inactivation of specific gene functions that contribute to the process of carcinogenesis ⁹. Genes, that when activated, contribute to the carcinogenesis are generally termed proto-oncogenes. The mutated forms of these genes are referred to as oncogenes. Genes, that when inactivated, contribute to the carcinogenesis are generally termed tumor suppressor genes.

Despite some progress in the clinical management of glioblastoma, prognosis of patients suffering from this deadly tumor remains dismal, and design of new and more effective therapies for glioblastoma is highly desirable. Arguably the most promising route to discoveries of innovative treatment strategies is to obtain better mechanistic insights into glioblastoma pathogenesis and biology. Indeed, recent research in this area of experimental and clinical oncology has identified the key signaling pathways, critical regulatory nodes, genes and their protein products, as well as their mutual cross-talks, thereby providing a solid molecular basis for selection of candidate therapeutic targets and drug discovery programs. These lines of investigation complement the recent efforts to sequence entire genomes of a growing number of human tumors including glioblastoma, formulation of new concepts and principles in tumor cell biology, and potential exploitation of these major advances for personalized disease management in oncology. Collectively, such efforts have begun to provide exciting leads to conceptual framework that afford innovative therapeutic strategies. This review will aim to review these critical concepts and their relevance for glioblastoma therapeutic development.

2. Concept 1: Glioblastoma subtypes

There is an old adage that cancer is a hundred diseases masquerading in one. While this adage is based on clinical and pathologic observations, systemic genomic characterization of a large number of glioblastoma specimens (TCGA) confirms the notion that subtypes with distinct pathologic molecular events and therapeutic response.

The Cancer Genome Atlas (TCGA) is a major NIH initiative involving institutions spanning the continental U.S. with the goal of tumor specimen collection and molecular characterization¹⁰. Glioblastoma was one of the first tumor types characterized in this effort. This vast wealth of data is unprecedented, and despite the enormous challenge to process and analyze this incoming information, correlations of such emerging 'genetic and expression profiles' or 'tumor landscapes' with tumor biology and clinico-pathological features of the patients including therapeutic responses are beginning to impact oncology.

This profiling approach¹¹ has led to the understanding that glioblastoma is but an umbrella term that encapsulates subtypes characterized by distinct molecular properties. Based on global transcript profiling, glioblastoma can be divided into three to four distinct subtypes^{11, 12}. Interestingly, each subtype harbor distinct genetic aberrations¹² and proteomic profiles¹³. The recognition that glioblastoma consists of subtypes varying in molecular circuitry and biologic behavior suggests that no therapy can be universally efficacious. The major importance of this concept of heterogeneity is that meaningful therapeutic gain can only be attained by customizing the therapy to the underlying molecular circuit.

One subtype (termed classical by the TCGA and proliferative by Philips et al) is characterized by frequent amplification or mutations in the Epidermal Growth Factor Receptor (EGFR) gene^{10, 11}. In contrast, in another subtype, termed proneural by both groups, harbored frequent mutations in p53, Platelet Derived Growth Factor Receptor A (PDGFRA), and Isocitrate Dehydrogenase 1 (IDH1)¹². A third type, termed mesenchymal by both groups, is characterized by frequent mutations in the Neurofibromatosis type 1 gene (NF-1). Of note, these subtypes differ in their clinical responses to therapy. Patients afflicted with the classical (proliferative) or mesenchymal subtypes benefit from radiation and temozolomide treatment¹². Such benefit was not observed in patients afflicted with the proneural subtype.

3. Concept 2: Oncogene addiction

The term “oncogene addiction” was initially coined by Dr. Bernard Weinstein to describe the phenomenon that some tumors exhibit exquisite dependence on a single oncogenic protein (or pathway) for sustaining growth and proliferation¹⁴. Such dependence has been convincingly demonstrated in both tissue culture and transgenic mice systems for oncogenic versions of MYC¹⁵⁻¹⁷ and RAS¹⁸. Application of this concept to the clinical setting has achieved variable success in various cancer types, including chronic myelogenous leukemia (CML) harboring the BCR-ABL translocation, Erb2 over-expression breast cancer, and Non-Small Cell Lung Cancer harboring selected EGFR mutations^{19, 20}. A simplistic application of this concept in glioblastoma would involve identification of the critical “addicted” oncogene followed by the inhibition of such oncogene(s). Unfortunately, the actual biology of glioblastoma is far more complex.

To understanding this complexity, a careful analysis of the fundamental notion of oncogenic addiction is needed. In some ways, the observation that tumors exhibit dependence on a particular oncogenic pathway at some point in its history is not surprising. However, taken in the context of the plethora of dynamic genetic changes that accumulated during cancer progression²¹, it is somewhat anti-intuitive to suspect that any particular pathway would play a prominent role in maintaining cell viability. Moreover, inactivation of the normal counterpart of the addicted oncogenic protein is often tolerated in normal tissue. These observations suggest that the genetic circuitry of the cancer cell have been extensively re-programmed to result in this “addicted” state¹⁴.

The molecular nature of this re-programming remains poorly understood. Several hypotheses have been put forward. One hypothesis involves the notion of “genetic streamlining”, where genetic instability in cancer cells is thought to mutationally or epigenetically inactivate certain signaling pathways that are operational in a normal cell but not required for growth in the cancer cell. In this “streamlined” state, the tumor cell becomes hyper-dependent on the oncogene driven processes²². A more generalized form of this explanation involved the notion of synthetic lethality. Two genes are considered synthetically lethal if cells remain viable with inactivation of either gene. Simultaneous inactivation of both genes, on the other hand, results in cell death²³. It is thought that the cancer cells have accumulated mutations that are synthetically lethal with the absence of critical oncogenes. The main difference between this hypothesis and the “streamline” hypothesis is that the mutation in the former can result in a gain or loss of function, whereas the later specifically proposes a loss of function. A third hypothesis suggests that oncogenes reprogrammed the tumor cell by both pro-survival and pro-apoptotic signaling²². With acute inactivation, the pro-survival signaling decayed faster than the pro-apoptotic signaling, resulting in tumor death.

The main reason for revisiting the framework of oncogene addiction is that mechanism by which the cells can evolve to avoid such addiction. For instance, in the context of synthetic lethality, EGFR inhibition may be cytotoxic to glioblastoma cells only in the appropriate genetic context. Indeed, therapeutic effects of EGFR inhibition were observed only in patients with tumors harboring an oncogenic form of EGFR and an intact PTEN tumor suppressor gene²⁴. To complicate the matter, recent studies demonstrate that glioblastomas harbor activation of multiple oncogenic Receptor Tyrosine Kinases (RTKs), such that inactivation of any single oncogene merely diverts signaling through other active oncogenes²⁵. In these contexts, it is evident that meaningful therapy will require simultaneous inhibition of multiple oncogenes or identification of the fitting genetic context.

4. Concept 3: Non-oncogene addiction

Emerging literature suggests an alternative strategy to the multi-target approach. These studies reveal that oncogene activation introduces secondary physiologic changes that stress cellular capacity for survival. Consequently, tumor cells become hyper-dependent on processes required to compensate for these stressful conditions^{26, 27}. This phenomenon is termed “non-oncogene addiction” since the compensatory processes required for tumor survival do not directly contribute to the cancer formation. In other words, even genes that are not themselves targeted by tumorigenic mutations may well become essential for the tumor to survive the stressful environment and fuel the demanding process of tumor progression. Consequently, interference with the function of such genes can be rate-limiting to the particular mechanism in the tumor, but not as much in the normal counterpart cells. Importantly, such adaptively essential genes that underlie the ‘non-oncogene addiction’^{26, 27} of cancer cells can be therapeutically targeted if suitable drugs or other approaches are available.

There are several examples of such critical non-oncogenic pro-survival functions required for maintenance of the tumorigenic state in glioblastoma. EGFR is a critical proto-oncogene in glioblastoma pathogenesis^{10, 28}. Our laboratory has demonstrated that EGFR hyperactivation results in increased accumulation of reactive oxygen species (ROS), which in turn cause cytotoxic DNA damage. To compensate for the deleterious effect of ROS, EGFR hyperactive glioblastomas exhibit increased reliance on DNA repair process that repair ROS related DNA damage²⁹. Selective targeting of EGFR hyperactive glioblastomas can, thus, be achieved by inhibition of these repair process. Other groups have demonstrated that EGFR hyperactivation in glioblastoma cell lines heightens requirement for lipogenesis^{30, 31}. Other examples of such critical non-oncogenic pro-survival functions required for maintenance of the tumorigenic state include dependency on mechanism for compensating mitotic and proteotoxic stress and interplay with the tumor microenvironment including the immune system²⁶. While illustrative examples of strategies based on these “non-oncogene” addiction paradigms have been established in other cancers, the pertinence to glioblastoma awaits rigorous interrogation.

The principle of non-oncogene addiction suggests that there is a wider spectrum of therapeutic options than afforded under the paradigm of “oncogene addiction”. In many cases, compensatory processes involved in “non-oncogene addiction” are the same as those that basic scientists have studied for years (for instance, DNA repair). Mechanistic investigations into these biologic processes by the basic scientists have yielded a rich database of inhibitors. Thus, identifying gene functions that compensate for oncogene induced cellular stress should afford opportunities to tap into this rich database and expand the denominator of drugs available for combinatorial therapy. Identifying genes that are synthetically lethal with oncogenes constitute an attractive means to this end.

It is important to note that effects of therapies designed based on the principles of “oncogene addiction” and of “non-oncogene addiction” are inherently antagonistic. For instance, EGFR inhibition leads to a reduction of ROS, obviating the need for DNA repair²⁹. In this context, combination of DNA repair inhibition and EGFR inhibition would not be desirable. Rational strategies for synthesizing the two therapeutic paradigms remains a major intellectual challenge.

5. Concept 4: Tumor initiating cells

Another advance that may profoundly change our thinking about solid tumors including glioblastoma involves the concept of tumor initiating cells. The experimental observation is

that within a total population of glioblastoma cells, there appears to be a small sub-population of cells that are highly tumorigenic (hence the term “tumor initiating cells” or “TICs”) with tremendous capacity for self-renewal^{32, 33}. To the extent that glioblastoma tumor initiating cells share many common properties when compared to neural stem cells, it is proposed that the TICs originated from stem cells. While there are some data supporting this hypothesis⁵, the universality of this hypothesis remain controversial.

Protein markers to prospectively identify and isolate these putative TICs such as the transmembrane glycoprotein CD133 (prominin-1) in glioblastomas have been identified⁵. However, the value of CD133 as a single marker of glioblastoma TICs remains controversial, partly because also CD133-negative glioblastoma cells could give rise to tumors in an intracranial mouse xenograft model³⁴⁻³⁶. These uncertainties motivate an ongoing search for additional candidate TIC markers. Candidate cell surface molecules suggested in this context include the adhesion glycoprotein L1CAM³⁷, surface carbohydrate antigen CD15 (SSEA-1)³⁸, surface marker A2B5³⁹, and integrin $\alpha 6$ ⁴⁰. Currently, there are no generally accepted cell surface markers for defining TIC. The definition of TICs remains a functional one as defined by the ability of a tumor cell to sustain self-renewal and initiate glioblastoma formation in immuno-compromised xenograft models.

Arguably, the most important aspect of the concept of TICs is that this population appeared particularly resistant to conventional radiation and chemotherapy³². In this context, TICs may be responsible for glioblastoma recurrence after conventional therapy. Given such properties, it is understandable that glioblastoma research has recently focused on identification and development of potential anti-TIC therapies. Two of these strategies, namely targeting the TICs as part of a vascular niche, and attempts to overcome their therapeutic resistance, will be discussed in the following sections on glioblastoma angiogenesis and the role of DNA damage response pathways, respectively. Here, we briefly consider strategies that are emerging as potentially fruitful approaches to treat glioblastoma through targeting TICs.

The first strategy reflects the efforts to identify suitable cell surface markers to reliably identify glioblastoma TICs – with the hope of conjugating the corresponding antibody to cytotoxic compounds as therapeutic agents. The second strategy is based on observations that some TICs, like neural stem cells, can be induced into a differentiated state whereby the self-renewal properties are lost. Among the suggested agents to induce such TIC differentiation, the bone morphogenetic proteins (BMPs) appear promising⁴¹. The third strategy involves modulating specific signaling pathways required for maintaining the TIC state. Pathways targeted include those mediated by EGFR, Wnt-beta catenin, STAT3, Sonic Hedgehog-Gli, and Notch pathways⁴². To the extent that these pathways are also regulated by miRNAs such as miR-21⁴³, such miRNA constitute therapeutic targets in this strategy. Finally, normal neural stem cells have been shown to migrate toward and track TICs. Based on this principle, neural stem cells have been used as delivery vehicles to increase local concentration of therapeutic agents in the vicinity of TICs⁴⁴.

6. Summary

In this chapter, we have discussed key principles underlying current development of glioblastoma therapeutics. Emphasis was placed on conceptual framework rather than specific drugs or targets. These frameworks should serve as the basis for translating fundamental biologic tenets into clinically useful therapeutic strategies.

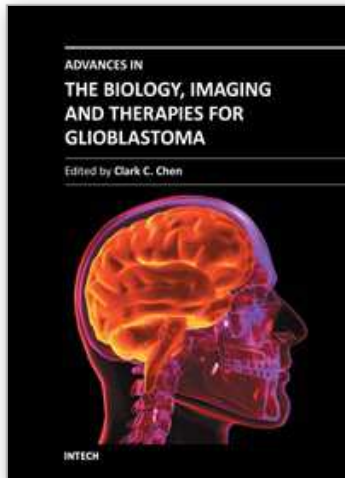
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This book is intended for physicians and scientists with interest in glioblastoma biology, imaging and therapy. Select topics in DNA repair are presented here to demonstrate novel paradigms as they relate to therapeutic strategies. The book should serve as a supplementary text in courses and seminars as well as a general reference.

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