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Molecular Etiology of Glioblastomas: Implication of Genomic Profiling From the Cancer Genome Atlas Project

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1. Introduction

In the landmark review by Hanahan and Weinberg¹, the authors distilled the essence of cancer into six distinct phenotypes, including evasion of apoptosis, self-sufficiency in growth signals, insensitivity to anti-growth signals, tissue invasion and metastasis, limitless replicative potentials, and sustained angiogenesis. The widely accepted paradigm suggests that cancer arises as a result of mutations or epigenetic events, which alter function of genes critical for attaining these phenotypes. These gene functions are intimately linked to the regulation of developmental processes², their aberrant function in tumor inevitably lead to cell states that resemble stages during normal development. These cell states can be captured using genomic technologies to define distinct molecular subtypes. With the advent of The Genome Cancer Atlas project for glioblastoma^{3,4}, we now have a glimpse of the genetic events underlying glioblastoma pathogenesis as well as distinct molecular subtypes. In this review, the genomic profiles of glioblastoma will be reviewed in the context of the properties described by Hanahan and Weinberg. Molecular subtypes of glioblastoma will be discussed in the context of developmental biology and the cell of origin.

2. Glioblastoma

Glioblastoma is the most common form of primary brain tumor, with dismal prognosis. The incidence of this tumor is fairly low, with 2-3 cases per 100,000 people in Europe and North America. Despite its rarity, overall mortality related to glioblastoma is comparable to the more prevalent tumors⁵. This is, in large part, due to the near uniform fatality of the afflicted patients. Indeed, glioblastoma is one of the most aggressive of the malignant tumors. Without treatment, the median survival is approximately 3 months⁶. The current standard of treatment involves maximal surgical resection followed by concurrent radiation therapy and

chemotherapy with the DNA alkylating agent, temozolomide⁷. With this regimen, the median survival is approximately 14 months. For nearly all affected, the treatments available remain palliative.

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 phenotype¹. The exact number and nature of genetic alterations and deregulated signaling pathways required for tumorigenesis remains an issue of debate⁸, although it is now clear that CNS carcinogenesis requires multiple disruptions to the normal cellular circuitry^{3,4}.

3. The Cancer Genome Atlas (TCGA) project

The Cancer Genome Atlas (TCGA) is a comprehensive and coordinated effort to catalogue the genetic and epigenetic changes in the cancer genome, with goals of identifying those responsible for carcinogenesis. The project constitutes a joint effort of the National Human Genome Research Institute (NHGRI), National Cancer Institute (NCI), and the U.S. Department of Health and Human Services, and collects tumor specimen from major cancer centers spanning across the continental U.S. The project aims to provide the genomic profile of 500 specimens of various cancer types using state-of-the-art platforms for sequencing, microRNA, mRNA, single-nucleotide polymorphisms, and methylation profiling.

TCGA started as a pilot project in 2006 with focus on glioblastoma as the first cancer type for study. With the success of the pilot project, TCGA plans to expand its efforts to aggressively pursue 20 or more additional cancers. This article will review the major insights derived from the TCGA in the context of the cancer phenotypes proposed by Hanahan and Weinberg¹.

4. The cancer phenotype

The aggregate of cancer research investigation spanning the past three decades suggest that cancer is a genetic disease characterized by mutations or epigenetic events that abrogate or compromise regulatory circuitry governing cell proliferation and homeostasis⁸. In the landmark review by Hanahan and Weinberg¹, the authors distilled the essence of these regulatory circuits into six distinct phenotypes, including evading apoptosis, self-sufficiency in growth signals, insensitivity to anti-growth signals, tissue invasion and metastasis, limitless replicative potentials, and sustained angiogenesis. The following section will review the TCGA findings pertinent to these phenotypes.

4.1 Self-sufficiency in growth signals – The Receptor Tyrosine Kinase (RTK)/Phosphoinositid 3 Kinase (PI3K) signaling cascade

Active cellular proliferation in normal cells requires signals from its environment. These signals typically involve the binding of a transmembrane receptor to growth factors, extracellular matrix components, or cell surface components. This mitogenic signaling process is under stringent regulation in normal cells. Typically, multiple ligand-receptor interactions in a permissive cellular state are required before cellular proliferation can take place. This regulation minimizes the probability of dysregulated, autonomous cell growth^{1,9}. The

importance of growth factors in biology was recognized by a Nobel Prize in Physiology or Medicine to Stanley Cohen and Rita Levi-Montalcini in 1986. Subsequent identification that many oncogenes participate in cellular signaling related to growth factor function was also awarded a Nobel Prize in Physiology or Medicine (to Michael Bishop and Harold Varmus in 1989).

To abridge this stringent growth regulation, tumors often mutate the transmembrane receptors or their downstream effectors in ways that constitutively activate the pathway. The pathway most commonly mutated to achieve this end in glioblastoma involves the RTK-PI3K pathway^{9,10}. RTKs are cell surface receptors that are normally activated only in response to growth factor binding⁹. Results from the TCGA revealed that nearly all glioblastomas harbor activating mutations or amplifications in genes required for this signaling cascade^{3,4,11,12}. Epidermal Growth Factor Receptor (EGFR) and Platelet Derived Growth Factor Receptor (PDGFR) are two prototypical members of RTK^{3,4,12}.

For EGFR and PDGFR, binding of the growth factor to the ligand leads to homo- or heterodimerization of the receptor. This dimerization facilitates autophosphorylation of the cytoplasmic domains of the dimerized receptor at select tyrosine residues⁹. The phosphorylated tyrosine residue, in turn, recruits and binds to other signaling proteins to the cell membrane. In some cases, the phospho-tyrosine bound proteins serve as a platform for the recruitment of other effector proteins. In other cases, the bound protein undergoes a conformational change upon binding to the RTK and becomes activated in the process⁹.

One of the critical cellular kinases that become activated upon binding to RTK is PI3K¹³. PI3Ks catalyze the phosphorylation of a critical component of the cell surface, phosphatidylinositol-4,5-isphosphate (PI(4,5)P₂). This phosphorylation generates phosphatidylinositol-1,4,5-isphosphate (PI(1,4,5)P₃), which in turn serves as a docking site for pro-proliferative down-stream effector proteins¹⁰. Thus, RTK activation transforms the cell membrane into a catalytic surface populated with a high density of pro-mitotic signaling molecules, ultimately leading to cell proliferation.

Expectedly, gene functions that inhibit the generation of this pro-proliferative “catalytic surface” function as tumor suppressors. For instance, the hydrolysis of PI(1,4,5)P₃ into PI(4,5)P₂ is catalyzed by a phosphatase termed Phosphatase and Tensin Homology (PTEN). PTEN inactivating mutations have been identified in up to 50% of tumor specimens¹⁴. Similarly, one of the effector proteins recruited to a phosphorylated RTK is Ras. Ras encodes a monomeric G-protein that cycles between an active form bound to GTP and an inactive form that binds to GDP¹⁵. It functions as a critical component of the pro-proliferative “catalytic surface”. Through a series of protein-protein interactions, RTK activation catalyzes the exchange of GDP for GTP in Ras, initiating signals required for cellular proliferation. The protein encoded by neurofibromatosis 1 (NF1) functions to catalyze the exchange of GTP for GDP in Ras, consequently preventing cell proliferation. In this context, it is not surprising that NF1 patients are predisposed to gliomagenesis¹⁶. The TCGA results showed that approximately 20% of glioblastomas harbor loss of function mutations in NF1^{3,4}. TCGA additionally revealed gain of function mutations in K-ras have also been identified in glioblastoma specimens³.

4.2 Insensitivity to anti-growth signals – The RB axis

In addition to receiving pro-growth signals from their environment, cells also receive multiple anti-proliferative signals to prevent cell growth. These anti-growth signals, like

their pro-mitotic counterparts, are sensed by the binding of transmembrane receptors to soluble factors, extracellular matrix components, or cell surface components.

Most of these anti-proliferative signals operate at the G1 phase of the cell cycle to trigger either 1) entry into a transient quiescent (G0) state or 2) entry into a post-mitotic, differentiated state. The importance of cell cycle regulation in biology was recognized by a Nobel Prize in Physiology or Medicine to Leland Hartwell, Tim Hunt, and Sir Paul Nurse in 2001.

At the molecular level, nearly all of these signals converge at the retinoblastoma protein (RB) ¹. In quiescent cells, the RB protein is hyper-phosphorylated. This form of RB binds and sequesters the E2F family of transcription factors¹⁷. The genes transcribed by these transcription factors are essential for the G1-S transition of the cell cycle¹⁸. Phosphorylation of RB releases the sequestered E2F transcription factors and allows for cell growth. During normal cell cycle progression, induction of cyclin D1 and its associated cyclin-dependent kinases, CDK4 and CDK6, at the G1-S transition is responsible for the phosphorylation of RB. The kinase activity of the CDK4/6-cyclin D complex is under complex regulation, including the critical negative regulators CDKN2A (p16^{Ink4a}), CDKN2B, and CDKN2C. TCGA results showed that mutations and gene amplifications disrupting RB function are found in approximately 80% of glioblastomas, suggesting the critical importance of escaping anti-growth signals^{3,4}. Additionally, single nucleotide polymorphisms in the *CDKN2A* and *CDKN2B* have been identified as risk factors for glioma development^{19,20}.

4.3 Evading apoptosis – The p53 axis

Apoptotic programs are inherent in all normal cells. These programs are activated by a number of physiologic signals during development and/or in response to cellular stress. Since the tumor state is associated with cellular stress capable of activating apoptosis (e.g. increased oxidative stress, increased DNA damage accumulation), inactivation of these programs constitute a critical step during carcinogenesis. The importance of apoptosis as a fundamental biologic process was recognized by a Nobel Prize in Physiology or Medicine awarded to Sydney Brenner, Robert Horvitz, and John Sulston in 2002.

The regulation of apoptotic pathways is highly complex²¹. Broadly speaking, there are two pathways of apoptosis that converge on the activation of effector proteases (termed caspases), which ultimately trigger the pathognomonic DNA fragmentation, cell shrinkage, and membrane blebbing. The intrinsic cell death pathway (often termed the mitochondrial apoptotic pathway) involves the release of cytochrome c from the mitochondrial membrane space²². Binding of cytochrome c to a protein termed apoptosis protease-activating factor 1 (APAF-1), in turn, initiates the caspase cascade. In contrast, the extrinsic apoptotic pathway operates independently of mitochondria and is activated by direct signaling from cell surface receptors to the effector caspase²³.

Both intrinsic and extrinsic apoptotic programs are profoundly influenced by the p53 tumor suppressor protein²⁴. *TP53* encodes a transcription factor that regulates gene sets critical for cell cycle progression and apoptosis. Under normal conditions, p53 is a short-lived protein²⁵. In response to cellular stress (for instance, DNA damage or oncogene expression), p53 undergoes post-translational modifications and protein-protein interactions that enhance its stability and transcriptional activity²⁵. Key among the transcripts regulated by p53 are pro-apoptotic genes (including BAX and Puma) that facilitate both the intrinsic and extrinsic pathway²⁴. Additionally, p53 interact with a number of anti-apoptotic proteins to inhibit their function²⁴.

There are several lines of evidence that point to the importance of the p53 axis in glioblastoma pathogenesis. In the TCGA database, mutations that inactivate this axis are found in greater than 70% of glioblastoma specimens^{3,4}. Patients harboring germ-line mutations in *TP53* are afflicted with cancer predisposition including increased risk for glioblastoma²⁶. Finally, inactivation of p53 is required for glioma formation in genetically defined murine models²⁷.

4.4 Replicative potential

The definition of cancer as a continuous growing entity implies that normal cells exhibit a limited capacity for proliferation. Indeed, estimates based on tissue culture work suggest that most normal cells have the capacity for 50 doublings²⁸. Studies over the past three decades suggest that the main reason for this limited life span involve progressive shortening of chromosomes due to loss of telomeres. Telomeres consist of thousands of six base pair sequence element of repeats that are located at the ends of every chromosome. Because of the inability of DNA polymerases to replicate the 3' ends of chromosomal DNA, approximately 60 base pairs of the telomeric sequence is lost with each replicative cycle²⁹. With progressive erosion of the telomeric sequence, the unprotected chromosomal ends participate in aberrant fusion events that inevitably result in cell death³⁰.

To overcome this inherent limitation, most cancer cells activate an enzyme called telomerase. Telomerase is a reverse transcriptase capable of elongating telomeres³¹. Various mechanisms are employed by tumors to activate telomerase in order to sustain continued cell growth. Elizabeth Balckburn, Carol Greider, and Jack Szostak were awarded the Nobel Prize in Physiology or Medicine in 2009 for their discovery of telomerase.

With regards to glioblastomas, single nucleotide polymorphisms in two genes encoding components of the telomerase (*RTEL1* and *TERT*) have been identified as risk factors for glioma development^{19, 20}. Additionally, elevated expression level of *TERT* in glioblastoma is associated with decreased patient survival³². These studies suggest a critical importance of telomeric biology in glioblastoma growth and survival.

Angiogenesis. The intense proliferation of cancer cells require continued supply of oxygen and nutrients. Due to inherent limitations on the distance that oxygen and macromolecules can travel, virtually all cells in a tissue reside within 100 μ m of a capillary. In xenograft model systems, solid tumors can only proliferate up to a size of 1-2 mm without development of new blood supply³³. Thus, angiogenesis necessarily constitutes a pre-requisite during solid tumor progression.

One way by which cancer cells signal angiogenesis is by secretion of soluble factors that bind to receptors present on the surface endothelial cells. A key soluble factor that functions in such capacity is the Vascular Endothelial Growth Factor (VEGF). VEGF binds to RTKs on the surface of endothelial cells to facilitate their proliferation – leading to angiogenesis³⁴. In normal cells, transcription of VEGF and other pro-angiogenic signaling factors are under strict regulation. The induction of Hypoxia Inducible Factor I (HIF1) is a pivotal element in this regulatory network³⁵. HIF1 encodes a dimeric transcription factor consisting of two subunits: HIF1 α and HIF1 β . HIF1 β is constitutively expressed irrespective of oxygen concentration, whereas HIF1 α levels increase dramatically in response to hypoxia. The underlying mechanism for this regulation is that HIF1 α is hydroxylated by HIF Prolyl-4-Hydroxylase (HPH) in the presence of di-oxygen (O₂), iron, and α -ketoglutarate. The hydroxylated HIF1 α is targeted for proteasome degradation. Without molecular oxygen,

HIF1 α is not hydroxylated and is free to dimerize with HIF1 β to activate the transcription of downstream pro-angiogenic factors.

Integrated analysis of genomic data in glioblastoma revealed recurrent mutations in the R132 residue of isocitrate dehydrogenase 1 (IDH1)⁴, a gene largely responsible for the production of α -ketoglutarate. The TCGA data revealed that the IDH1 mutation is predominantly found in one particular molecular subtype of glioblastoma^{12, 36} (see following section on **molecular subtypes**). The wildtype IDH1 normally functions as a homodimer that converts isocitrate to α -ketoglutarate³⁷. Biochemical characterization of the R132 mutated IDH1 revealed that it functions in a dominantly negative fashion to inhibit the process. Expectedly, glioblastoma harboring the R132 IDH1 mutation harbor decreased levels of α -ketoglutarate. Given the importance of α -ketoglutarate in HIF1 α degradation, one would anticipate increased HIF1 α accumulation and increased VEGF secretion in glioblastoma harboring the IDH1 mutation. These observations were confirmed in a panel of primary glioblastoma specimens³⁸. Thus, the IDH1 mutation constitutes an example of how glioblastoma subverts the endogenous molecular circuit to facilitate angiogenesis. It should be noted that the effect of the IDH1 mutation appears pleiotropic. Another study revealed that the R132 mutant IDH1 proteins exhibits a gain-of-function phenotype by generating R(-)-2-hydroxyglutarate, a carcinogenic metabolite³⁹.

In glioblastomas without IDH1 mutation, alternate mechanisms are utilized to facilitate angiogenesis. It is somewhat intuitive that during normal development, periods of cellular proliferation must be coordinated with angiogenesis. Indeed, a large body of work suggests that gene functions that facilitate cell-autonomous growth or insensitivity to growth inhibition and apoptosis also tend to facilitate angiogenesis^{40, 41}. It is likely that most glioblastoma cells attain angiogenesis by aberrant activation of such coordinated developmental programs. For instance, EGFR activation has been shown to up-regulate VEGF in both HIF dependent and independent manner⁴². Inactivation of Rb increases VEGF expression and angiogenesis *in vivo*⁴⁰. Similarly, p53 normally up-regulates thrombospondin 1, an inhibitor of angiogenesis⁴³; inactivation of p53 can facilitate angiogenesis by ablation of this up-regulation.

4.5 Invasion and metastasis

The ability to invade and metastasize constitutes the fundamental distinction between benign and malignant tumors. It is important to note that invasion refers not just to distortion of normal tissue secondary to tumor growth. Instead, it refers to a coordinated set of cellular activities to destroy and migrate into the surrounding normal tissue. Metastasis refers to the capacity to travel via circulation to a distant tissue site³³. Glioblastoma is unique in that while it is one of the most invasive of cancers, it rarely metastasizes outside of the central nervous system.

It is a truism that cancer cells generally retain some general properties of the cell of origin. Since glioblastoma originates from astrocytes, which normally possess significant migratory capacity, the invasive nature of glioblastoma would be anticipated. During normal development, astrocytes migrate in a centripetal manner to establish a scaffold for neuroblasts⁴⁴. Additionally, in response to injury, astrocytes migrate to the affected region to form a gliotic scar⁴⁵. This migratory capacity is the phenotypic expression of carefully orchestrated interactions between cellular cytoskeletal proteins, cell adhesion molecules, and extracellular matrix³³.

To date, the TCGA has not uncovered gain of function mutations in these proteins. However, enhanced invasive properties have been associated with mutations establishing autonomous growth or suppressing apoptosis. For instance, aberrant EGFR activation results in increased expression and phosphorylation of cell adhesion molecules that ultimately lead to increased invasiveness⁴⁶. Similarly, the p53 mutation drives cancer invasiveness by facilitating the recycling of integrin, a class of cell surface receptor that interacts with extracellular matrix during cell migration⁴⁷.

The aggregate of the data suggest that both angiogenesis and cell migratory properties are intimately integrated into a master circuitry controlled by critical proteins that dictate cellular response to growth or apoptotic signals. In this context, mutations facilitating self-autonomous growth or suppression of apoptosis also contribute to angiogenesis and cell invasion.

4.6 Cross-talk between canonical pathways

The conceptualization of distinct pathways contributing to the various critical phenotypes constitutes a simplification aimed to consolidate distinct biological concepts. The reality is that pathways mediating the cancer phenotype exhibit high degrees of cross-talk and functional redundancy. For instance, EGFR hyperactivation is associated with increased tumor growth (replicative potential), angiogenesis, and increased tumor motility⁴⁸. Similarly, many genes mediating cell motility, telomere function, and angiogenesis are under transcriptional regulation by p53 and RB associated E2Fs⁴⁹.

5. Pathway of glioblastoma progression

It was previously thought that glioblastoma arises from the acquisition of a defined set of mutations that occur in a particular temporal order. This model is largely grounded on the framework established in colon cancer, where a series of genetic alterations characterizes different phases of neoplastic progression⁵⁰. The framework is supported by the observation that Grade II astrocytomas typically harbor mutations in p53; Grade III astrocytomas harbor activating mutations/amplifications of CDKN2A (p16^{Ink4a}); and Grade IV astrocytomas harbor mutations in PTEN and EGFR⁵¹. This data was interpreted to mean that glioblastoma results from sequential inactivation of the p53, RB, and RTK/PI3K axes.

While such a paradigm may hold true for a subset of the secondary glioblastomas, the picture emerging from the genomic characterization of primary glioblastomas reveals a much more dynamic process^{3,4}. The profile of somatic mutations in different glioblastomas is highly variable. These results suggest that most glioblastomas evolve along a multitude of pathways in response to differing selective pressures to achieve the phenotypes described by Hanahan and Weinberg⁵². This somewhat stochastic model of cancer progression further implies that mutations critical at one juncture in the neoplastic process may lose relevance as additional mutations are acquired. Thus, while a mutational profile constitutes an archeological profile of the history of the neoplasm, extrapolating therapeutic targets from such a profile may be challenging.

6. Molecular subtypes

Genome-scale gene expression profiling using microarray technology have revealed distinct molecular subtypes within tumors previously classified as glioblastomas^{12, 53-55}. The number

of subtypes varies depending on the study, however, three subtypes consistently appear across independent studies and reflect distinct biologic and clinical behaviors^{12, 55, 56}. Importantly, the transcript signature parallels those obtained during distinct stages in neural development, suggesting the tumor may have arisen from different stages of neurogenesis⁵⁵.

The first subtype is termed pro-neural. The transcript signature resembles those of neuroblasts and oligodendrocytes derived from fetal and adult brain⁵⁵. This subtype harbors molecular and clinical features that closely mirror those previously classified as secondary glioblastomas. Molecularly, pro-neural glioblastomas harbor mutations classically associated with the secondary subtype, including p53 and PDGFR¹². Accordingly, grade II and III gliomas harbor molecular signatures most reminiscent of the pro-neural subtype⁵⁵. Clinically, this subtype typically affects younger patients, is associated with improved overall survival⁵⁵, and responds poorly to concurrent radiation/temozolomide treatment upon disease progression¹². Interestingly, mutations in the isocitrate dehydrogenase 1 gene (*IDH1*), a metabolic protein required for conversion of isocitrate to α -ketoglutarate during the citric acid cycle, is frequently observed in pro-neural glioblastomas (see section on glioblastoma predisposition syndromes). The molecular basis of how this mutation contributes to the cancer phenotype remains an active area of investigation.

Classical (also termed proliferative by some authors) constitutes the second molecular subtype. Transcript signature in the classical subtype resembles those observed in transit amplifying neural progenitor cells⁵⁵ and murine astrocytes¹². This subtype is exclusively found in WHO grade IV tumors and constitutes a form of primary glioblastoma⁵⁷. Molecularly, this subtype is characterized by amplification of (or activating mutations in) EGFR and CDKN2A (p16^{ink4a}). Genes involved in pathways highly active in neural stem and progenitor cells (including the Notch and Sonic hedgehog pathway) are highly expressed in the classical subtype⁵⁸. The patients afflicted are typically older than those with the pro-neural subtype. Relative to the other subtype, patients afflicted with the classical subtype exhibit the worst prognosis, but the best therapeutic response to concurrent radiation/temozolomide treatment.

The mesenchymal subtype makes up the final category. The transcript signature in the mesenchymal subtype mirrors those observed in the neural stem cells of the forebrain⁵⁵ and cultured astroglial cells⁵⁹. Most cultured glioblastoma cell lines exhibit transcript signatures that fall into this subtype. Molecularly, the subtype is characterized by inactivating NF1 and PTEN mutations¹². This subgroup also has the highest expression of angiogenesis markers including VEGF (Vascular Epithelial Growth Factor) transcripts and highest density of microvascular proliferation¹². The patients afflicted are typically older than those with the pro-neural subtype. Relative to the other subtypes, mesenchymal glioblastomas exhibit clinical response similar to the classical subtype, and a trend toward slightly improved prognosis and response to radiation/temozolomide therapy¹².

There is significant debate with regards to the origin of the distinct molecular subtypes. On one extreme is the thought that the subtypes originate from the same cell type with differences driven by distinct signaling pathways. The other extreme suggests that subtypes are determined by the same signaling pathways activated in a different cell of origin. The observation that the same canonical pathways are altered irrespective of subtype would tend to support the latter hypothesis. However, it is conceivable that different genes thought to participate in the same canonical pathway may modulate processes distinct of that

pathway. Such functions may contribute to the distinct molecular subtypes. Still, it is conceivable that differences in signaling and cell of origin both contribute to subtype formation. This critical debate awaits experimental resolution.

7. Summary

The past three decades of work in cancer research has generated a sophisticated conceptual framework for the process of neoplastic transformation. The framework suggests that genetic and epigenetic events inactivating critical pathways that regulate several key aspects of cellular function are an etiology. These cellular functions can be categorized as self-sufficiency in growth signaling, evasion of apoptosis, insensitivity to anti-growth signals, tissue invasion, and limitless replicative potential and angiogenesis. This framework has largely been validated by a large scale, high-throughput characterization of the genomic and epigenomic landscape in glioblastomas. The picture emerging from these analyses suggests that most glioblastomas evolve along a multitude of pathways in response to differing selective pressures to achieve the cancer phenotypes. Transcript based analysis revealed distinct subtypes with potential implications with regards to the cell of origin. The dynamic interplay of growth dysregulation and the cell of origin during the neoplastic transformation process harbors vital implications with regards to therapeutic development.

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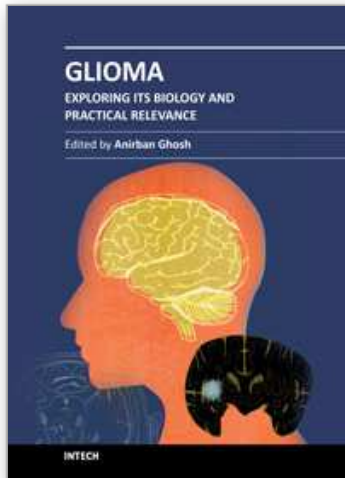
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The title 'Glioma - Exploring Its Biology and Practical Relevance' is indicative of its content. This volume contains 21 chapters basically intended to explore glioma biology and discussing the experimental model systems for the purpose. It is hoped that the present volume will provide supportive and relevant awareness and understanding on the fundamental advances of the subject to the professionals from any sphere interested about glioma.

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