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Advances in the genetics of glioblastoma: are we reaching critical mass?

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Abstract

Glioblastoma is the most common and highest-grade brain tumor, causing over 10,000 deaths each year in the US alone. Given the resistance of this tumor to standard surgery, radiation and chemotherapy, an understanding of the underlying genetic lesions is vital. Recent efforts to comprehensively profile glioblastomas using the latest technologies, both by The Cancer Genome Atlas (TCGA) project and by other groups, are addressing this need. Some genetic aberrations in glioblastoma have been known for decades, but early output from the new profiling initiatives has further illuminated the relevant genetics in this disease. Some genetic lesions, such as *TP53* mutation, *NF1* deletion or mutation, and *ERBB2* amplification, have been found to be more common than was previously reported. New and unexpected discoveries have also been made, such as frequent mutations of the *IDH1* and *IDH2* genes in secondary glioblastoma. We might be tempted to speculate that we are approaching a comprehensive knowledge of the genetic lesions involved in glioblastoma, although other major discoveries doubtless remain to be made. In addition, the complex task of incorporating our updated knowledge into new—and possibly personalized—therapies for patients with glioblastoma still lies ahead.

Introduction

Glioblastoma is the most common primary malignant brain tumor in adults, with an incidence of approximately 10,000 cases per year in the US alone.[1] Glioblastoma is one of the most aggressive cancers, with affected indivi duals having a median survival of 12-15 months following diagnosis.[2] Most patients with glioblastoma are diagnosed at presentation (so-called primary glioblastoma), but some tumors progress from previously diagnosed lower-grade gliomas and are termed secon dary glioblastomas. The tumor is characterized by rapid growth, a high degree of invasiveness, and resistance to standard treatments, but does not tend to metastasize outside the brain. Unfortunately, treatment for patients with glioblastoma, which generally consists of maximal surgery, external beam radiotherapy and chemotherapy, has changed little over the past few decades, other than the addition of one proven chemotherapy—the alkylating drug temozolomide. Chemotherapy agents generally have little efficacy against glioblastoma, but this relatively new drug provides marked benefits in a subset of patients.[2,3] The limited treatment options for glio blastoma have driven an intensive search into the genetic lesions underlying this deadly cancer, with the aim of developing more-rational and more-effective therapies.

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Some of the most common mutations in glioblas toma were uncovered several decades ago, but have yet to substantially influence the treatment of this disease. Further discoveries regarding the genetics of glio blastoma have been scarce until recently. Now, however, a plethora of new genetic findings are emerging that might not only illuminate the origins of these cancers, but also define treatment-sensitive or treatment-resistant subsets and guide our therapeutic decision-making. Many of these discoveries have been made through focused work by individual laboratories, but some were achieved through multicenter, high-throughput screening efforts enabled by the latest sequencing and profiling technologies. The Cancer Genome Atlas (TCGA) is a prominent example of the latter approach. A central theme that has emerged from these recent efforts is that the genetics of glioblastoma remains highly complex, with no single unifying thread emerging.

In light of this latest influx of information, we now take stock of our current knowledge of the genetics of glioblastoma. In this Review, we will first describe the techniques and approaches that have been used over the years to dissect the genetics of glioblastoma, from the older methods to the most recent high-throughput efforts. We will then describe lesions in key signaling pathways, focusing on genetic alterations such as mutations and copy number changes and generally excluding the parallel field of epigenetics. Finally, we will discuss the evolving influence of genetics on the clinical management of glioblastoma and possible future directions for the field. After decades of frustration in treating these aggressive cancers, our knowledge of glio blastoma genetics could finally be reaching a critical mass at which it begins to guide our therapies.

Screening approaches

The first reports on genetic lesions in glioblastoma began to emerge around 35 years ago.[4,5] For many years, well-known oncogenes or tumor suppressor genes that had been identified in other cancers, such as epidermal growth factor receptor (*EGFR*) and tumor protein p53 (*TP53*), were studied in glioblastoma. Early tools that were used to identify genetic differences in glio blastoma included the study of restriction fragment length polymorphisms, as well as slow and labor-intensive methods for DNA sequencing. Later techniques included compara tive genomic hybridization to identify regions of amplification or deletion. Over the past 10-15 years, other high-throughput methods, such as microarrays to global ly characterize gene expression, have been introduced, with pronounced expression changes sometimes pointing the way towards underlying genetic lesions. Methods for DNA sequencing have also evolved, enabling rapid completion of projects on a whole-genome scale.

The advances in high-throughput profiling of tissue samples at multiple levels raised the prospect of dissecting the genetics of a given cancer in a comprehensive and systematic fashion, as opposed to the piecemeal approach permitted by older methods. Performing such studies as a large-scale effort among multiple institutions, with a large number of tissue samples and good quality control, should allow both low-frequency and high-frequency genetic changes to be identified. The simulta neous use of multiple profiling modalities on the same large sample sets enables the results to be correlated at the genetic, epigenetic and gene expression levels. These considerations provided the basis for the foundation of TCGA —a national, multi-institutional effort funded by the NIH that is applying several profiling modalities to three cancer types in a high-throughput fashion. The three cancer types—glioblastoma, squamous-cell lung cancer and ovarian carcinoma—were chosen in view of their poor prognosis and the availability of relatively large amounts of high-quality tissue samples stored in biorepositories. The techniques used to characterize the numerous samples include sequencing of a select number of genes, microarray analysis of gene expression, comparative genomic hybridization (CGH) arrays to study copy number variation,

methylation arrays, and microRNA (miRNA) expression profiling. The first publica tion to emerge from TCGA was an interim analy sis of 206 glioblastomas, nearly all of which were of the primary type.[6] This report did not provide output from all of the modalities studied, but it did include gene expression, methylation, DNA copy number and mutational analysis of 91 of the 206 tumors. The results did not cause a dramatic paradigm shift, but they provided some useful new information, reinforced or weakened some previously held dogmas, and indicated an overall schema of the few pathways that must be dysregulated for glioblastoma to occur.

Other high-throughput profiling projects have been developed to complement the work by TCGA, including one that performed near-total genome sequencing of numerous glioblastomas.[7] The results of these studies will be integrated below into an overview of the genetic aberrations observed in glioblastoma.

Changes in key pathways

Figure 1 illustrates the main signaling pathways that seem to be affected in glioblastoma.

The Ras and PI3K-Akt oncogenic pathways

The initial discovery that a high percentage of human glioblastoma samples (35-40%) harbor amplifications of *EGFR* dates back to 1985.[6,8] Later, investigators determined that glioblastomas also commonly contain activating mutations in this gene, or overexpress it through a mechanism other than amplification.[9,10] Dysregulation of *EGFR* has generally been associated with primary glioblastoma (Box 1). *EGFR* functions as an oncogene in several cancers. The EGFR protein stimulates cell division, cell survival and invasion through its role as a receptor tyrosine kinase that activates key oncogenic pathways. EGFR is best known as a driver of the Ras pathway, but in some settings it can also upregulate the phosphatidylinositol 3-kinase (PI3K)-Akt pathway. In view of the dysregulation of *EGFR* in a high percentage of glioblastoma cases, EGFR inhibitors were enthusiastically received in the clinic but have proved to be disappointing as single agents, with response rates of ~10% being reported.[11,12]

Other genetic lesions that activate the Ras pathway also seem to have a role in glioblastoma. It has long been known that patients with neurofibromatosis type 1, which is caused by mutations of the neuro fibromin 1 (*NF1*) gene, are at an increased risk of gliomas.[13] While usually low-grade in nature, these tumors can sometimes progress to glioblastoma. The functions of the NF1 protein are not completely understood, but they seem to include inhibition of Ras activity. Familial mutations in the *NF1* gene act in a dominant-negative fashion to inacti vate NF1 function and upregulate Ras activity.[14,15] Until recently, *NF1* mutations were thought to be relatively rare in glioblastoma, but the TCGA data indicate they are present in as many as 18% of cases—far more than was previously suspected.[6]

Genes encoding receptor tyrosine kinases other than EGFR have been found to be mutated, amplified or otherwise overexpressed in small subsets of glioblastoma. Like EGFR, these molecules activate the Ras pathway, and can potentially also stimulate the PI3K-Akt pathway. One such molecule is the ERBB2 receptor,[6] a member of the EGFR family. The TCGA study revealed *ERBB2* mutations in 8% of glioblastomas—a much higher frequency than had been anticipated.[6] The TCGA study also showed higher-than-expected frequencies for amplification of the platelet-derived growth factor receptor (*PDGFR*)[16] and c-MET receptor genes, at 13% and 4%, respectively.[6,17] Individual glioblastoma tumors have recently been shown to have activating lesions in multiple genes encoding oncogenic tyrosine kinases, a phenomenon that might ultimately necessitate the therapeutic use of customized inhibitor cocktails.[6,18]

The PI3K-Akt pathway is a powerful oncogenic pathway that is activated by mutations in numerous cancer types, and glioblastoma is no exception. PI3K-Akt acts through many mediators, notably mammalian target of rapamycin (mTOR) complexes, which regulate translation and cell growth. The PI3K-Akt and Ras pathways can collaborate to achieve potent effects, and dysregulation of both together is sufficient to induce malignant cancers. Data from mouse models indicate that lesions in both pathways can combine to yield glioblastoma-like tumors.[19] Though known for some time to be activated in glioblastoma by deletion or mutation of the tumor suppressor *PTEN* (phosphatase and tensin homolog) gene,[20,21] the PI3-Akt pathway has now been found to be activated also by mutations in the PI3K component genes *PIK3CA* and *PIK3R1*.[6,22] The TCGA study found that almost 10% of the glioblastomas that were subjected to DNA sequencing had mutations in the *PIK3R1* gene—a PI3K component and driver of Akt not previously reported to have frequent mutations in any cancers.[6]

The *PTEN* gene is mutated or deleted in a high percentage of glioblastomas (~35-40%),[6,20] as it is in many advanced cancers.[21] PTEN is a potent inhibitor of the oncogenic Akt pathway, and PTEN inactivation causes hyperactivation of Akt.[23] This results in increased cell division, migration, angiogenesis, and resistance to numerous therapies.

The p53 tumor suppressor pathway

The *TP53* gene is thought to be mutated or deleted in approximately 50% of human cancers.[24] The p53 protein acts both as a transcription factor and by other means to drive apoptosis or senescence of cells in which DNA damage has occurred, and removal of this checkpoint is critical for tumorigenesis in many settings. *TP53* is mutated less frequently in glioblastoma than in other cancers, although the TCGA study noted *TP53* mutations in 35% of cases, a surprisingly high percentage.[6] Mutations in *TP53* have traditionally been correlated with secondary glioblastomas (Box 1), but this recent report also found *TP53* mutations in many primary glio blastomas.[6] Notably, mutant forms of p53 have been found not only to lose tumor suppressor functions but also to act in an oncogenic fashion.[25,26] The p53 pathway can be suppressed through mechanisms other than direct mutation of the *TP53* gene, however, and a subset of glioblastomas manifest some of the other genetic lesions that can contribute to p53 pathway suppression. The gene encoding the ubiquitin ligase MDM2, which causes degradation of p53,[27,28] among other proteins, is amplified in roughly 10% of glioblastomas.[29,30] A gene that codes for a similar ubiquitin ligase, MDM4, has also been found to be amplified in a subset of glioblastomas.[31]

The p53 pathway can also be downregulated through deletion of *CDKN2A* (cyclin-dependent kinase inhibitor 2A), a gene that encodes two transcripts for proteins with different tumor suppressor functions. One of these proteins, p14ARF, acts to downregulate MDM2, so the loss of *CDKN2A*, and, consequently, its product p14ARF, upregulates MDM2 expression and thereby suppresses p53 function.[32,33] *CDKN2A* is deleted in approximately 40-50% of glioblastomas.[6,34]

RB and cell cycle kinases

The other transcript of *CDKN2A*, p16INK4A, encodes a protein that binds and inhibits the cyclin-dependent kinase CDK4,[35] an inhibitor of the RB (retinoblastoma-associated) protein, which in turn acts to inhibit the E2F transcription factor.[36] Deletion of p16INK4A thus upregulates E2F function, which drives cell proliferation. Recent work has shown that p18INK4C is also a tumor suppressor in glioblastoma, and interestingly the gene encoding this protein, *CDKN2C*, is often co-deleted with *CDKN2A* in these tumors.[37,38] An alternative genetic means of upregulating E2F function is mutation or deletion of the *RB1* gene itself. *RB1* is commonly knocked out in many cancers, but deletion of this gene is a

less frequent event in glioblastomas, with an approximate frequency of 11-14%.[6,39] Amplification of *CDK4*, which occurs in 14-18% of cases, is another means by which the cell cycle could be upregulated in glioblastomas.[6,40]

Metabolic pathways

Findings from cancers other than glioblastoma have strongly indicated that aberrant metabolism has a prominent role in carcinogenesis. From a metabolic perspective, tumors are quite different from normal tissues, and they use a process of aerobic glycolysis called the 'Warburg effect'. Metabolic pathways exhibit crosstalk with many oncogenic and tumor suppressor pathways— in particular, the hypoxia response pathway driven by hypoxia-inducible factor 1α (HIF1α).

The first report of mutation of a metabolic gene in glioblastoma emerged around the same time as the first TCGA glioblastoma publication. This seminal study, from groups at Johns Hopkins and Duke Universities, USA, took a DNA sequencing approach.[41] Instead of the TCGA approach of sequencing a limited number of genes in a large number of primary glioblastomas, however, the authors sequenced over 20,000 genes in a set of 22 mixed primary and secondary glioblastomas. This un biased approach revealed mutations in many genes, including the surprising finding that the metabolism-related isocitrate dehydrogenase 1 (*IDH1*) gene was mutated in 12% of the tumors studied, with a bias towards secon dary glioblastomas (Box 1). A subsequent report from the same authors, involving a larger set of secondary glioblastomas, has shown that *IDH1* is mutated in over 70% of cases, with a similar mutation frequency in the grade II and III gliomas that give rise to the secondary glioblastomas.[42] Many of the tumors that lacked *IDH1* mutations were found to have *IDH2* mutations. These striking findings could offer new therapeutic approaches to this large subset of gliomas, either through targeting of IDH function or through another metabolism-directed strategy.

Genomic regions with frequent changes

Several regions of the genome are commonly found to have amplifications or deletions in glioblastomas. Many of the most common alterations, such as amplifications in chromosomes 7 and 12 and deletions in chromosomes 1, 9 and 10, were identified 15-25 years ago.[43-47] Additional copy number alterations have been identified through high-throughput comparative genomic hybridization as part of the efforts of TCGA.[48] These amplifications or deletions provide powerful mechanisms for, respectively, increasing or decreasing the expression of oncogenes or tumor suppressor genes. In some cases, the regions of copy number alteration identified in glioblastomas contain known oncogenes or tumor suppressor genes, such as *EGFR* on chromosome 7 and *PTEN* on chromosome 10, but other regions contain genes of unknown relevance or even no genes at all. The areas that seem to contain no genes could, however, code for small RNAs that are not translated into proteins but are active and relevant to glioblastoma formation. These molecules could include miRNAs, a recently discovered class of small, noncoding, hairpin RNAs that regulate an estimated 30% of the human genome.[49] A simple survey does indeed reveal several known miRNAs and a few examples of other forms of noncoding RNAs within the regions of copy-number change noted in the TCGA results; these RNAs include miRNA-31 and miRNA-26a-2, both of which were previously found to be dysregulated in cancers.[50-52] It seems possible, therefore, that the latest examples of DNA copynumber changes will serve as leads for further discoveries of genes and RNAs that have relevance for glioblastoma.

Broadly speaking, the term loss of heterozygosity (LOH) refers to mechanisms by which the remaining functional copy of a tumor suppressor gene is lost. Glioblastomas have frequent regions of LOH, including deletions in chromosomes 1p, 10p, 10q, 13q, 19q and 22q.[53-57]

LOH 10q, in the region of the *PTEN* tumor suppres sor gene, might be lost in as many as 60-70% of glioblastomas.[58] LOH 13q, 19q and 22q are all more common in secondary than in primary glioblastoma.[53,54]

Inherited glioblastoma predisposition

Familial gliomas account for 5% of glioma cases and could be attributable to environmental or genetic factors or a combination of both.[59] Some familial gliomas are attributable to recognized cancer predisposition syndromes (Table 1), one of the more common of which, the Li-Fraumeni syndrome, features germline mutation of *TP53* or, in rare cases, the *CHEK2* gene. Turcot syndrome is characterized by the association of colonic polyposis with primary brain tumors, including glioblastoma and medulloblastoma. Families with this condition can be divided into two groups: those with germline adenomatosis polyposis coli (*APC*) gene mutations who are predisposed to malignant astrocytomas and even more so to medulloblastomas, and others with germline mutations of DNA mismatch repair (MMR) genes, including *MLH1* and *PMS2*, who develop glioblastoma.[60] Inherited mutations of *NF1*, and, in rare cases, *CDKN2A*, also pre dispose to glioblastomas. Genealogical and tumor database studies indicate a modest increased risk of glioblastoma in first-degree and second-degree relatives of patients with glioblastoma, but no increased spousal risk, suggesting that a hereditary influence is more likely than an environmental influence.[59,61]

Single-nucleotide polymorphisms

To date, the only heritable conditions that are known to predispose to glioblastoma are multi-cancer syndromes. A strong likelihood exists, however, that more-subtle genetic alterations could also increase glioma and glioblastoma risk. Findings reported over the past 2 years suggest that single-nucleotide polymorphisms (SNPs) found at low frequency within the population can predispose families to glioma. SNPs in DNA repair genes—most notably *XRCC, LIG4*, and possibly *ERCC1* and/or *ERCC2*—have been implicated in several reports.[62-65] SNPs that could influence the risk of gliomagenesis have also been identified within apoptosis and cell cycle genes, including the caspase 8 and cyclin genes.[66,67] Metabolism genes, such as those encoding members of the folate pathway and the gluta thione *S*-transferases, might also have a role in glioma genesis, although the involvement of the latter is debated.[68-71] SNPs within genes associated with immunity and inflammation could also be involved. A SNP within the interleukin 4 receptor gene is one controversial candidate.[59,72] Another recent study demonstrating that chronic NSAID use decreases glioma incidence, while antihistamine use might increase it, supports a role for inflammation and the immune system in reducing glioblastoma incidence.[73]

Therapeutic implications

Mutations that predict treatment sensitivity

Given the common overexpression of *EGFR* in glioblastomas and the availability of oral inhibitors (gefitinib and erlotinib) of the EGFR tyrosine kinase, the fact that several studies have tested these inhibitors in recurrent and newly diagnosed glioblastomas is unsurpris ing. Occasional favorable responses in recurrent glioblastomas led to attempts to correlate tumoral EGFR status with response to EGFR tyrosine kinase inhibitors (TKIs). These studies have yielded inconsistent—albeit intriguing—results. The first study indicated that only tumors containing *EGFR* amplifications responded to EGFR TKIs, and that absence of phosphorylated Akt was also necessary.[12] A follow-up study, by contrast, revealed no association between *EGFR* amplification and sensitivity to EGFR TKIs, but reported that tumors with the constitutively activating *EGFRvIII* mutation and *PTEN* positivity (that is,

lacking a *PTEN* mutation) responded to these drugs.[74] Other studies have shown no correlation between *EGFR* status and sensitivity to TKIs.[75]

Clinical trials in which erlotinib was added to the standard therapy of radiotherapy plus temozolomide yielded equally inconclusive results; one study reported that PTEN positivity was predictive of survival whereas *EGFR* expression was not,[76] but a larger study found no association between survival and *EGFRvIII* status, *EGFR* amplification status or *PTEN* expression.[77] Further studies are required to clarify this issue.

Acquired DNA mismatch repair mutations

Not only do inherited mutations in DNA MMR genes predispose to glioblastoma development, but acquired mutations in such genes also help to mediate chemotherapy resistance in these tumors. In mammals, DNA MMR corrects errors arising from DNA replication and surveillance, and also repairs errors in DNA modified by chemicals such as alkylating chemotherapy agents. Several well-characterized genes, including *MSH2, MSH3, MSH6, MLH1, MLH3, PMS1* and *PMS2*, are involved in MMR. Cells with defective MMR generate mutations at a rate up to 100-fold higher than normal cells—a phenomenon known as the ‘mutator phenotype’.

For the DNA-methylating agent temozolomide to induce cytotoxic effects in glioblastoma cells, MMR must be intact so as to trigger a futile repair cycle; MMR-deficient tumors are highly resistant to methylating agents.[78] MMR genes are rarely mutated in newly diagnosed glioblastomas, but acquired mutations of *MSH6* have sometimes been identified in glioblastoma tissue taken from patients who received temozolomide,[79,80] as was loss of expression of the MSH6 protein, even in the absence of an *MSH6* mutation. Moreover, glioblastomas with *MSH6* mutations exhibit the mutator phenotype.

Extending these observations, TCGA compared tissue from 72 untreated glioblastomas with 19 treated ones. They found that treated glioblastomas had four times the mutation rate of the untreated ones, and that this effect was entirely attributable to seven hypermutated tumors, all of which had been treated with temozolomide or lomustine, another alkylator.[6] Six of these seven hypermutated samples harbored mutations in at least one of the MMR genes *MLH1, MSH2, MSH6* or *PMS2*, as compared with only one sample among the 84 non-hypermutated samples ($P = 7 \times 10^{-8}$). These findings suggest that alkylators such as temozolomide, despite having marked clinical benefits, induce strong selective pressure for MMR mutations that confer not only resistance to these alkylators, but, through the develop ment of a hypermutator phenotype, a potentially broader pattern of resistance. Attempts are ongoing to block or exploit this effect through targeting of one of the DNA repair pathways parallel to the MMR pathway. For example, clinical trials that combine temozolomide with an inhibitor of the poly-(ADP-ribose) polymerase DNA repair enzyme are now underway.

Conclusions and future prospects

Many of the genetic aberrations that are present in glioblastomas have been known for years or decades, but only with the results from recent high-throughput efforts such as TCGA, and the pan-sequencing project that gave rise to the data on *IDH1* and *IDH2*, are we beginning to approach a complete picture of glioblastoma genetics. Indeed, these studies have been so thorough that we might be tempted to speculate that we are at the ‘end of history’ with the genetic study of glioblastoma, and that there will be no more major discoveries in this area. Such speculation is, however, belied by recent seminal findings such as the *IDH1* and *IDH2* gene mutations, or, on a larger scale, the discovery of whole new entities such as miRNAs. The output from TCGA and other high-throughput projects is still being digested, and further exciting findings are anticipated from these datasets.

Emerging evidence indicates that the genetic profiles of glioblastoma influence the susceptibility of these tumors to both older treatments, such as radiation and chemotherapy, and—to an even greater extent—newer targeted therapies. Application of this knowledge in the clinic will require new diagnostic capabilities and new trials to confirm the utility of genetic testing, both of which have already been initiated. A test for the methylation status of the *MGMT* promoter, which correlates with sensitivity to temozolomide chemotherapy, is now commercially available in the US. Tests for the presence of the *EGFRvIII* mutation and *PTEN* status are not yet routinely available, but the relevant technology already exists. Rapid characterization of specific features of an individual patient's glioblastoma is, therefore, entering the clinic, and in several years' time we could have the capability to sequence the full genome of each tumor at diagnosis. Immediate identification of between two and four aberrant pathways in the tumor, and the use of a customized cocktail of inhibitors to match these aberrations, might be possible. We are not yet in a position to use the genetic profiles of individual glioblastomas to guide the treatment of patients, but such personalized therapy now seems years rather than decades away.

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Key points

- Glioblastoma is the most common and lethal brain tumor
- Given the resistance of glioblastoma to standard therapies, an understanding of the genetic underpinnings of this cancer is crucial
- New reports from high-throughput profiling efforts, such as The Cancer Genome Atlas, have contributed to a more comprehensive understanding of the genetic aberrations that drive glioblastoma
- This influx of new data has blurred some of the classic genetic distinctions between primary and secondary glioblastoma, such as the association of *TP53* mutations with secondary glioblastomas
- New characteristics, such as *IDH1* or *IDH2* mutations in a majority of secondary glioblastomas, have been identified
- Genetic findings are beginning to influence the application of treatments to patients with glioblastoma

Box 1 | Relative frequencies of genetic lesions

Genetic lesions more common in primary than secondary glioblastoma

- *EGFR* amplification or mutation[82]
- *MDM2* amplification[88]
- *PTEN* mutation[89]

Genetic lesions more common in secondary than primary glioblastoma

- *IDH1* or *IDH2* mutation[41,42]
- *TP53* mutation[82]
- *PDGFR* amplification[16,20,90]

Genetic lesions common in both glioblastoma types or frequencies unclear

- *CDKN2A* deletion or mutation[35]
- Loss of heterozygosity on chromosome 10q[6,20]
- *RB1* mutation[6]
- *CDKN2C* deletion[37,38]
- *CDK4* amplification[6,40]
- *HER2* amplification[6]
- *c-MET* amplification[6]

Review criteria

Literature searches were done on PubMed in February and March 2009 for references in English with the term “glioblastoma AND [genetics OR mutation OR amplification OR deletion OR LOH OR EGFR OR PTEN OR p53 OR PDGFR OR NF1 OR RB1 OR CDKN2A OR INK4A OR INK4C OR ERBB2 OR CDK4 OR PI3K OR IDH1 OR TCGA OR SNP OR risk OR familial OR heritable OR MSH6]”. The reference lists of relevant papers were also reviewed for other useful leads.

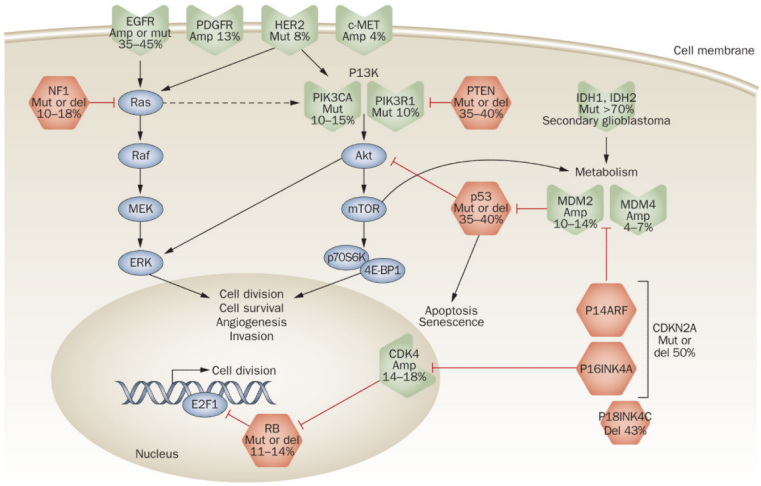

Figure 1.

Products of prominent oncogenes and tumor suppressor genes in glioblastoma. Oncogene products are shown as green arrows and tumor suppressors are depicted as red octagons. Approximate frequencies of genetic lesions in glioblastoma are included for each oncogene or tumor suppressor gene. Abbreviations: 4E-BP1, eukaryotic translation initiation factor 4E-binding protein 1; amp, amplification; CDK4, cyclin-dependent kinase 4; CDKN2A, cyclin-dependent kinase inhibitor 2A; del, deletion; E2F1, transcription factor E2F1; EGFR, epidermal growth factor receptor; ERK, extracellular signal-regulated kinase; HER2, human epidermal growth factor receptor 2; IDH, isocitrate dehydrogenase; MEK, mitogen-activated protein kinase kinase; mTOR, mammalian target of rapamycin; mut, mutation; NF1, neurofibromin 1; p70S6K, p70S6 kinase; PDGFR, platelet-derived growth factor receptor; PI3K, phosphatidylinositol 3-kinase; PTEN, phosphatase and tensin homolog; RB, retinoblastoma-associated protein.

Table 1

Familial syndromes with elevated incidence of glioma and their corresponding genetic lesions

Syndrome name	Mutated gene	Comments
Li–Fraumeni syndrome 1	TP53 on chromosome 17p	Autosomal dominant Associated with sarcomas, breast cancer, leukemia, and adrenocortical carcinoma Found in 6 of 4481 and 1 of 1582 patients with familial gliomas 60% of associated brain tumors are astrocytic
Li–Fraumeni syndrome 2	*CHEK2* on chromosome 22q	Autosomal dominant Isolated reports[44,83] of glioma and other brain tumors
Hereditary nonpolyposis colorectal cancer (HNPCC or Lynch syndrome)	Multiple DNA mismatch repair genes, including *MSH2, MLH1, MSH6* and *PMS2*	Autosomal dominant 50–70% risk of colorectal cancer; accounts for 2–3% of colorectal cancers and 2% of uterine cancers CNs tumors principally glioblastoma, but other gliomas sometimes seen Lifetime brain tumor risk ~2%[84]
Neurofibromatosis 1 (NF1)	*NF1* on chromosome 17q	Autosomal dominant 15–20% of patients with NF1 develop brain tumors Two-thirds of NF1-associated brain tumors are optic pathway tumors, usually pilocytic astrocytomas Of 104 NF1 patients with brain tumors, 2 had glioblastoma and 2 had anaplastic astrocytoma[85] Large intragenic germline deletions could increase risk of nonpilocytic gliomas[86]
Melanoma–astrocytoma syndrome	CDKN2A locus encompassing p16iNK4A and p14ArF transcripts on chromosome 9p	Autosomal dominant rare families observed with melanomas and astrocytomas, as well as meningiomas, schwannomas and neurofibromas[13,87]