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Solid Tumour Section

Review

Nervous System: Glioma: an overview

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Classification

Note

Primary CNS tumors constitute a spectrum of pathological entities each with a distinct natural history that reflects the sequential accumulation of genetic lesions and the deregulation of growth-factor signalling pathways during neoplastic transformation. For simplicity, CNS tumors may be classified as **GLIOMAS** or **NONGLIOMAS** (see Table 1 which provides a summary of 2007 World Health Organization (WHO) classification). Relevant features in the present section will concern GLIOMAS, tumors that are thought to be of glial cell origin.

Clinics and pathology

Etiology

Gliomas account for >70% of all primary brain tumors. The most common (65%) and most malignant type is glioblastoma. With the exception of pilocytic astrocytomas, the prognosis of glioma patients is still poor. Less than 3% of glioblastoma patients are still alive at 5 years after diagnosis, higher age being the most significant predictor of poor outcome. Table 2 reports the population-based data of incidence rates (per 100,000 person per year) in 1992-1997 in United States adjusted to 2000 US population and the incidence rates in Zurich, Switzerland in 1980-1994 adjusted to 2000 US population.

Epidemiology

Descriptive epidemiology largely depends on population-based cancer registries, which record cases according to the International Classification of Diseases for Oncology (ICD-O). The Central Brain tumor Registry of the United States is available at http://www.CBTRUS.org.

No underlying cause has been identified for the majority of malignant gliomas. Epidemiologic factors including specific occupational exposures, environmental carcinogens, foods containing N-nitroso compounds, electromagnetic fields, etc. have been associated to only a small proportion of gliomas.

The only two firmly established factors of primary brain tumors are the exposure to high doses of ionizing radiation and inherited mutations of highly penetrant genes associated with rare syndromes (Table 3).

In addition, preliminary evidence points to a lower glioma risk among people with allergic conditions and high levels of serum IgE.

Polymorphisms of genes that affect detoxification, DNA repair, and cell-cycle regulation have also been implicated in the development of gliomas.

Recently, two international Brain Tumor consortia have been formed: the Brain Tumor Epidemiology Consortium (BTEC) (http://epi.grants.cancer.gov/btec/) to identify potential genetic and environmental risk factors and the GLIOGENE to study the genetic basis of familial gliomas.

GLIOMAS						NONGLIOMAS
	grade	I	II	III	IV	
Astrocytic tumors						Choroid plexus tumors
Pilocytic astrocytoma		*				
Pituicytoma (**)		*				Neuronal and mixed neuronal-glial tumor
Pilomyxoid astrocytoma (**)			*			
Subependymal giant cell astrocytoma			*			Tumors of the pineal region
Pleomorphic xanthoastrocytoma			*			
Diffuse astrocytoma			*			Embryonal tumors, including Medulloblastoma
Fibrillary astrocytoma			*			
Gemistocytic astrocytoma			*			Meningeal tumors
Protoplasmic astrocytoma			*			
Anaplastic astrocytoma				*		Primary CNS Lymphomas
Glioblastoma					*	
- Giant cell glioblastoma					*	Germ cell tumors
- Gliosarcoma					*	
Gliomatosis cerebri	nd					Pituitary adenomas
Oligodendroglial tumors						
Oligodendroglioma			*			Tumors of cranial and paraspinal nerves
Anaplastic oligodendroglioma				*		
Oligoastrocytic tumors						Tumors of the sellar region
Oligoastrocytoma			*			
Anaplastic oligoastrocytoma				*		Metastatic tumors
Ependymal tumors						
Subependymom		*				
Myxopapillary ependymoma		*				
Ependymoma			*			
- Cellular						
- Papillary						
- Clear Cell						
- Tanycytic						
Anaplastic ependymoma				*		
nd = not defined						

Table 1 WHO classification of Central Nervous System Tumors

Tumor	WHO grade	Region	Incidence rates	M:F ratio	Mean age at diagnosis	Survival					
						Median (months)	Mean (months)	1 year	2 years	5 years	10 years
Pilocytic astrocytoma	I	USA	0.23	1.09	17			95%	93%	89%	86%
		Zurich	0.39	1.12	20		142	100%	100%	100%	96%
Diffuse astrocytoma	II	USA	0.13	1.46	47			73%	60%	45%	34%
		Zurich	0.26	1.7	41	67	77	92%	88%	58%	26%
Anaplastic astrocytoma	III	USA	0.49	1.20	50			60%	43%	28%	19%
		Zurich	0.25	1.19	44	20	30	65%	43%	11%	7%
Glioblastoma	IV	USA	2.96	1.26	62			28%	8.2%	2.9%	1.7%
		Zurich	3.39	1.28	61	4.9	7.3	18%	3.3%	1.2%	0.2%
Oligodendroglioma	II	USA	0.34		42			88%	80%	66%	47%
		Zurich	0.27	0.92	40	139	106	98%	96%	78%	51%
Anaplastic oligodendroglioma	III	USA	0.10	1.15	46			75%	57%	38%	25%
		Zurich	0.11	2.33	49	16	37	50%	45%	30%	7.5%
Oligoastrocytoma	II	Zurich	0.10	1.0	40	79	85	95%	90%	70%	49%
Anaplastic oligoastrocytoma	III	Zurich	0.08	0.77	46	18	30	62.5%	43.8%	12.5%	0%
Mixed glioma *	II / III	USA	0.12	1.21	40			84%	72%	54%	39%
Ependymoma / Anaplastic ependymoma	II / III	USA	0.23	1.29	35			86%	79%	66%	55%

Oligoastrocytoma (WHO grade II) and anaplastic oligoastrocytomas (grade III) are combined

Table 2 Population-based data of incidence rates, age and sex, and survival of patients with gliomas. From: Ohgaki H and Kleihues P. Epidemiology and etiology of gliomas. Acta Neuropathol 2005, 109: 93-108.

Syndrome	Gene name	Chromosomal location
Neurofibromatosis 1	*NF1*	17q11
Neurofibromatosis 2	*NF2*	22q12
Tuberous sclerosis	*TSC1* *TSC2*	9q34 16p13
Retinoblastoma	*RB1*	13q14
Li–Fraumeni syndrome	*TP53*	17p13
Turcot's syndrome and multiple hamartoma	*APC* *hMLH1* *hMSH2* *PMS2* *PTEN*	5q21 3p21.3 2p22–21 7p22 10q23.3

Table 3 Inherited mutations in members of families at increased risk of glioma. From Epidemiology and molecular pathology of glioma. Schwartzbaum JA, Fisher JL, Aldape KD and Wrensch M. Nat Clinical Practice Neurology 2006, 9:494-503.

Table 4 Summary of Current Treatments for Malignant Gliomas.
(from Malignant Gliomas in Adults.
Wen PY and Kesari S. N Engl J Med 2008 359:5: 492-507)

Type of Tumor	Therapy
Newly diagnosed tumors	
Glioblastomas (WHO grade IV)	Maximal surgical resection, plus radiotherapy, plus concomitant and adjuvant TMZ or carmustine wafers (Gliadel)†
Anaplastic astrocytomas (WHO grade III)	Maximal surgical resection, with the following options after surgery (no accepted standard treatment): radiotherapy, plus concomitant and adjuvant TMZ or adjuvant TMZ alone†
Anaplastic oligodendrogliomas and anaplastic oligoastrocytomas (WHO grade III)	Maximal surgical resection, with the following options after surgery (no accepted - standard treatment): radiotherapy alone, TMZ or PCV with or without radiotherapy afterward, radiotherapy plus concomitant and adjuvant TMZ, or radiotherapy plus adjuvant TMZ†‡
Recurrent tumors	Reoperation in selected patients, carmustine wafers (Gliadel), conventional chemotherapy (e.g., lomustine, carmustine, PCV, carboplatin, irinotecan etoposide), bevacizumab plus irinotecan, experimental therapies‡

Table 4 Data are from Sathornsumetee et al.(3), Furnari et al.(18), Chi and Wen (20) and Sathornsumetee et al.(21).
PCV denotes procarbazine, lomustine (CCNU), and vincristine, and TMZ temozolomide.
† Radiotherapy is administered at a dose of 60 Gy given in 30 fractions over a period of 6 weeks. Concomitant TMZ is administered at a dose of 75 mg per square meter of body-surface area per day for 42 days with radiotherapy. Beginning 4 weeks after radiotherapy, adjuvant TMZ is administered at a dose of 150 mg per square meter per day on days 1 to 5 of the first 28-day cycle, followed by 200 mg per square meter per day on days 1 to 5 of each subsequent 28-day cycle, if the first cycle was well tolerated.
‡ PCV therapy consists of lomustine (CCNU), 110 mg per square meter, on day 1; procarbazine, 60 mg per square meter, on days 8 to 21; and vincristine, 1.5 mg per square meter (maximum dose, 2 mg), on days 8 and 29.

Treatment

Management of Gliomas:

Pilocytic Astrocytomas

Pilocytic astrocytoma, when totally resected, has a favourable outcome compared to other astrocytomas. However, when residual tumor remains, the prognosis is less satisfactory. It has been reported that radiation treatment after surgery suppresses residual tumor. Tumor location reveals a cerebellar predominance in both children and adults.

Low-grade Astrocytomas

Favorable prognostic features include younger age at diagnosis, tumor size < 5cm and, possibly, greater extent of tumor resection. Late recurrences are relatively common, and patients should be followed up for at least 15 years. Despite their relatively indolent course, most astrocytomas eventually evolve into more anaplastic lesions and cannot be cured by surgery and radiation therapy.

Low-grade Oligodendrogliomas/Oligoastrocytomas

Approximately half of oligodendrogliomas are characterized by loss of heterozygosity of chromosomes 1p and 19q, a pathognomonic diagnostic feature. For recurrent low-grade oligodendroglial tumors, surgery, radiation, and chemotherapy may each play an important role.

Anaplastic Oligodendroglioma/Oligoastrocytoma

Although uncommon, these tumors are recognized by their unique molecular, histologic and clinical features. Radiation therapy is the most commonly prescribed post-surgical therapy. The role and timing of adjuvant chemotherapy are less clear. Patients with 1p and 19q deletions have significantly better outcomes, regardless of treatment.

Anaplastic Astrocytomas

Anaplastic astrocytomas comprise 10-15% of all glial neoplasms. Currently, the only factors that have been shown to influence prognosis in patients with AA are age and Karnofsky performance status. The most important predictor of response to therapy and survival in AA tumors is the presence or absence of the 1p19q co-deletion, a molecular feature that defines a subset of oligodendroglial tumors, and anaplastic oligodendrogliomas in particular. A further likely prognostic biomarker is the methylation status of O(6)-methylguanine-DNA-methyltranferase gene (the predominant DNA repair enzyme following alkylator-based chemotherapy-induced injury). Evidence-based management of patients with AA recommends maximum safe resection followed by involved-field radiotherapy for newly diagnosed patients, and temozolomide (TMZ) for recurrent disease.

Glioblastoma Multiforme (GBM)

Glioblastomas are among the most devasting neoplasms claiming the lives of patients within a median of 1 year after diagnosis. Although glioblastoma can occur at all ages, including childhood, the average age at which it is diagnosed is 55 years. Poor prognostic clinical variables include increasing age, poor performance status, increased severity of neurologic deficits ad diagnosis and the inability to achieve substantial tumor resection. Treatments include surgery, radiotherapy, chemotherapy and so on. The extremely infiltrative nature of this tumors makes

complete surgical removal impossible. Concurrent radiotherapy and the oral alkylating agent TMZ followed by adjuvant TMZ has become the standard of care for patients with newly diagnosed GBM, although the methylation status of the promoter region of the MGMT gene in the tumor specimen is associated with superior survival, regardless of received treatment.

Low-grade and anaplastic ependymomas

Ependymomas may occur anywhere in the spinal axis. In children, they are more commonly found in the posterior fossa and spinal cord. Both the low-grade and anaplastic lesions may disseminate along the leptomeningeal surfaces. Low-grade lesions in the spine are usually treated with surgery alone. Anaplastic or incompletely resected low-grade tumors are usually treated with postoperative radiation therapy. The role of chemotherapy is uncertain and in general should be reserved patients having previously failed surgery and radiotherapy (see Table 4).

There is growing evidence that glioma stem cells may contribute to the resistance of malignant gliomas to standard treatments. Radioresistance in stem cells generally results from the preferential activation of DNA-damage-response pathways, whereas chemoresistance results partly from the overexpression of O^6-methylguanine-DNA methyltransferase (MGMT), the up-regulation of multidrug resistance genes, and the inhibition of apoptosis. Therapeutic strategies that effectively target stem cells sparing normal cells and overcome their resistance to treatment will be necessary if malignant gliomas are to be completely eradicated. **Another determined obstacle to effective therapy is the invasive nature of glioma cells into the surrounding brain.**

Cytogenetics

Note

Cytogenetic markers of glioma in adults

The gain of chromosome 7 is the most frequent numerical aberration observed in astrocytomas (WHO grade I) and anaplastic astrocytomas (WHO grade II). In AA other chromosomes showing a tendency toward gain are chromosomes 19 and 20. Chromosomes most often lost include 10 and 22 and a single sex chromosome. Among the oligodendroglioma karyotypes the majority have normal or nonclonal chromosomal pattern often associated with isolated sex chromosomes. The genetic instability of glioblastoma results in numerous subpopulations and isolated cell types: nonetheless several non-random chromosome changes, in particular aneuploidies, are associated with the progression of this tumor. The numerical abnormalities are similar to the lower-grade tumors, involving the gain of chromosomes 7 and 20 and the loss of chromosomes 10 and 22 and sex chromosomes. In general, numerical changes appear to include more loss than gain of chromosomes, and this is reflected in the frequent loss of 9p and chromosomes 13 and 14. Monosomy of chromosome 22 is the most frequent alteration observed in ependymomas, in addition to deletions or translocations involving 22q.

In addition to alterations in chromosome number, most solid tumors are also characterized by centrosome amplification. Centrosome nucleates and organizes the cytoplasmic and mitotic spindle microtubules (MTs) in interphase and mitotic cells, respectively. Because the centrosome is actively involved in proper chromosome segregation during mitosis, it has been hypothesized that centrosome amplification drives tumor aneuploidy by increasing the frequency of abnormal mitosis that lead to chromosome missegregation. In a recent work on primary diffuse astrocytic gliomas Katsetos et al. reported the overexpression of gamma-tubulin, the key structural component of centrosome, associated with supernumerary centrosomes .Interphase and -metaphase amplified centrosomes in glioma cell lines are visible in Figure 1, a and b respectively (personal observations).

Chromosomal imbalances of glioma in childhood and adolescence

Pilocytic astrocytomas account for 23.5% of pediatric brain tumors. The most common aberration consisted of 6q, followed by 7q gain, and loss of 9q. The imbalance +7q is observed in other gliomas such as pleomorphic xanthoastrocytomas and ependymomas, whereas -9q is the most frequent alteration in pleomorphic xanthoastrocytomas and is also present in anaplastic astrocytomas.

Anaplastic astrocytomas account for 7.2% of childhood brain tumors. Among the investigated tumors the most common chromosomal alterations were gains of 5q and 1q and losses of 22q, 9q and 12q.

Glioblastomas account for 7.2% of pediatric brain tumors. The most frequent reported chromosomal imbalances were losses of 17p and 13q whereas gains included 1q, 2q, 3q and 17q .Compared with adult cases, gains of 1p, 2q and 21q as well as losses of 6q, 11q and 16q were more frequently observed among pediatric malignant astrocytomas, supporting differences between childhood and adult chromosomal abnormalities and different genetic pathways.

Oligodendroglial tumors are rare in the pediatric population and only isolated cases have been investigated.

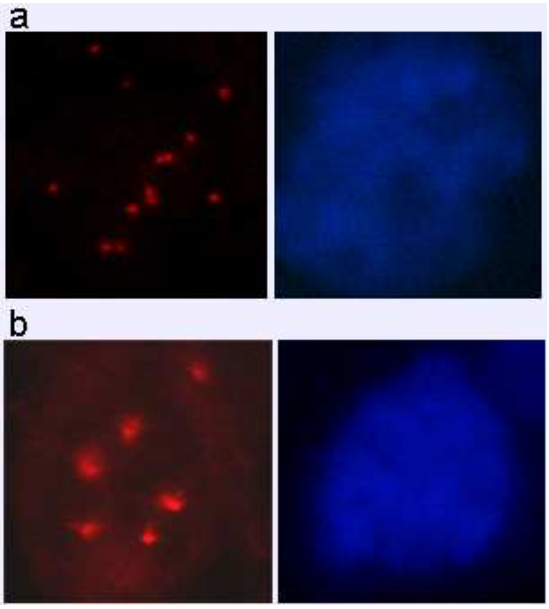

Figure 1. Interphase and -metaphase amplified centrosomes in glioma cell lines.

Ependymomas comprise 10.1% of pediatric brain tumors. Among the tumor group investigated classic and anaplastic ependymomas are characterized by +1q, whereas all 3 entities (including the myxopapillary variant) frequently show +9. Other imbalances observed were +7q as well as -22q.

Cytogenetics Molecular

Molecular pathology of glioma

Different studies applying cytogenetic, comparative genomic hybridization (CGH), array-CGH and loss of heterozygosity (LOH) methods demonstrated non-random genomic aberrations in gliomas. The characterization of genomic abnormalities enhanced to identify specific genes involved in tumor initiation and progression.

Table 5 summarizes the most common detectable chromosome changes in glioma.

1p/19q loss

Deletions of 1p and 19q are associated with tumors with oligodendroglial components. Combined alterations have been observed in up to 70% of oligodendrogliomas and 50% of mixed oligoastrocytomas. Besides being a relevant diagnostic marker, 1p/19q loss has been recently validated for its prognostic relevance by prospective data suggesting that 1p /19q deletion is predictive of radio-chemosensitivity in anaplastic oligodendroglial tumors and mixed oligoastrocytomas. Based on the observation that the majority of 1p and 19q deletions seem to involve the entire 1p and 19q arms, in a recent paper Jenkins RB et al showed that an unbalanced t(1;19)(q10;q10) underlies the formation of the combined 1p and 19q deletion in gliomas and in addition it predicts a better prognosis of patients with oligodendroglioma.

Table 5 Common chromosomal alterations in gliomas.

Chromosomal region	Type of alteration	Candidate glioma genes
1p36.31-pter	Gains and deletions	Not known
1p36.22-p36.31	Gains and deletions	Not known
1p34.2-p36.1	Gains and deletions	Not known
1q32	Gains	*RIPK5, MDM4, PIK3C2B* and others
4q	Deletions	*NEK1, NIMA*
7p11.2-p12	Amplifications or gains	*EGFR*
9p21-p24	Deletions	*CDKN2*
10q23	Deletions	*PTEN*
10q25-q26	Deletions	*MGMT*
11p	Deletions	Between *CDKN1C* and *RRAS2*
12q13.3-q15	Amplifications	*MDM2, CDK4* and others
13p11-p13 and 13q14-q34	Loss	*RB1*
19q13	Loss	*GLTSCR1, GLTSCR2, LIG1, PSCD2* and many others
22q11.21-q12.2	Loss	28 genes, including *INI1*
22q13.1-q13.3	Loss	Not known

Table 5 From Epidemiology and molecular pathology of glioma. Schwartzbaum JA, Fisher JL, Aldape KD and Wrensch M. Nat Clinical Practice Neurology 2006, 9:494-503.

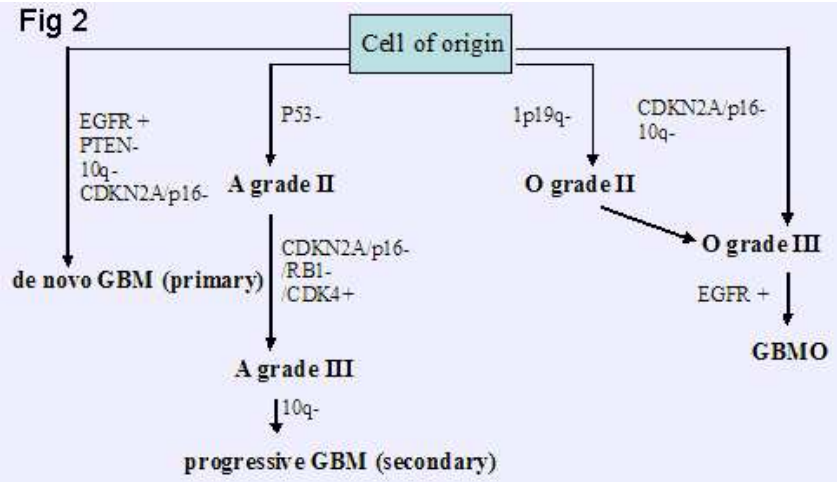

Figure 2: Genetic pathways associated with glioblastoma formation. A (astrocytomas), O (oligodendroglioma), GBMO (glioblastoma with oligodendroglial component). The amplified genes are indicated by "+". The chromosomes deleted and the genes inactivated are indicated by "-".

Genes involved and proteins

Genetic pathways to Glioblastoma

Note

Genotype/phenotype correlation studies of gliomas elucidate the genetic pathways that lead to GBM. They include:

- two main early alterations such as p53 inactivation (associated with astrocytomas) and the loss of chromosomes 1p and 19q (more specific to oligodendrogliomas), both mutually exclusive.
- The P16/CDKN2A deletion on 9p21, mutation/amplification of EGFR and inactivation of PTEN, two genes acting in a key signalling pathway in the development of primary GBM.
- The TP53 pathway playing a crucial role in the development of secondary GBM.

The p16/RB1 pathway seems to be important in pathways to both primary and secondary GBM. The RB1 inactivation on 13q and CDK4 amplification, also mutually exclusive, are more frequent in anaplastic gliomas. PTEN inactivation on chromosome 10q and epidermal growth factor receptor (EGFR) amplification and/or rearrangement are more frequent in glioblastomas.

The scheme in Figure 2 depicts the genetic pathways to glioblastoma.

The major signalling pathways involved in the pathogenesis of glioblastomas are depicted in Figure 3 and then shortly commented.

EGFR/PTEN/Akt/mTOR pathway

Note

EGFR is activated upon the binding of growth factors to its extracellular domain, resulting in recruitment of P13K to the cell membrane. P13K in turn phosphorylates phosphatidynositol-4,5-biphosphate to the 3-phosphate(PIP3), which activates downstream effector molecules such as AKT (protein kinase B) and mTOR leading to cell proliferation and enhanced cell survival by blocking apoptosis. PTEN downregulates the PIP3 signal, thereby inhibiting cell proliferation. The PTEN gene is mutated in up to 40% of glioblastomas and almost exclusively in primary glioblastomas (Fig.1).

TP53/MDM2/p14^{ARF} pathway

Note

The TP53 is involved in several cellular processes, including the cell cycle, response of cells to DNA damage, cell death, cell differentiation, and neovascularisation. After DNA damage, TP53 is activated and induces transcription of genes such as p21. MDM2 binds to mutant and wild-type TP53 proteins, thereby inhibiting the ability of wild-type TP53 to activate the transcription. Conversely, transcription of the MDM2 gene is induced by wild-type TP53. Whereas TP53 activity and MDM2 expression in normal cells are regulated by the above autoregulatory feedback loop and by the p14^{ARF} gene product that inhibits MDM2-p53 degradation, in human cancer cell lines p14^{ARF} expression inversely correlates with TP53.

This means that loss of TP53 function may result from abnormal expression of any of the TP53, MDM2, or p14^{ARF} genes.

P16/RB1 pathway

Note

The RB1 protein controls the progression through G1 to S phase of the cell cycle. The CDK4/cyclin D1 complex phosphorylates the RB1 protein, determining the release of the E2F transcription factor that activates genes involved in the G1 -S transition. P16^{INK4a} binds to CDK4, inhibits the CDK4/cyclin D1 complex and in turn blocks the G1 -S transition. Consequently, the loss of normal RB1 function may depend on the altered expression of any of the RB1, P16^{INK4a}, or CDk4 genes.

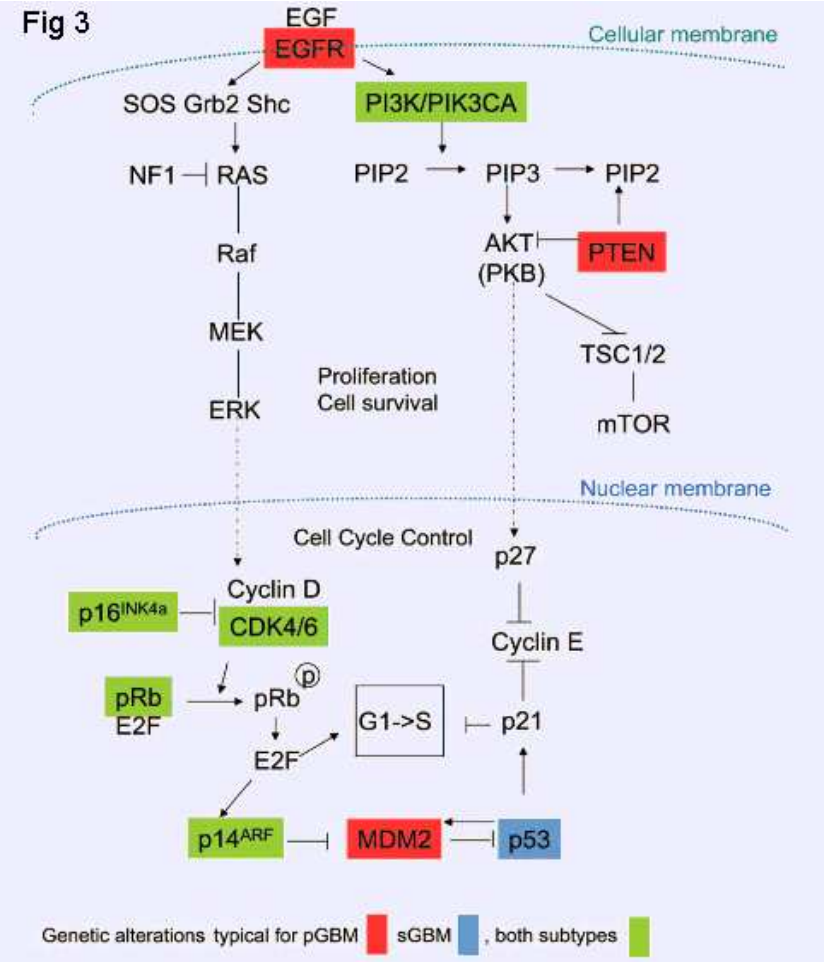

Figure 3: From Genetic Pathways to primary and secondary glioblastoma. Hiroko Ohgaki and Paul Kleihues The Am J Pathol 2007 May;170(5):1445-53 review.

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