We are IntechOpen, the world’s leading publisher of Open Access books
Built by scientists, for scientists

6,600
Open access books available

177,000
International authors and editors

195M
Downloads

154
Countries delivered to

TOP 1%
Our authors are among the most cited scientists

12.2%
Contributors from top 500 universities

WEB OF SCIENCE™
Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected. For more information visit www.intechopen.com
Novel Endocrine Targets for GBM Therapy

Judith Marcela Dueñas-Jiménez,
Irene Aguilar-García,
María de la Luz Galván-Ramírez,
Sergio Horacio Dueñas-Jiménez,
Jorge David Rivas-Carrillo, Anne Santerre and
Erika Priscilla Domínguez-Rangel

Abstract

Astrocytomas are brain tumors from glial cells, and they are classified by the World Health Organization (WHO) as astrocytoma, grade I or benign; astrocytoma, grade II or malignant; anaplastic astrocytoma, grade III; and glioblastoma multiforme or grade IV. The high-grade gliomas have an incidence of 6.03/100,000. The frequency of GBM is higher in men than in woman by a 50%. The survival of patients with GBM varied between 14 and 18 months, and less than 10% patients survive for 5 years. The main treatments for GBM consist of surgical tumor resection, radiotherapy, and chemotherapy. These tumors present different endocrine characteristics, such as expression of aromatase enzyme, estrogen, progesterone, as well as testosterone receptors. In addition, patients with GBM produce estradiol in high concentrations when compared to those with low-grade astrocytomas. The highest mRNA expression of ERα and aromatase in GBM patients had been postulated as prognostic biomarkers. The aromatase inhibitors had been used in the treatment of breast cancer in postmenopausal women with satisfactory results. At present time, several research groups are interested in testing these inhibitors for treating GBM.

Keywords: glioblastoma, endocrine characteristics, estradiol receptor, aromatase, aromatase inhibitors
1. Introduction

Glioblastoma multiforme (GBM) tumor occurs either as a primary tumor when it is formed de novo or a secondary tumor when the tumor progresses from grade II or III to grade IV. GBM is a diffuse and infiltrative tumor with a high mitotic activity, nuclear atypia, pleomorphism, and necrosis. GBM is the most frequently occurring brain tumor (12–15%) and represents 50–60% of all astrocytomas. There are two variants of glioblastoma: Glioblastoma of giant cells and gliosarcoma. GBM affects the cerebral hemispheres, mostly the white substance of the cerebral hemispheres. GBM primary has a bad prognostic due to its molecular heterogeneity. On the basis of its transcriptional subtype, GBM primary is also classified as neural, classical, and mesenchymal as well as proneural for GBM secondary. In GBM primary occurs the amplification of epidermal growth factor (EGF), and the PTEN gene is mutated in 45% of GBM primary cases, whereas in GBM secondary, the EGF amplification does not occur. The chromosome alteration in GBM involves a loss of the chromosome 10. The treatment for this kind of tumor after a safe surgical process also involves radiotherapy (RT) and the pharmacological treatment using the alkylating agent Temozolamide (TMZ), and different combinations of this agent with antitumor drugs such as the Bevacizumab. In spite of these treatments, there is a short survival period for GBM patients (14–18 months), which promotes the development of different clinical trials (II or III) to provide the patient a treatment with a better outcome. These new approaches are based on the molecular aspects of GBM to make the treatments more individualized. This chapter describes the main GBM endocrine and molecular characteristics now known and makes a proposal on future treatments for GBM patients on the basis of these molecular characteristics.

2. Epidemiology

The incidence can change by age; in adults, for example, gliomas are the most frequent primary central nervous system tumors recurring in 70% of the patients. The average age of patients with GBM primary is 62 years, while for secondary GBM patients, it is approximately 45 years. The ethnicity and geographical localization are also of great importance in their epidemiology [1]. These tumors represent about 31% of newly diagnosed tumors in the United States and 81% of malignant tumors of the brain. The incidence of brain cancer in Europe is of 5.5/100,000 individuals, and the minor incidence is in sub-Saharan Africa with 0.8/100,000 individuals [2]. High-grade gliomas, anaplastic astrocytoma (AA) and GBM, have an incidence of 6.03/100,000 [3,4]. It has been shown that the incidence of GBM with respect to gender and ethnicity was different. The white people had the highest incidence of 2.5/100,000, Latin white people 1.8/100,000, and black people 1.5/100,000 [5].

3. Molecular characteristics of GBM

The current molecular characterization of GBM has allowed different classifications of the tumor subtypes and revealed intracellular pathways that might contribute to the development
of new and effective therapeutic targets. The new molecular classification can distinguish individual somatic mutations within the same tumor grade, since tumors are highly variable from patient to patient [6,7]. Thus, using molecular markers facilitate study of heterogeneity of glioma, and subsequently its diagnosis and treatment.

Intensive molecular analyses have revealed a variety of deregulated genetic pathways involved in the DNA damage and repair, apoptosis, cell migration, angiogenesis, and in the cell cycle. Molecular analyses show that they arise from different genomic alterations, which may influence the response to therapy. The Cancer Genome Atlas (TCGA) Research Network (2008) has established a comprehensive catalog of genomic abnormalities driving tumor genesis, thus subclassifying glioblastoma into at least four molecular subtypes, featuring distinct genetic, epigenetic, and transcriptional alterations [6,8]. Tumor variants are classified based on somatic mutations as: isocitrate dehydrogenase (IDH) and Tumor Protein (TP53). Glioblastoma is also classified based on it’s transcriptional signature as: classical, mesenchymal, neural or proneural. Classification is also given by variations in the number of gene copies, by mutations in Epidermal Growth Factor Receptor (EGFR) or by DNA hypermethylation of promoter-associated CpG islands [9].

The majority of glioblastoma cases are primary brain tumors that grow rapidly without major clinical or histological evidence of a less malignant precursor lesion. These tumors mainly affect the elderly and are genetically characterized by loss of heterozygosity (LOH) on 10q, EGFR amplification, p16INK4a deletion, and fosfatidilinositol-3,4,5-trisfosfato 3-fosfatasa (PTEN) mutations [10,11]. Secondary glioblastoma tumors develop through progression from low-grade diffuse astrocytoma or AA and are pronounced in younger patients [12]. The disruption of tumor-suppressor gene TP53 is implicated in the progression of many types of human malignancies; adult glioblastoma patients with TP53 mutation may have a more severe consequence than those without TP53 mutations [10]. It has also been shown that TP53 mutations, but not p53 expression, correlate with a more aggressive form of the disease. Studies have also reported that glioblastoma with TP53 mutations are more frequent in women than in men, and may occur in younger patients [13]. In addition, some studies suggest that TP53 mutations may occur in patients of any age group. In contrast, EGFR amplification preferentially occurs in older patients. Thus, multiple genes are involved in the initiation of the disease, and variability occurs in different age and sex groups in the progression of GBM. It is of interest that after careful analysis of age and disease progression, no significant difference in survival was observed in patients with primary and secondary glioblastoma. During the progression of glioblastoma, additional mutations and genetic alterations accumulate, which may alter disease severity and patient survival.

GBM primary and secondary can also differ significantly, depending on their pattern of promoter methylation and in the expression of profiles at the RNA and protein levels. LOH on 10q is shown to be most frequent in both primary and secondary glioblastomas [14]. TP53 mutations are detected early in the pathway, and frequent genetic alterations can lead to secondary glioblastoma. In 77 Japanese patients with GBM primary, 22% had TP53 mutations, 21% PTEN mutations, 32% EGFR amplification, 42% p16 INK4a homozygous deletion, and 69% LOH on chromosome 10q in those patients [15]. The frequencies of these
genetic alterations at the population level were similar to those reported in Europe. This study noted a positive association between EGFR amplification and p16 INK4a deletion.

4. Glioblastoma multiforme risk factors

GBM is the most aggressive form of malignant glioma. Several syndromes are associated with the increased incidence of GBM, such as Lynch syndrome, Li–Fraumeni syndrome, melanoma–neural system tumor syndrome, Ollier disease, and Maffucci syndrome [16]. A small proportion (5–10%) of patients has a family history of glioma. Genes too exist that are involved in gliomagenesis and participate in glioma growth, such as telomerase reverse transcriptase (TERT) [17], EGFR [18,19], coiled-coil domain containing protein 26 (CCDC26) [20], Cyclin-dependent Kinase inhibitor 2B [17], TP53 [21,22,23], and the regulator of telomere elongation helicase 1 (RTEL1) [24,25].

5. Endocrine characteristics of GBM

5.1. Estrogen receptors

GBM exhibits different endocrine characteristics. GBM expresses high levels of estrogen receptor alpha (mRNA ERα) and low levels of estrogen receptor beta (ERβ); expression of mRNA ERα is positively correlated to the survival of GBM patients and could be used as a prognostic factor [26]. In contrast, the low expression of ERβ in GBM has been related to a worse prognosis for survival and could be used as a biomarker for prognosis too [27,28]. Furthermore, activation of the signaling pathways induced by ERβ suppresses glioma growth in a model in vivo [29].

The coactivator family of estrogen receptors (SRC) is composed of three members, SRC-1, SRC-2, and SRC-3 [30,31]. SRC-1 increases the transcriptional activity of ER [32,33]; it also participates in the tumor progression and survival of several lines of human cancer [34,35]. SRC-2 is localized in different regions of the brain and mediates a variety of steroids-dependent functions [36,37]; SRC-3 is overexpressed in different types of cancer (breast, ovary, prostate, stomach, endometrium, esophagus, and pancreas) [38,39,40,41]. In astrocytoma cell lines, SRC1 and SRC-3 have been detected [42]. 17-i>estradiol induces the growth of several cell lines of human astrocytoma through the ERα, and its interaction with SRC-1 and SRC3 suggests that ERα has an important role in the growth of astrocytoma [43].

5.2. Progesterone receptors in GBM

Progesterone receptors (PRs) are expressed in 100% of high-grade astrocytomas. The predominant isoform expression of PR in GBM is PRB. In astrocytomas, the molecular mechanisms involved in the differential expression of PR isoforms are unknown. It is important to know what PR isoform is expressed in the brain tumor, because progesterone can exert different cell functions depending on the expression pattern of PR isoforms [44,45].
In several cell contexts, human PRB functions as a transcriptional activator of progesterone-responsive genes, whereas PRA acts a repressor of transcriptional steroid hormone receptors inclusive PRB [46]; PR expression assessed by immunohistochemistry directly correlates with the histological grades of astrocytomas; these results suggest that PR-positive tumors possess a high proliferative potential [47]. However, no conclusive data exists about the PR as a marker of prognosis.

Progesterone significantly decreases GBM tumor growth and promotes the survival time in approximately 60% of mice. Synergistic effects of progesterone and Temozolomide (TMZ) have been observed in the glioblastoma cell lines U87MG and U118MG. A significant decrease in PCNA (a marker of cell proliferation) expression in both U87MG and U118 cell lines was observed by the effect of progesterone alone (80 μM) or by the combination of 80 μM progesterone and 100 μM TMZ, when compared to control, and this has a significantly statistic outcome than that with TMZ alone. Cell survival was reduced in 58%, with the combined treatment of progesterone and TMZ (P 80 μM + TMZ 100 μM after) when compared to that with TMZ alone. Further, progesterone inhibited O-6-methylguanine-DNA-methyltransferase (MGMT) expression as well as the EGFR/P13K/Akt/mTOR signaling pathway, which is highly active in GBM. Progesterone + TMZ also inhibited the cell migration, suggesting that the combination therapy could contain the spread of tumor in vivo [48].

5.3. Androgen receptor in GBM

The androgen receptor (AR) is present in astrocytomas of low and high grades, with a higher expression in AA compared to astrocytomas grade I, II, and GBM. AR expression no affect the survival time of GBM patients [49,50] described a higher expression of AR in GBM tumors in women and men compared to periphery normal brain tissue.

5.4. Aromatase

Aromatase is an enzyme encoded by CYP19 gene localized in chromosome 15q 21.2. It converts androgens in estrogens; this enzyme is expressed mainly in ovary, testis, placenta, brain, lung, stomach, and adipose tissue [51]. Aromatase is composed of 503 amino acids and is the major source for estrogen production in postmenopausal women. The aromatase works in three steps; first, the C19 methyl group of androgenic substrate is oxidized to formic acid in concomitant aromatization of ring A to the characteristic phenolic ring A of estrogen [52].

Aromatase expression in GBM tumor is negatively correlated to the survival of GBM patients and has been proposed as a possible prognosis biomarker for astrocytomas [29].

17–ß estradiol levels in GBM tumor are highest, compared to low-grade astrocytomas (I, II) or astrocytoma anaplastic (grade III). The concentration of 17–ß estradiol in GBM seems to be directly involved in the tumor growth.
6. GBM treatment

GBM tumors show a large number of aberrations with a pronounced mitotic activity, neoangiogenesis, and necrosis. Its proliferative rate is three to five times more than the proliferative rate in AA [53].

On the basis of a recent GBM classification as proneural, neural, classical, and mesenchymal, diverse types of treatments must be created to make a molecular personalized therapy [6] (Table 1). Performing molecular assays is complex, as their cost may be an obstacle for a routine use.

| Treatment               | Overall survival (OS) | Progression-free survival (PFS) | Side effects                                                   | Author                  |
|-------------------------|-----------------------|---------------------------------|---------------------------------------------------------------|-------------------------|
| TMZ/RT                  | 14.6 months          | 6.9 months                      | Myelosuppression                                              | Stupp (2005)            |
| RT                      | 12.1 months          | 5.0 months                      | Skin reactions, cardiac complications                        | Stupp (2005)            |
| Bev/TMZ/RT              | 20.5 months          | 10.7 months                     | Myelosuppression, arterial thromboembolism, gastrointestinal perforation | Gilbert (2014)           |
| Bev                     | 15.7                 | 10.6                            | Arterial thromboembolism, arterial gastrointestinal perforation | Chinot (2014)           |
| Cilengitide/RT          | 26.3 months          | 13.5 months                     |                                                               | Stupp (2014)            |
| Nimotuzumab/RT          | 22.3 months          | 7.7 months                      | Headache, nausea, vomiting, anemia, myalgia                  | Westphal (2015)          |
| Nimustine               | 28.4 months          | 18.9 months                     | Chest pain and cianosis peribucal                            | Kim (2011)              |
| Enzastaurin             | 17.1 months          | 9 months                        | Lymphopenia                                                   | Wick (2013)             |
| Tipifarnib              | 80.3 weeks           | 18.1 weeks                      | Headache, nausea, vomiting                                  | Ducassou (2013)         |
| Everolimus              | 13.9 months          | 11.3 months                     | Anemia, higher levels of cholesterol in the blood, low phosphorus | Hainsworth (2012)       |

Table 1. Effects on survival of different treatments for GBM patients and their side effects.

The standard treatment for GBM patients includes brain radiation, a maximal surgery and chemotherapy with the alkylating agent TMZ.

A larger number of new drugs and virus-based therapy are being evaluated in phase II and III trials as well.

In a phase III trial including recently diagnosed GBM patients, the median overall survival (OS) for GBM patients was 14.6 months with chemotherapy and RT, and 12.1 months with RT alone with a median follow-up of 28 months [63].
In phase III of another study, 978 patients received standard radiation and TMZ with or without Bevacizumab, an angiogenesis inhibitor used at 10 mg/kg, every 2 weeks with a median follow-up of 20.5 months. The OS between bevacizumab group and placebo group was no different, and side effects such as hypertension, thromboembolic events, intestinal perforation, and neutropenia were more common in the bevacizumab group. The progression-free survival (PFS) was significantly improved in the experimental arm (10.7 vs 7.3 months, \( P = 0.007 \)) [64]. In another phase (III) trial with 458 patients, newly diagnosed GBM received radiation and TMZ with or without bevacizumab (10 mg/kg each for 2 weeks and TMZ for six cycles). With bevacizumab monotherapy (15 mg/kg), the median of PFS was of 10.6 months in the bevacizumab group as compared to 6.2 months in the placebo group.

6.1. Aromatase inhibitors (AIs)

The conversion of androstenedione and testosterone to estrogens can be blocked by the aromatase inhibitors; these pharmacological agents have a high specific activity to reduce, importantly, estrogen production. The AIs are classified in two types: I.—steroid inhibitors and II.—nonsteroid inhibitors; they are reactive species that bind covalently and irreversibly or noncovalently and reversibly to aromatase, respectively. The latter class interacts with the heme cofactor by employing its azole moiety. Third generation inhibitors are composed of triazole derivatives: anastrozole, letrozole, and the steroidal exemestane. These inhibitors provided greater clinical benefits with a robust aromatase inhibition of 98% or more. The aromatase inhibitors have been successfully used for the treatment of estrogen receptor-positive breast cancer in postmenopausal women [65]. Letrozole has a more potent inhibitory effect on estrogen synthesis than anastrozole [66]. Letrozole has been tested in a GBM model using Sprague–Dawley rats orthotopically implanted with C6 cells. Imaging analysis employing \( \mu \)PET/CT showed an important reduction in the volume of tumor (>75%) after 8 days of letrozole treatment (4 mg/kg/day) [67].

The AIs, namely 3b-hydroxyandrost-4-en-17-one (1), androst-4-en-17-one (12), 4a,5a-epoxy androstan-17-one (13a), and 5a-androst-2-en-17-one (16), induced an antiproliferative effect on MCF7 breast cancer cells, and this effect was due to a cell cycle arrest and cell death by apoptosis [68]. Table 1 shows different treatments for GBM and their effect on OS. It also exhibits the progression-free survival, with the side effects observed in these studies.

6.2. Hormone release growth hormone (GHRH) inhibitors

GHRH inhibitors had been used for the treatment of various cancers or disorders that express growth hormone (GH) or GHRH production. GHRH antagonists suppress GH or insulin-like growth factor (IGF-1) in transgenic mice overexpressing the GHRH gene; GHRH antagonists can inhibit the rat pituitary tumor cells overexpressing the GHRH receptors (p-GHRH-R). These antagonists also inhibit GH secretion [70]. There is evidence that GHRH antagonists are well tolerated in humans; however, more phase I–III clinical trials are necessary to probe the efficiency of these antagonists [71]. GHRH antagonists inhibit cancers that depend on IGF-1 as a growth factor [72–74]. GHRH antagonists can also inhibit various autocrine factors such as GHRH, GH, or VEGF by binding to the tumoral GHRH receptors, resulting in a tumor.
growth suppression [75,76]. In addition, GHRH antagonists could provoke tumor cell death by active cell pathways producing apoptosis [77,78].

The presence of the GHRH-R variant SV1 differs from the pGHRH by a short segment of the extracellular ligand-binding domain of the receptor protein in normal tissue and in various neoplastic tumors, lymphomas, small-cell lung carcinomas, pancreatic cancer, glioblastomas, and prostate cancer [79–81]. In several experimentally formed tumors, GHRH antagonist inhibits the growth and metastasis of cells expressing these receptor types. This inhibition occurs by binding to the full length of the GHRH-R or SV1 [79,80,82]. Kovácks et al., 2010 observed a strong GH release inhibition by the JV-1-63, reducing tumor growth (46%) of DBTRG-05 glioblastomas. Their experiments were conducted on nude mice. JV-1-63 antagonists caused an upregulation of mRNA expression of pGHRHR and downregulation of SV1 expression in vitro [82].

The use of aromatase and GHRH inhibitors could have a clinical use in patients with GBM once adequate phase II or III clinical trials are made.

Author details

Judith Marcela Dueñas-Jiménez¹, Irene Aguilar-García¹, María de la Luz Galván-Ramírez¹, Sergio Horacio Dueñas-Jiménez¹, Jorge David Rivas-Carrillo¹, Anne Santerre² and Erika Priscilla Domínguez-Rangel¹

*Address all correspondence to: judithmarceladuenas@gmail.com

1 University Center for Health Sciences, University of Guadalajara, Guadalajara, Jalisco, México

2 University Center for Biological and Agricultural Sciences, University of Guadalajara, Guadalajara, Jalisco, México

References

[1] Hou LC, Veeravagu A, Hsu AR. Tse VC recurrent glioblastoma multiforme: a review of natural history and management options. Neurosurg Focus 2006; 20(4):E5.

[2] Rosen ST. Cancer Treatment and Research, vol. 163. Duarte, CA, 2015; pp. 1–14. DOI: 10.1007/978-3-319-12048-5

[3] Dolececk TA, Propp J, Stroup N, Kruch C. CBTRUS statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2005–2009. Neuro Oncol 2009; 15(Suppl 5): 1–49. DOI: 10.1093/neuonc/nos218
[4] Wen P, Kesari S. Malignant gliomas in adults. N Engl J Med 2008; 359: 492–507. DOI: 10.1056/NEJMra0708126

[5] Chakrabarti I, Cockburn M, Cozen W, Wang Y-P, Preston-Martin S. A. population-based description of glioblastoma multiforme in Los Angeles County, 1974–1999. Cancer 2008; 104(12): 2798–2806. DOI: 10.1002/cncr.21539

[6] Verhaak RG, Hoadley KA, Purdom E, Wang V, Qi Y, Wilkerson MD, et al. Integrated genomic analysis identifies clinically relevant subtypes of glioblastoma characterized by abnormalities in PDGFRA, IDH1, EGFR, and NFI. Cancer Cell 2010; 17(1): 98–110. DOI: 10.1016/j.ccr.2009.12.020

[7] Dunn G, Rinne M, Wykosky J, Genovese G, Quayle S, Dunn I, et al. Emerging insights into the molecular and cellular basis of glioblastoma. Genes Dev 2012; 26(8): 756–784. DOI: 10.1101/gad.187922.112

[8] Noushmehr H, Weisenberger DJ, Diefes K, Phillips HS, Pujara K, Berman BP, et al. Identification of a CpG island methylator phenotype that defines a distinct subgroup of glioma. Cancer Cell 2010; 17(5): 510–522. DOI: 10.1016/j.ccr.2010.03.017

[9] Brennan CW, Verhaak RGW, McKenna A, Campos B, Noushmehr H, Salama SR, et al. The somatic genomic landscape of glioblastoma. Cell 2013; 155(2): 462–477. DOI: 10.1016/j.cell.2013.09.034.

[10] Huang PH, Mukasa A, Bonavia R, Flynn RA, Brewer ZE, Cavenee WK, Furnari FB, White FM. Quantitative analysis of EGFRvIII cellular signalling networks reveals a combinatorial therapeutic strategy for glioblastoma. Proc Natl Acad Sci U S A 2007; 104: 12867–12872. DOI: 10.1073/pnas.0705158104

[11] Khasraw M, Lassman AB Advances in the treatment of malignant gliomas. Curr Oncol Rep 2010; 12(1): 26–33. DOI: 10.1007/s11912-009-0077-4.

[12] Ohgaki H, Kleihues P. Genetic pathways to primary and secondary glioblastoma. Am J Pathol 2007; 170(5): 1145–1453. DOI: 10.2353/ajpath.2007.070011

[13] Zawlik I, Kita D, Vaccarella S, Mittelbronn M, Franceschi S, Ohgaki H. Common polymorphisms in the MDM and TP53 genes and the relationship outcomes in glioblastomas. Brain Pathol 2009; 19(2): 188–194. DOI: 10.1111/j.1750-3639.2008.00170.x.

[14] Nagajaran R, Costello J. Molecular epigenetics and genetics in neuro-oncology. Neurotherapeutics 200; 6(3): 436–446. DOI: 10.1016/j.nurt.2009.04.002.

[15] Fukushima T, Favereaux A, Huang H, Shimizu T, Yonekawa Y, Nakazato Y, Ohagki H. Genetic alterations in primary glioblastomas in Japan. J Neuropathol Exp Neurol 2006; 65(1):12–18. DOI: http://dx.doi.org/10.1097/01.jnen.0000196132.66464.96

[16] Temel JS, Greer JA, Muzikansky A et al. Early palliative care for patients with metastatic non-small-cell lung cancer. N Engl J Med 2010; 363(8):733–742. DOI: 10.1056/NEJMoa1000678.
[17] Rajaraman P, Melin BS, Wang Z, McKean-Cowdin R, Michaud DS, Wang SS, et al. Genome-wide association study of glioma and meta-analysis. Hum Genet 2010; 131(12): 1877–1888. DOI: 10.1007/s00439-012-1212-0

[18] Walsh KM, Anderson E, Hansen HM, Decker PA, Kosel ML, Kollmeyer T, et al. Analysis of 60 reported glioma risk SNPs replicates published GWAS findings but fails to replicate associations from published candidate-gene studies. Genet Epidemiol 2013; 37(2): 222–228. DOI: 10.1002/gepi.21707

[19] Sanson M, Hosking FJ, Shete S, Zelenika D, Dobkins SE, Ma Y et al. Chromosome 7p11.2 (EGFR) variation influences glioma risk. Hum Mol Genet 2011; 20(14): 2897–2904. DOI: 10.1093/hmg/ddr192

[20] Jenkins RB, Wrensch MR, Johnson D, Fridley BL, Decker PA, Xiao Y, et al. Cancer genetics. Cancer Genet 2011; 204(1): 13–18. DOI: 10.1016/j.cancergenet.2010.10.002

[21] Enciso-Mora V; Hosking FJ, Di Stefano AL, Zelenika D, Shete S, Broderick P, et al. Low penetrance susceptibility to glioma is caused by the variant rs 783782222. Br J Cancer 2013; 108(10): 2178–2185. DOI: 10.1038/bjc.2013.155

[22] Stacey SN, Sulem P, Jonasdottir A, Masson G, Gudmunson J, Gudbartsson DF et al. A germline in the TP53 polyadenylation signal confers susceptibility. Nat Genet 2011; 43(11): 1098–1103. DOI: 10.1038/ng.926.

[23] Egan KM, Nabors LB, Olson JJ, Monteiro AN, Browning JE, Madden MH, et al. Rre TP53 genetic variant associated with glioma risk and outcome. J Med Genet 2012; 49(7): 420–421. DOI: 10.1136/jmedgenet-2012-100941

[24] Shete S, Hosking FJ, Robertson LB, Sanson M, Malmer B, et al. Genome-wide association study identifies five susceptibility loci for glioma. Nat Genet 2009; 41(8): 899–904. DOI: 10.1038/ng.407

[25] Wrensch M, Kenkins RB, Chang JS, Yeh RF, Xiao Y, Decker PA, et al. Variants in the CDKN2B and RTEL1 regions are associated with high grade glioma susceptibility. Nat Genet 2009; 41(8): 905–908. DOI: 10.1038/ng.408.

[26] Dueñas JM, Candanedo A, Santerre A, Orozco S, Sandoval H, Feria R, et al. Aromatase and estrogen receptor alpha mRNA expression as prognostic biomarkers in patients with astrocytomas. J Neurooncol 2014; 119(2): 275–284. DOI: 10.1007/s11060-014-1509-z.

[27] Batistatou A, Kyzas PA, Goussia A, Arkoumani E, Voulgaris S, Polyzoidis K, et al. Estrogen receptor beta (ER – β), protein expression correlates with BAG – 1, and prognosis in brain glial tumors. J Neurooncol 2006; 77(1): 17–23. DOI: 10.1007/s11060-005-9005-0

[28] Batistatou A, Stefanou D, Goussia A, Arkoumani E, Papavassiliou AG, Agnatis N. Estrogen receptor beta (ERβ) is expressed in brain astrocytic tumors and declines with
[29] Sareddy GR, Nair BC, Gonugunta VK, Zhang QG, Brener A, Brann DW, et al. Therapeutic Significance of estrogen receptor β agonists in gliomas. Mol Cancer Ther 2012; 11(5): 1174–1182. DOI: 10.1158/1535-7163.MCT-11-0960

[30] Oñate SA, Tsai SY, Tsai MJ, O’Malley BW. Sequence and characterization of a coactivator for the steroid hormone receptor superfamily. Science 1995; 270(5240): 1334–1337. DOI: 10.1126/science.270.5240.1354

[31] Anzick SL, Kononen J, Walker RL, Azorsa DO, Tanner MM, Guan XY, et al. ALB1, a steroid receptor coactivator amplified in breast and ovarian cancer. Science. 1997; 277(5328): 965–968. DOI: 10.1126/science.277.5328.965

[32] Tetel MJ, Auger AP, Charlier TD. Who’s in charge? Nuclear receptor coactivator and corepressor function in brain and behavior. Front Neuroendocrinol 2009; 30(3): 328–342. DOI: 10.1016/j.yfrne.2009.04.008

[33] Molenda-Figueira HA, Murphy SD, Shea K, Slegal NK, Zhao Y, Chadwick JG. Steroid receptor coactivator – 1 from brain physically interacts differentially with steroid receptor subtypes. Endocrinology 2008; 149(10): 5272–5279. DOI: 10.1210/en.2008-0048

[34] Vienonen A, Miettinen S, Manninen T, Altuci L, Willhelm E, Ylikomi T. Regulation of nuclear receptor and cofactor expression in breast cancer cell lines. Eur J Endocrinol 2003; 148(4): 469–479. DOI: 10.1530/eje.0.1480469

[35] Weldon CB, Elliott S, Zhu Y, Clayton JL, Curiel TJ, Jaffe BM, Burow ME. Regulation of estrogen-mediated cell survival and proliferation by p160 coactivators. Surgery 2004;136(2): 346–354. DOI: 10.1016/j.surg.2004.05.010

[36] Apostolakis ED, Ramamurphy M, Zhou D, Oñate S, O’Malley BW. Acute disruption of select steroid receptor coactivators prevents reproductive behavior in rats and unmasks genetic adaptation in knockout mice. Mol Endocrinol 2002; 16(7): 1511–1523. DOI: 10.1210/mend.16.7.0877

[37] Nishihara E, Yoshida H, Chan C-S, Liao L, Davis RL, O’Malley BW, et al. SRC–1 null mice exhibit moderate motor dysfunction and delayed development of cerebellar Purkinje cells. J Neurosci 2003; 23(1): 213–222.

[38] Tognoni CM, Chadwick JG, Ackeifi CA, Tetel MJ. Nuclear receptor coactivators are coexpressed with steroid receptors and regulated by estradiol in mouse brain. Neuroendocrinology. 2011; 94: 49–57. DOI: 10.1159/000323780

[39] Lonard DM, Lanz RB, O’Malley BW. Nuclear receptor coregulators and human disease. Endocr Rev. 2007; 28(5): 575–587. DOI: 10.1210/er.2007-0012
[40] Sakaguchi H, Fujimoto J, Sun W-S, Tamaya T. Clinical implications of steroid receptor coactivator (SRC – 3) in uterine endometrial cancers. J Steroid Biochem Mol Biol 2007; 104(3–5): 237–240. DOI: 10.1016/j.jsbmb.2007.03.007

[41] Sakakura C, Hagiwara A, Yasuoka R, Fujita Y, Nakanishi M, Masuda K, et al. Amplification and over expression of the AIB1 nuclear receptor coactivator gene in primary gastric cancers. Int J Cancer 2000; 89(3): 217–223. DOI: 10.1002/1097-0215(20000520)89:3<2.

[42] Hernández O, Rodríguez M, González A, Camacho I. Progesterone and estradiol effects on SRC–1 and SRC–3 expression in human astrocytoma cell lines. Endocrine 2010; 37(1): 194–200. DOI: 10.1007/s12020-009-9288-6

[43] González A, Hansberg V, Hernández O, González T, Henderson J, Lemus D, et al. Estradiol increases cell growth in human astrocytoma cell lines through ERa activation and its interaction with SCR–1, SCR–3, coactivators. Biochim Biophys Acta. 2002; 1823(2): 379–386. DOI: 10.1016/j.bbamcr.2011.11.004

[44] Giangrande P, McDonnel DP. The A and B isoforms of the human progesterone receptor: two functionally different transcription factors encoded by a single gene. Recent Prog Horm Res 1999; 54: 291–313.

[45] Tora L, Gronemeyer H, Turcotte B, Gaub MP, Chambon P. The N-terminal region of the chicken progesterone receptor specifies target gene activation. Nature 1988; 333(6169): 185–188. DOI: 10.1038/333185a0

[46] Vege E, Shahbaz MM, Wen DX, Goldman ME, O'Malley BW, McDonnell DP. Human Progesterone receptor A for is a cell – and promoter – specific repressor of human progesterone receptor B function. Mol Endocrinol 2013; 7(10): 1244–1255. DOI: org/10.1210/mend.7.10.8264658#sthash.FjZjmlYb.dpuf

[47] Khalid H, Shibata S, Kishikawa M, Yasunaga A, Iseki M, Hiura T. Immunohistochemical analysis of progesterone receptor and Ki – 67 labelling index in astrocytic tumors. Cancer. 1997; 80(11): 2133–2140. DOI: 10.1002/(SI CI)1097-0142(19971201)80:11<2133::AID-CNCR13>3.

[48] Atif F, Patel N, Yosuf S, Stein D. The synergistic effect of combination progesterone and temozolomide on human glioblastoma cells. Plos One 2015; 10(6): e0131441. DOI: 10.1371/journal.pone.0131441

[49] Yong GC, Kim HK, Kap Lee H, Chan Lee K. Expression of androgen receptors in astrocytoma. J Korean Med Sci 1996; 11(6): 517–521. DOI: 10.3346/kjms.1996.11.6.517

[50] Yu X, Jiang Y, Wei W, Cong P, et al. Androgen receptor signalling regulates growth of glioblastoma multiforme in men. Tumor Biol 2015; 36(2): 967–972. DOI: 10.1007/s13277-014-2709-z

[51] Miller W, Larionov A. Aromatase 2004, Edinburgh, UK, 6–8 September 2004. Breast Cancer Res 2004; 7: E2. DOI: 10.1186/bcr964
[52] Simpson E, Clyne C, Rubin G, Boon W, Robertson K, Brit K, et al. Aromatase—a brief overview. Annu Rev Physiol 2002; 64: 93–127. DOI: 10.1146/annurev.physiol.64.081601.142703

[53] Kleihues P, Luois D, Scheithauer B, Rorke L, Reifenberger G, Burger P, et al. The WHO classification of tumors of the nervous system. J Neuropathol Exp Neurol. 2002; 61(3): 215–225. DOI: org/10.1093/jnen/61.3.215

[54] Stupp R, Weber D. The role of radio and chemotherapy in glioblastoma. Onkologie. 2005; 28(6–7): 315–317. DOI: 10.1159/000085575

[55] Gilbert M, Dignam J, Armstrong T, Wefel J, Blumenthal D, Vogelbaum M, et al. A randomized trial of bevacizumab for newly diagnosed glioblastoma. N Engl Med. 2014; 370(8): 699–708. DOI: 10.1056/NEJMoa1308573

[56] Chinot O, Reardon D. The future of antiangiogenic treatment in glioblastoma. Curr Opin Neurol 2014; 26(6): 675–682. DOI: 10.1097/WCO.0000000000000142.

[57] Stupp R, Picard M, Weller M. Does cilentigide deserve another chance? – Authors reply. Lancel Oncol 2014; 15(13): 585–586. DOI: 10.1016/S1470-2045(14)71121-0

[58] Westphal M, Heese O, Steinbach J, Schnell O, Schackert G, Mehdorn M, et al. A randomised, open label phase III trial with nimotuzumab, an anti epidermal growth factor receptor monoclonal antibody in the treatment of newly diagnosed adult glioblastoma. Eur J Cancer 2015; 51(4): 522–532. DOI: 10.1016/j.ejca.2014.12.019.

[59] Kim I, Park C, Heo D, Kim C, Rhee C, Nam D, et al. Radiotherapy followed by adjuvant temozolomide with or without neoadjuvant ACNU—CDDP chemotherapy in newly diagnosed glioblastomas: a prospective randomized controlled multicenter phase III trial. J Neurooncol 2011; 103(3): 595–602. DOI: 10.1007/s11060-010-0427

[60] Wick W, Steinbach J, Platten M, Hartmann C, Wenz F, von Deimiling, et al. Enzastaurin before and concomitant with radiation therapy, followed by enzastaurin maintenance therapy, in patients with newly diagnosed glioblastoma without MGMT promoter hypermethylation. Neuro Oncol 2013; 15(10): 1405–1412. DOI: 10.1093/neuonc/not100.

[61] Ducassou A, Uro-Coste E, Verelle P, Filleron T, Benouaich A, Lubrano V, et al. αvβ3 integrin and Fibroblast growth factor receptor (FGFR1): pronostic factors in a phase II clinical trial associating continuous administration of tipifarnib with radiotherapy for patients with newly diagnosed glioblastoma. Eur J Cancer 2013; 49(9): 2161–2169. DOI: 10.1016/j.ejca.2013.02.033

[62] Hainswoth J, Shih K, Shepard G, Tillinghast G, Brinker B, Spigel D. Phase II study of concurrent radiation therapy, temozolomide, and bevacizumab followed by bevacizu-mab /everolimus as first line treatment for patients with glioblastoma. Cin Adv Hematol Oncol. 2012; 10(4): 240–246.

[63] Burtsein H, Prestud A, Seidenfeld J, Anderson H, Bucholz T, Davidson N, et al. American Society of Clinical Oncology Clinical Practice guideline: update on adjuvant
endocrine therapy for women with hormone receptor–positive breast cancer. J Clin Oncol. 2010; 34(7): 3784–3796.

[64] Geisler J, Haynes B, Anker G, Dowselt M, Lonning E. Influence of letrozole and anastrozole estrogen levels in postmenopausal breast cancer patients evaluated in a randomized, cross-over Study. J Clin Oncol. 2002; 20: 751–757. DOI: 10.1038/bjc.2011.58

[65] Amaral C, Varela C, Borges M, Tavares da Silva E, Roleira F, Correia da Silva G, et al. Steroidal aromatase inhibitors inhibit growth of hormone–dependent breast cancer cells by inducing cell cycle arrest and apoptosis. Apoptosis 2013; 18(11): 1426–1436. DOI: 10.1007/s10495-013-0879-6

[66] Kovaes M, Kineman R, Schally A, Zarandi M, Groot K, Frohman L. Effects of antagonist of growth hormone—releasing hormone (GHRH) on GH and insulin—like growth factor 1 levels in transgenic mice overexpression the human GHRH, an animal model of acromegaly. Endocrinology 1997; 138(11): 4536–4542. DOI: 10.1210/endo.138.11.5498

[67] Kovaes M, Schally A, Lee E, Busto R, Armatis P, Groot K, Varga J. Inhibitory effects of antagonistic analogues of GHRH on GH3 pituitary cells overexpressing the human GHRH receptor. J Endocrinol. 2002; 175(2): 425–434. DOI: 10.1677/joe.0.1750425

[68] Jenkins PJ, Bustin SA Evidence for a link between IGF-I and cancer. Eur J Endocrinol. 2004; 151:S17–S22. DOI: 10.1530/eje.0.151S017

[69] Kahan Z, Gardi J, Nyari T, Foldesi I, Ormandi K, Lazar G, et al. Elevated levels of circulating insulin-like growth factor-I, IGF-binding globulin-3 and testosterone predict hormone-dependent breast cancer in postmenopausal women a case–control study. Int J Oncol 2006; 29(1):193–200. DOI: 10.3892/ijo.29.1.193

[70] Le Roith D. The insulin-like growth factor system. Experimental Diab Res. 2003; 4(4): 205–212. DOI: 10.1155/EDR.2003.205

[71] Kovaes M, Schally A, Varga J, Zaradi M. Endocrine and antineoplastic actions of growth actions of hormone–releasing hormone antagonists. Curr Med Chem 2008; 15(4): 314–321. DOI: 10.2174/092986708783497355

[72] Schally A, Varga J, Engel J. Antagonists of growth–hormone–releasing hormone: an emerging new therapy for cancer. Nat Clin Pract Endocrinol Metab. 2008; 4(1): 33–43. DOI:10.1038/ncpendmet0677

[73] Hohla F, Buchholz S, Schally A, Rick F, Szalontay L, Varga J, et al. GHRH antagonist causes DNA damage leading to p53 mediated cell cycle arrest and apoptosis in human colon cancer cells. Cell Cycle 2009; 8(19): 3149–3156.

[74] Kanashiro C, Schally A, Zaradi M, Hammann B, Varga J. Alterations of EGFR/HER, angiogenesis and apoptosis pathways after therapy with antagonists of growth hormone releasing and bombesin in non–small cell lung cancer. Int J Oncol 2007; 30(4): 1019–1028. DOI: 10.3892/ijo.30.4.1019
[75] Halt A, Schally A, Halmos G, Varga J, Toller G, Hovarh J, et al. The expression of the pituitary growth hormone – releasing hormone receptor and its splice variants in normal and neoplastic human tissues. PNAS 2005; 102(48): 17424–17429. DOI: 10.1073/pnas.

[76] Heinrih E, Schally A, Bulchholz S, Rock F, Halmos G, Mile M, et al. Dose dependent growth inhibition in vivo of PC – 3 prostate cancer with a reduction in tumoral growth factors after therapy with GHRH antagonist MZ – J – 7 – 138. Prostate 2008; 68(16): 1763–1772.

[77] Resaki Z, Czompoly T, Shally A, Halmos G. Isolation and sequencing of CDNA for splice variants of growth hormone—releasing hormone receptors from human cancers. PNAS 2000; 97(19): 10561–10566. DOI: 10.1073/pnas.

[78] Kovacs M, Schally A, Hohla F, Rick F, Pozsagai E, Szalontay L. A correlation of endocrine and anticancer effects of some antagonists of GHRH. Peptides 2010; 31(10): 1839–1846. DOI: 10.1016/j.peptides.2010.07.006

[79] Chiot O, Reardon D. The future of antiangiogenic treatment in glioblastoma. Curr Opin Neurol. 2014; 27(6): 675–682. DOI: 10.1097/WCO.

[80] Kim I, Park C, Heo D, Kim C, Rhee C, Nam D, et al. Radiotherapy followed by adjuvant temozolomide with or without neoadjuvant ACNU—CDDP chemotherapy in newly diagnosed glioblastomas: a prospective randomized controlled multicenter phase III trial. J Neurooncol 2011; 103(3): 595–602. DOI: 10.1007/s11060-010-0427.
