

REVIEW

On the Concepts and History of Glioblastoma Multiforme - Morphology, Genetics and Epigenetics

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Glioblastoma multiforme (GBM) is a grade IV WHO malignant tumor with astrocytic differentiation. As one of the most common clinically diagnosed central nervous system (CNS) oncological entities, there have been a wide variety of historical reports of the description and evolution of ideas regarding these tumors.

The first recorded reports of gliomas were given in British scientific reports, by Berns in 1800 and in 1804 by Abernety, with the first comprehensive histomorphological description being given in 1865 by Rudolf Virchow. In 1926 Percival Bailey and Harvey Cushing gave the base for the modern classification of gliomas. Between 1934 and 1941 the most prolific researcher in glioma research was Hans-Joachim Scherer, who postulated some of the clinico-morphological aspects of GBM. With the introduction of molecular and genetic tests the true multifocality of GBM has been established, with different genotypes bearing the same histomorphological and IHC picture, as well as some of the aspects of gliomagenesis. For a GBM to develop, a specific trigger mutation needs to occur in a GBM stem cell – primary GBM, or a slow aggregation of individual mutations, without a distinct trigger mutation – secondary GBM.

Knowledge of GBM has been closely related to general medical knowledge of the CNS since these malignancies were first described more than 200 years ago. Several great leaps have been made in that time, in the footsteps of both CNS and advancements in general medical knowledge.

INTRODUCTION

Glioblastoma Multiforme (GBM) is a grade IV World Health Organization (WHO) malignant glial tumor with astrocytic differentiation, one of the most common intracranial oncological entities and is widely considered to be the most malignant primary intracranial tumor (**Fig. 1**).^{1,2} As one of the most common clinically diagnosed central nervous system (CNS) oncological entities, there have been a wide variety of historical reports of the description and evolution of ideas regarding these tumors ranging from purely morphological to genetic, with emphasis on both population based finding and personalized medicine.³⁻⁸

The evolution of the concepts of origin of GBM and other glial tumors has been closely related to the general knowledge and understanding of the functionality of the CNS, as well as general

medical knowledge. Discovering the cells of origin of these tumors, their physiological functions and the general evolution of the tumors has been closely related to fundamental discoveries in the field of neuroanatomy, neuropathology, oncology and cell biology.

GROSS MORPHOLOGY ERA

The first recorded reports of primary, non-metastatic, CNS tumors were described in British scientific reports, only on a gross morphological level in autopsy material, by Berns in 1800 and in 1804 by Abernety as diffuse tumors formation in the CNS, which do not show a clear border with healthy tissue and are distinctly different from it. At that time the term *Medullary Sarcoma* was used in British literature, while *Encephaloide* was later coined in the French and *Fungus Medullare* in the German

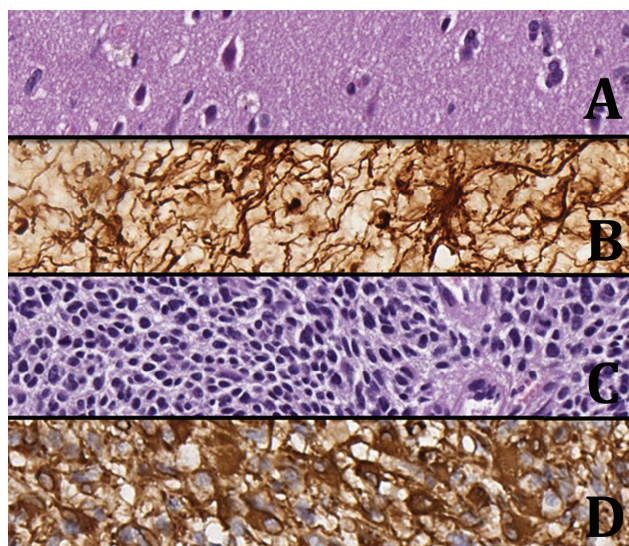


Figure 1. Cellular contrast between healthy brain tissue and GBM. **A** – Healthy brain tissue, H&E, original magnification x200. **B** – Healthy astrocytes, IHC stain with GFAP, original magnification x400. **C** – Hypercellularity and cellular atypism of GBM, H&E, original magnification x400. **D** – Neoplastic astrocytes of GBM, IHC stain with GFAP, original magnification x400.

speaking regions of the world.³ These reports were, however, based only on gross morphological observation of these tumor formations, as light microscopy had not yet been incorporated into the pathological investigation practices.

HISTOLOGICAL ERA

The first comprehensive histomorphological description of glial tumors was given in 1865 by the German pathologist Rudolf Virchow (1821-1902) as malignant tumor formations originating from the glial cells of the CNS, showing clear tissue and cellular structural contrast with healthy brain tissue and invading neighboring structures.⁶ Virchow was also the first to coin the term *glioma* for such lesions. Due to the severity of the contrast between some of the tumors on a histological level, Virchow segregated gliomas into two groups according to their cellularity and general contrast when compared to normal brain tissue.⁶ These two distinct groups of gliomas correspond to low grade gliomas (grades I and II) and high-grade gliomas (grades III and IV) when compared to the 2016 WHO classification of CNS tumors.¹

CNS PARADIGM SHIFT AND CELLULAR CONCEPTS

These descriptions came nearly a decade after the

glial cells, still viewed as a homogenous cellular population, were themselves described by Virchow during a lecture held on the April 3, 1858. The term *glia*, from the Greek word for glue was coined as these cells were viewed as the extracellular matrix producing cells of the CNS – neurocement.^{6,9}

The discovery and description of CNS glial cells and tumors originating from them turned out to be an integral part of the nervous system paradigm shift spanning the whole length of the 19th century.¹⁰ Other key moments of this paradigm shift are marked by the discovery and description of the first neurons in 1837 by the Czech anatomist and physiologist Jan Purkinje (1787-1869) in the cortex of the *cerebellum* – the trivially named Purkinje cells and the special silver stains developed by Camilo Golgi (1843-1926) in 1873 and Santiago Ramon y Cajal in 1887 (1852-1934).^{11,12} All these discoveries were later used as the foundation for the neuronal doctrine and as counterargument to the now obsolete reticular theory regarding the structure and functionality of the CNS.¹¹ During the latter half of the 19th and first couple of decades of the 20th century the individual fractions of glial cells were described and their functionality established. The Hungarian histologist Michael von Lenosec (1863-1937) first described astrocytes in 1893, the Spaniard Pio del Rio Horteiga (1882-1945) described oligodendrocytes and microglial cells in 1919, while also postulating the individual functions of the distinct glial fractions into his neuroglial theory, complying and adding to the already dominant neuronal doctrine.^{13,14}

GOLDEN ERA

In 1926, nearly 100 years after gliomas were first described and more than 50 years after the description of the precursor cells and the first proposed classification by Virchow, the American neuropathologist Percival Bailey (1892-1973) and the father of modern neurosurgery Harvey Cushing (1869-1939) gave the base for the modern classification of gliomas, on which the current 2016 WHO classification is based on.^{1,4}

Bailey and Cushing called the most clinically malignant and histologically atypical form of glioma – *Spongioblastoma Multiforme*, due to the *multiform* appearance of cells within the same tissue samples. They firmly believed that this tumor type had a different cellular origin to other gliomas due to the atypical and polymorphic monstrous cells, which bear no resemblance to healthy glial and even other

glioma cells. Other distinct tumors according to their classification are astrocytomas which originate from the astrocytic glia and their neoplastic cells and still bear some resemblance to them.⁴ With time, however, the term *spongioblastoma* was phased out and replaced with *glioblastoma* and the common origin of astrocytoma and GBM established.

Between 1934 and 1941 the most prolific researcher of gliomas was the German neuropathologist Hans-Joachim Scherer (1906-1945), who published a great number of research articles on the topic.^{3,15,16} Scherer postulated that the histomorphological diagnosis should be based on the whole tumor sample and not on individual tumor cells found in the material. Based on his research he reached the conclusion that GBM and astrocytoma share the same precursor cell of origin and that some astrocytoma cases can, in time, progress to GBM.³ Therefore, Scherer coined the terms primary *glioblastoma* (pGBM) which arises *de*

novo and secondary *glioblastoma* (sGBM) arising on the basis of a previously existing astrocytoma. Based on Scherer's estimates pGBM and sGBM share the same histomorphological hallmarks, but are widely diverse in their biological properties. The two types of GBM did not only differ in their evolution, but also in their clinical manifestation and progression – while pGBM is extremely aggressive and has a dramatic clinical course, sGBM has slower progression and a better general prognosis for the patient.^{1,3}

Scherer also heavily researched the neovascular proliferation in GBM samples, which in some cases can even mimic the kidney glomeruli – glomerulisation phenomenon (**Fig. 2**) and the pseudopalisadic necrosis found commonly and considered pathognomonic for GBM. The latter term is also often referred to as geographical necrosis and Scherer formation (**Fig. 3**) in honor of his contributions in the field of glioma research.

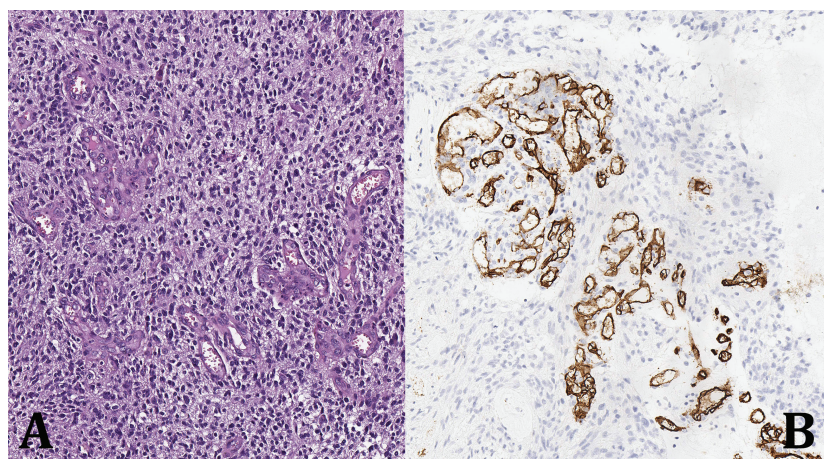


Figure 2. Neovascular proliferation in GBM. **A** – Immature tumor blood vessels, H&E, original magnification x 200. **B** – Endothelium of the immature tumor blood vessels, IHC stain with CD34, original magnification x200.

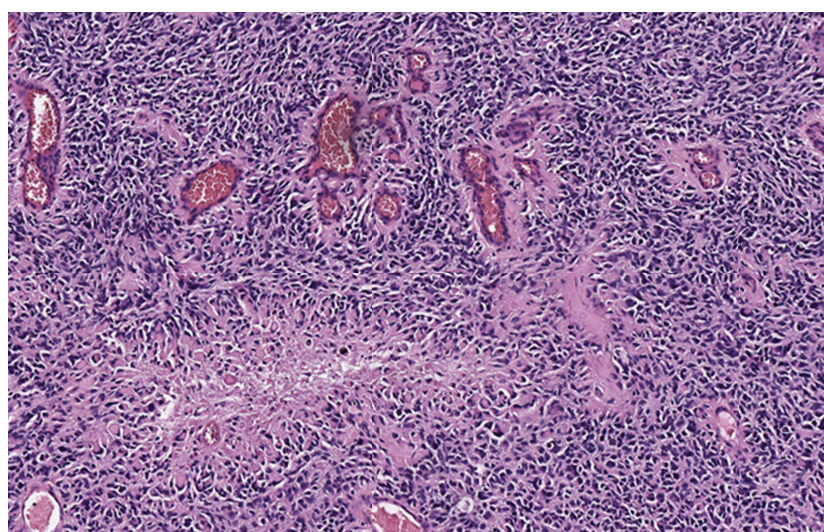


Figure 3. Tumor pseudopalisadic geographical necrosis - Scherer formation, H&E, original magnification x200.

PHENO- AND GENOTYPISATION

During the second half of the 20th century, research in the field of cerebral gliomas took a step back, despite the introduction of new methods of morphological and non-morphological examinations. The term *multiforme* was also phased out and the most malignant primary brain tumor was referred to as *glioblastoma* for a long period of time. The biggest innovations in the field for this period were the commercial introduction of immunohistochemical (IHC) markers such as GFAP, S100, Vimentin and others which give a constant positive reaction and often help with the differential diagnosis of GBM and CNS metastatic diseases, while others give a varying IHC reaction.^{17,18}

With the introduction of modern molecular pathological and genetic test in oncopathology practices, however, the term *multiforme* has once again been popularized in the last fifteen years of glioma research due to the multifomity of different genotypes bearing the same histomorphological and IHC picture.¹⁷⁻²¹

As part of the research in this area and its relevance to therapeutic approaches, based on the presence of mutations, correlating with their biological potential and not the histomorphological and IHC hallmarks, some key mutations have been identified in both pGBM and sGBM, giving a modern explanation to Scherers observations and estimations.^{1,3,6} The common presence of some mutations in different combinations has led to the discovery of a clinical correlation and even new therapeutic approaches to the diagnosis and treatment of GBM.^{1,22,23}

Some mutations, such as the suppression of MGMT, have no effect on the clinical manifestation, but are extremely important in the therapeutic strategies. When the MGMT levels in the GBM cells are decreased, the cells are more susceptible to DNA alkylation, by some alkylating agents such as temozolomide and therefore bear a better clinical and therapeutic prognosis.^{22,23} Temozolomide, taken orally, actively alkylates the guanine portions of DNA at the N-7 and O-6 positions, which in turn in the absence of the dealkylating effect of MGMT promotes cell death, increasing post-operative median survival to more than 13 months in case controlled studies, independent of higher dosage.

MODERN CONCEPTS

The age of molecular pathology GBM has truly

revealed its multiformity, not only on the morphologic and phenotypic but also on the genotypic side, as it shows a wide variety of interlinked and independent mutations. For molecular pathology, GBM represents a heterogeneous malignant group with multiple distinct genetic and epigenetic alterations associated with a distinct clinical course.¹⁹

The differences between the two ways of occurrence of GBM are most profoundly understood at the level of genotype and epigenetic alterations. Certain mutations occur predominantly in pGBM or sGBM, however, still no single mutation has been found to be characteristic of or triggering only one forms of GBM.²⁴

CANCER STEM CELLS

Currently, the most widely accepted hypothesis for the initiation, progression and even recurrence of GBM, regardless of it being pGBM or sGBM, incorporates the concept of mutation accumulation in neural stem cell, which develop into gliogenic cancer stem cells.²⁵ This hypothesis also explains the existence of genotypical differences between the cells found in the same tumor sample and those of its recurrence, as the process is dynamic. These GBMsc can be identified by the presence of CD24, CD44, CD133 and Hes3 positivity and are highly resistant to treatment due to active mechanisms of DNA repair and self-regeneration.^{26,27} These cells can easily migrate out of the primary tumor bed, giving rise to recurrences. Though these GBMsc have similarities with neuronal stem cells, they exhibit only gliogenic potential in cell cultures and experimental models.²⁶

The GBMsc concept explains the presence of genotypically different clonal populations of cells in the same tumor.^{26,28} It also explains relapses even at 100% eradication of the primary tumor.²⁵ Some studies have shown that both GBMsc can not only initiate tumor cell lines, but these tumor cell lines possess the ability to revert back to GBMsc. This concept opens new therapeutic doors, but also presents new challenges due to the different treatment approach, as GBMsc have been shown to be quite resistant to treatment and able to migrate, grouped together with the mutual convertibility of both cell types.^{26,28}

Due to the process of accumulation of mutations in GBMsc, mature GBM cell lines have been known to have a great variety of mutations, the most common and explicit role in oncogenesis processes.

EGFR ASSOCIATED MUTATIONS

The gene encoding epidermal growth factor receptor (EGFR) is located on the seventh chromosome at locus 7p12.²⁹ Several mutant variants are encountered, resulting in over stimulation of the cell by activation of the cellular stimulation of the tyrosine kinase pathway and inhibition of apoptosis leading to gliogenic potential.^{19,21,30,31} The two major types of EGFR hyperstimulation in gliomagenesis are ligand-dependent and ligand-independent.

Ligand-dependent pathways are mediated primarily by receptor amplification, expression of mutant receptors that react more strongly and sustainably to normal stimuli, ligand overexpression (autocrine stimulation), or a combination of these.^{19,32} The ligand-dependent pathway is more common (more than 50% of all GBM) and is the result of deletion of 267 amino acids from the extracellular ligand binding domain of the receptor.³¹ The resulting mutant EGFRvIII receptor is constantly active regardless of the presence or absence of a ligand.³⁰ Regardless of their type, mutations in EGFR occur and are characteristic of almost all pGBM and in much less (about 5%) for sGBM.¹⁹ However, unlike other tumors expressing EGFR mutations, anti-EGFR drugs have no effect on tumor progression and patient survival.^{33,34}

PDGFR ASSOCIATED MUTATIONS

Platelet derive growth factor (PDGF) has two major forms of platelet derived growth factor receptor (PDGFR) - PDGFRA and PDGFRB, with PDGFRA being of greater importance in the processes of gliomagenesis.^{19,21,31} The PDGFRA coding gene is located on the fourth chromosome in locus 4q12, this PDGFRB encoding the fifth chromosome at locus 5q33.1.³⁵

The PDGFR activating ligands are PDGF-A, PDGF-B, PDGF-C and PDGF-D, with mutated combinations associated with PDGFRa PDGF-A amplifications performing auto- and paracrine overstimulation of cells and activation on a tyrosine kinase pathway like the EGFR-associated mutations.^{19,31} This pathway of autocrine stimulation is common in glial tumors of all classes, and may be considered an early and fundamental phenomenon in the process of gliomagenesis.^{36,37}

In animal models' overstimulation with PDGFR-A in the subventricular zone (a mitotically active region of the CNS) cause the development of PDGFRa stem cells, which subsequently develop into GBM-like lesions.³⁸ This suggests that a por-

tion of stem cells in the CNS of adult individuals through over-stimulation can be transformed into GBMsc, which initiates cell lines with glioma potential. The mutations in PDGF and its ligands are predominantly characteristic of pGBM.¹⁹

RAS AND NF1 ASSOCIATED MUTATIONS

The Ras superfamily are a group of guanosine-bound protein (G-protein) involved in the signal transduction process of cellular stimuli for proliferation and blocking apoptosis.³⁹ Ras is a complex relay station for the pathways of cellular stimulation and its activation by a tyrosine kinase mechanism leads to activation of other intracellular pathways, including the PI3K pathway.^{19,31,34}

The main role in the processes of gliomagenesis from this group is attributed to HRAS.^{19,40,41} The HRAS coding gene is located at the eleventh chromosome at locus 11p15.5.⁴² Its over-activation is observed in almost all GBM, but this is extremely rare due to mutations in the coding gene.

The exogenous stimuli that activate the Ras pathway in oncogenesis of GBM are not yet fully understood, but EGFR and PDGFa are thought to play a role in tyrosine kinase stimulation.³¹

Neurofibromin 1 has a proven endogenous inhibitory effect on Ras.^{21,40,41} Neurofibromin 1 is encoded by the NF1 gene located on the seventeenth chromosome at locus 17q11.2.⁴³ A mutation in NF1 resulting in loss of function and subsequent over-activation of the Ras cycle has been observed in type 1 neurofibromatosis, a syndrome known as von Recklinghausen disease, in which both peripheral nervous system tumors and almost all variants of glioma in the CNS.^{40,41,44-46}

The MET gene has an endogenous stimulating effect on the Ras superfamily and as such is often amplified in GBM. This gene plays an important role in the PI3K pathway and processes of tumor angiogenesis.^{34,47}

RB1 AND CDK ASSOCIATED MUTATIONS

The RB1 gene is located on the thirteenth chromosome at locus 13q14.2 and encodes the phosphoprotein pRB, which is the key molecule in the RB cycle of cell proliferation suppression/activation, depending on the state of pRB - hypophosphorylated (active) or phosphorylated (inactive).^{19,48} The active form prevents cell proliferation, while the inactive allows for its course.

In the presence of activated pRB, transcription of genes important for mitosis is prevented and the

cell remains blocked in the G1 phase of mitosis. In the presence of an external stimulus of growth factor, pRB is phosphorylated and inactivated by the formation of an active CDK4/6-cyclin D1 complex by degradation of its p27^{Kip1} inhibitor by the CDK2-cyclin E complex.^{19,32} This allows the cell to transition from the G1 to S phase of the cell cycle and subsequently through the G2 and M phases through which the pRB is also maintained in an inactive state. Amplifications of CDK4/CDK6 and cyclin-D encoding genes are also often observed independent of RB mutations.

Proteins with the property of maintaining pRB in the active state by competition with cyclins for CDK are Ink4 family proteins that also form CDK complexes. P16 and its CDKN2A-p16^{INK4a} complex, p15 and its CDKN2B-p15^{INK4b} complex, p18 and CDKN2C-p18^{INK4c} complex and p19 with their CDKN2D-p19^{INK4d} complex, each inhibiting the phosphorylation of pRB and maintaining it in the active state.^{19,36}

Mutations in RB associated with loss of function or mutations in cyclin-dependent kinase-cyclin complexes by overproduction of enzymes or cofactors result in over-phosphorylation of pRB and result in sustained stimulation for cell proliferation.¹⁹ Other mechanisms associated with sustained inactivation of the RB cycle are related to the loss of the endogenous cyclin antagonists of the Ink4 family.^{19,36}

An especially important role is played by the CDKN2A gene located on the ninth chromosome in locus 9p21 encoding both CDKN2A-p16^{INK4a} (p16) and CDKN2A-p14^{ARF} (p14ARF) by alternative splicing.^{19,32,36,49} This gene is key and common for RB and p53 pathways, as its products are common activators for both pathways.^{41,50,51}

Mutations associated with the RB pathway are more common in pGBM, with the most frequent mutation associated with loss of function in CDKN2A-p16^{INK4a} (p16) or homozygous deletion of the coding genes found in more than half of the cases, followed by homozygous deletion of RB gene in about 10% of primary and more than one third of sGBM.¹⁹

BRAF ASSOCIATED MUTATIONS

The BRAF gene is encoded on the seventh chromosome at locus 7q34 and encodes the protein of the same name, which is a serine-threonine kinase that is actively involved in signal transduction in the cytoplasm.³⁵ Upon activation of BRAF, by the

tyrosine kinase pathway from the ligand-dependent EGFR/PDGFR systems, it actively phosphorylates the threonine regions of MAPK.^{34,40} MAPK is a group of kinases that further transmit the cell proliferation signal by a mechanism similar to that of CDK-cyclin complexes. The BRAF chain is susceptible to NF1 repression similar to the RB loop, which further underlines the importance of NF1 in oncogenesis processes.^{41,52}

BRAF mutations associated with constant MAPK pathway activity are most common in pilocytic astrocytomas and, rarer in other glial tumors with higher differentiation.⁵² The presence of such mutations in GBM is a sure sign of secondary progression from lower-grade glial tumors.^{52,53}

PI3K AND PTEN ASSOCIATED MUTATIONS

PI3K are a group of cytoplasmic enzymes of which the PIK3CA, encoded by a gene located on the third chromosome in locus 3q26.3 and PIK3R1, encoded by a fifth chromosome gene at locus 5q13.1 are of highest significance to glial tumors.^{54,55} These proteins are subject to activation by ligand-dependent systems located on the surface of the plasma membrane, as the EGFR/PDGFR systems and as a result of their activation activate the AKT pathway of cell stimulation and blockade apoptosis.⁵⁶ Because of these properties, PI3K associated mutations, most commonly gene amplifications, play an important role in gliomagenesis.

The PI3K system is subject to stimulation and activation by the MET oncogene encoded by a gene located on the seventh chromosome at locus 7q31.⁵⁴ MET amplifications are often observed to stimulate PI3K and Ras pathways and stimulate tumor angiogenesis.⁴⁷

The tumor-suppressor factor for P13K is PTEN, encoded by a gene located on the tenth chromosome at locus 10q23.3.⁵⁷ The single loss of function mutations of PTEN is extremely rare in GBM (less than 2%).^{56,58,59} However, the PTEN gene plays an important role in the GBM oncogenesis, giving its position on the long arm of the tenth chromosome (10q Loss of 10q or the whole tenth chromosome leaves the cell with only one copy of PTEN, and even at normal levels of P13K, it leads to oncogenic stimulation.²⁰ Loss of homozygosity with respect to the 10q or the entire tenth chromosome is a mark found in almost all GBMs.³² This highlights the importance of P13K-PTEN in the processes of gliomagenesis.

P53 ASSOCIATED MUTATIONS

P53 is a tumor suppressor protein encoded on the seventeenth chromosome at locus 17p13.1 and is involved in the cell cycle regulation, proliferation and death through a complex network of interactions tracking and regulating the DNA replication processes.^{60,61} In case of cellular damage, p53 activates a cascade of reactions involving epigenetic control of target genes and direct modulation of other proteins by binding to them.⁵¹ P53 alterations have a direct role in survival and maturation of GBMsc.

One of the proteins subjected to positive epigenetic control by p53 is p21, encoded by the CDKN1A gene located on the sixth chromosome in locus 6p21.2, the product of which blocks the cell cycle in phase G1 by binding and inactivating the cyclin-D proteins.^{50,61,62}

Another gene undergoing positive epigenetic control by p53 in the presence of DNA damage is MDM2 localized on the twelfth chromosome at locus 12q14.3-15. MDM2 is an antagonist and inactivates p53, but only in the G1 phase of the mitotic cycle. MDM2 is bound to CDKN2A-p14^{ARF}, thereby resulting in its inactivation. By this mechanism CDKN2A-p14^{ARF} in turn leads to the activation of p53.^{19,63-65} Through this cascade, the two genes carry out a mutual regulatory process through a negative feedback. In GBM amplifications of MDM2 are often observed, inducing p53 inactivation.^{64,65}

MDM4/MDMX is encoded by a gene located on the first chromosome at locus 1q32 and is with a similar function as MDM2 to p53, which also includes reciprocal feedback by binding to CDKN2A-p14^{ARF}. Mutations in p53-MDM2 / MDM4-CDKN2A-p14^{ARF} (p14^{ARF}) and p53-p21 cycles of cellular regulation occur at each step in GBM oncogenesis.^{54,66} Mutations or amplification of the p53 gene, overexpression of MDM2/MDM4 or loss of expression of CDKN2A-p14^{ARF} occur in various combinations with one another in over 50% of pGBM and about 70% of sGBM.^{19,66}

IDH ASSOCIATED MUTATIONS

IDH are represented by two proteins - IDH1 encoded on the second chromosome at locus 2q33.3 and IDH2 encoded on the fifteenth chromosome at 15q26.1 locus.⁶⁷⁻⁶⁹ IDH1 is located in the cytoplasm of the cell and in the peroxisomes, while IDH2 is located in the mitochondria.⁷⁰ Both proteins are involved in the oxidative decarboxylation of isocitrate to alpha-ketoglutarate and the reduction of NAD and

NADP to NADH and NADPH. Both enzymes play an important role in the metabolism of tricarboxylic acids and the neutralization of free oxygen radicals in the cell. As a result of mutations in the genes encoding these two proteins, the cell reduces the amount of alpha-ketoglutarate and begins to accumulate an alternative product produced by the mutant forms of the 2-hydroxyglutarate enzymes that may have potential gliomagenic effects.^{23,71}

Mutations in IDH1/IDH2 often occur together and in combination with other mutations. They are almost exclusively characteristic of sGBM and as such are common in lower-grade gliomas.⁶⁹

AKT3 ASSOCIATED MUTATIONS

AKT3 is a protein kinase encoded on the first chromosome at locus 1q44, involved in the insulin cycle of cell-stimulation and other ligand-dependent tyrosine kinase systems.⁷² Often GBM have an amplification in this gene, which results in constant stimulation for cell proliferation.^{73,74}

LOSS OF HETEROZYGOSITY (LOH) 10

LOH 10 is a common feature in glial tumors. Most commonly occurring with the loss of a whole shoulder (10p or 10q), but also with separate deletions in important loci play an important role.^{19,20,32,75,76} As already mentioned, the role of PTEN deletion in locus 10q 23-24 plays a major role.⁵⁶⁻⁵⁹ Single deletions in other chromosome loci, with a proven role in gliomas, are genes encoded in 10p14-15 and 10q25 loci, which are also often spotted in gliomas. Deletion in 10q25 is often associated with progression of lower-grade gliomas to sGBM.^{32,75,77,78}

Various forms of LOH 10 occur in 80% of pGBM and significantly rarer in sGBM. A 10q deletion occurs in about one-third of sGBM, while 10p deletions are very uncommon.^{75-77,79}

LOH 22q

Loss of the long arm of the 22 chromosome is common in GBM. The most commonly deleted loci are the 22q12.3-13.2 and 22q13.31.^{77,80,81} The genes encoded in these loci have a still unclear role in gliomagenesis.

LOH 22q is characteristic of about half of the pGBM and more than 80% of sGBM, with its incidence varying in lower-grade gliomas.

TRISOMY 7

A common occurrence in GBM.^{19,32} This phenomenon is of particular importance in gliomagnesis due to the location of genes encoding EGFR,

MET and BRAF, which have a strong oncogenic potential.^{30,47,53}

LOH IN OTHER CHROMOSOMES

The loss of 13q occurs in about 10% of pGBM and more than 30% of sGBM, most often including the locus of the RB gene.^{82,83}

The loss of 19q, most commonly in 19q13.3 locus, is a common occurrence in sGBM, occurring in more than half of the cases and considered to be less than 10% in pGBM.^{8,83-86} A similar deletion in other tumors suggests the presence of a still undetected tumor suppressor gene in this locus.

The loss of 1p occurs in just over 10% of cases, both in pGBM and sGBM, most often in combination with LOH 19q.⁸⁴⁻⁸⁶ This form of codeletion is strongly associated with higher survival.⁸⁴⁻⁸⁶

Loss of 6q occurs in a small portion of sGBM and in about one-third of lower-grade gliomas.^{77,87}

The loss of 9p is a common occurrence with high importance due to the localization of CDKN2A in locus 9p21 and locus 9p23-24.1 where the PTPRD tumor suppressor gene is encoded. Deletions here are common in both pGBM and sGBM.^{32,82}

Apart from classical genetic mutations, a number of epigenetic alterations have also been registered in GBM.^{25,26,88-91} Epigenetics can be defined as mitotic hereditary changes in gene expression that are not due to changes in the primary DNA sequence.⁹² Epigenetic mechanisms, including those involving DNA and histone modification to regulate gene expression, are a recognized source of phenotypic variability in biology.^{93,94} Mechanism of epigenetic alteration, with relation to gliomagenesis, are:

COMPLETE GENOMIC EPIGENETIC HYPOMETHYLATION

It occurs in about 80% of GBM, ranging from approximately normal for healthy astrocytes to less than 50% as compared to them.^{24,25} This mechanism unlocks the transcription of multiple genes and is associated with rapid progression of the grade and high index of proliferative activity.⁸⁹ Demethylation of the suspected oncogene MAGE-A1 is a common phenomenon amid general hypomethylization and is with a still unclear role.⁹⁵⁻⁹⁷

EPIGENETIC ACTIVATION OF SAT2 AND D4Z4

It is carried out by hypomethylation, most likely occurring on the background of general hypomethylation. These are nucleotide sequences located respectively in the pericentromeric region of the 1, 9 and 16 chromosomes and in the 4q35 and 10q26 loci, which are sites of increased fragility and

strongly associated with LOH.^{20,82} This highlights the importance of epigenetic control in GBM genesis. These phenomena are most likely to develop in parallel with prolonged nucleotide sequences in these regions and the decreased expression of DNMT3a and DNMT3b involved in DNA replication.^{93,98}

EPIGENETIC SUPPRESSION OF RB, PTEN, p53, p16 AND p14

It is carried out by direct hypermethylation of the genes and some of their promoters and further emphasizes their importance in the processes of tumor suppression. Their hypermethylation is another mechanism for their inactivation in gliomagenesis, an alternative to classical mutations and deletions. This type of suppression is strongly associated with sGBM.^{99,100}

EPIGENETIC SUPPRESSION OF EMP3

EMP3 is a suggested tumor suppressor gene with a clear oncogenic role in the nervous system. In GBM similar to other tumors, the gene is deactivated by hypermethylation of its promoter.¹⁰¹

EPIGENETIC SUPPRESSION OF PDGF-b

It is accomplished by hypermethylation of its promoter. The result of this suppression is the non-functionality of the TGF- β cycle in GBM, as it is associated with increased transcription of PDGF- β .⁹⁰

EPIGENETIC SUPPRESSION OF PCDH- γ A11

The protein encoded by this gene is involved in building intercellular contacts. Its epigenetic exclusion by hypermethylation has a potential role in the invasion of healthy tissues.^{102,103}

EPIGENETIC SUPPRESSION OF SOCS1

Hypermethylation of this gene is associated with increased activity of the MAPK system. This epigenetic repression is also associated with a decrease in the radiosensitivity of GBM, which further worsens the patient's prognosis.^{104,105}

EPIGENETIC SUPPRESSION OF MGMT

Hypermethylation of the MGMT promoter is a particularly important indicator for clinical practice.¹⁰⁶ MGMT encodes a protein that is actively involved in the reprocessing and dealkylation of DNA in normal and oncological processes.²² In the presence of suppression of the gene, GBM are much more sensitive to alkylating agents such as temozolomide.²² This type of suppression is strongly associated with sGBM.¹⁰⁷

EPIGENETIC SUPPRESSION OF TIMP-3

The TIMP-3 encoded gene belongs to the tissue inhibitors of metalloproteases.¹⁰⁸ Its suppression is associated with a stronger ability to invade healthy tissues. This type of suppression is strongly associated with sGBM.¹⁰⁸

EPIGENETIC SUPPRESSION OF CASPASE-8

This gene actively participates in the apoptosis cascade.⁷⁴ Its hypermethylation is associated with a higher probability of relapse.¹⁰¹

EPIGENETIC SUPPRESSION OF CITED4

This gene encodes a transcription factor and its suppression by hypermethylation is associated with less likelihood of recurrence and a longer period between them.⁹⁰

Epigenetic control in gliomagenesis is also achieved by many microRNAs (miR).¹⁰⁹ According to their level of expression, they can be divided into three groups - with increased, decreased and dynamic levels.⁷

More than 260 miR are known to have elevated GBM levels relative to healthy brain tissue. Among those with the most frequently elevated levels and role in GBM oncogenesis are

INCREASED LEVELS OF miR-10B

Its expression is directly proportional to an increase in the anaplasticity of the process. A positive relationship between miR-10b and the urokinase receptor and Ras homologues has been established due to the HOXD10 gene, which in turn is in a feedback loop with them.¹¹⁰

INCREASED LEVELS OF miR-15B

Increased levels of miR-15b are directly related to tumor progression. The gene encoding cyclin-E1 is under transcriptional control under miR-15b and its overexpression is associated with an increase in the number of cells in the G0 / G1 phase and ready to enter the S phase from the mitotic cycle.¹¹¹

INCREASED LEVELS OF miR-17-3P, miR-17-5P, miR-18A, miR-19A, miR-19B, miR-20A, miR-92A

Tagged as cluster miR-17 ~ 92, due to their similarity in function and expression. This group possesses oncogenic properties due to inhibition of the anti-proliferative TGF- β RII, SMAD4 and CAMTA1 genes and positive regulation of CTGF and POLD2 playing a role in angiogenesis and DNA replication.^{7,112}

INCREASED LEVELS OF miR-21

At this stage, the best studied miR with a role in GBM oncogenesis. Its overexpression increases with the anaplasticity of the process. miR-21 stimulates the expression of ANP32A, SMARCA4, PTEN, SPRY2, LRRFIR1, HNRPK, TAp63 and PDCD4 and consequent increase in caspase levels, decreasing the activity of apoptosis pathways.¹¹³⁻¹¹⁵ miR-21 also aids the invasion of surrounding tissues by suppressing TIMP-3 and RECK, without changing the levels of matrix metalloproteases. Missense miR-21 transfection in laboratory conditions, in turn, leads to increased sensitivity to radio and chemotherapeutics.⁷

INCREASED LEVELS OF miR-23A

miR-23a is directly involved in GBM proliferation, migration and invasion. miR-23a epigenetically silences APAF1, a key element of the apoptotic cascade.¹¹⁶

INCREASED LEVELS OF miR-93

miR-93 participates in the suppression of integrin- β 8, which disrupts the interaction between tumor and endothelial cells and stimulation of the PI3K/AKT pathways.^{7,117} As a result, the expression of miR-93 is strongly associated with tumor angiogenesis and cell proliferation.^{117,118}

INCREASED LEVELS OF miR-221 AND miR-222

They are associated with an increase in CDK levels by negative regulation of their inhibitors p27^{Kip1} and p57^{Kip2}.^{119,120} In this way, they are assisted in entering the S phase of the mitotic cycle. Their elevated levels are associated with pGBM.⁷

INCREASED LEVELS OF miR-335

They are associated with an increase in the proliferative index of cells and the ability to invade healthy tissues by overexpression of DAAM1.^{7,121}

INCREASED LEVELS OF miR-381

They are associated with an increase in the proliferative index by inhibition of LRRC4.^{121,122} As a result, MAPK, AKT and MEK are permanently phosphorylated and their pathways are permanently activated.¹²¹

INCREASED LEVELS OF OTHER miRS

The role of some of the miR with increased expression in GBM has not yet been fully established. These include miR-16, which has been shown to

play a role in several oncological conditions. miR-106b, which is closely associated with the levels of the miR-17-92 cluster, but with a yet undefined role.¹¹² miR-182 and miR-183, whose role is also not yet fully specified.^{7,122} miR-210 which, in other oncological processes and myocardial infarction, is associated with an increase in hypoxic resistance of cells and neoangiogenesis by overexpression of HIF-1 α .^{123,124}

More than 100 miRs are known to have decreased levels in GBM, relative to healthy brain tissue. Among those with the most commonly lowered levels and role in GBM oncogenesis are:

DECREASED LEVELS OF miR-7

Targets are the genes encoding EGFR, IRS-2, FAK and MMPs.¹²⁵⁻¹²⁷ As a result of the decreased levels and the epigenetic enhancement of their expression, proliferative processes are stimulated and MMP-2 and MMP-9 levels are increased.⁷ This plays an important role in the processes of tumor migration and invasion.

DECREASED LEVELS OF miR-32

Targets are the genes encoding MDM2 and TSC1.¹²⁸ These genes are involved in the inactivation of the p53 cycle and at reduced levels of miR-32, are involved in stimulating tumor proliferation.¹²⁸

DECREASED LEVELS OF miR-34A

Targets are genes encoding Notch1/2, MET, SIRT1, Musashi1 and PDGFRA.¹²⁹⁻¹³³ The rise in SIRT1 levels in the absence of its silencing by miR-34a results in persistent phosphorylation of p53 and inactivation of its cascade.¹³³ miR-34a and PDGFRA are in reciprocal feedback and possibly the amplification of PDGFRA resulting in its decreased levels in GBM.¹²⁹ Increased activity of Notch1/2 and MET on this background supports the process of tumor angiogenesis, increase in the proliferation index, accumulation of new mutations, invasion of healthy tissues and suppression of apoptosis.¹³¹

DECREASED LEVELS OF miR-101

Targets are the genes encoding Msi1 and EZH2 encoding the enzyme portion of the PRC2 PcG protein.¹³⁴ Due to decreased levels of miR-101 and stimulation of EZH2, global hypomethylation of DNA in GBM increases and assists in the activation of multiple suppressed genes, whilst the lack of suppression of Msi1 leads to increased proliferation.¹³³

DECREASED LEVELS OF miR-128

Targets are the genes encoding Bmi-1, E2F3a, EGFR, PDGFRA, WEE1, Msi1 and p70SK1.¹³⁵⁻¹³⁷ Bmi-1 is a PcG protein with a known oncogene effect. E2F3A is a transcription factor and together with elevated levels of EGFR and PDGFRA stimulates cell proliferation.¹³⁸ This is aided by the effects of protein kinase WEE1 involved in regulating mitotic cycles and cell size.¹³⁹ Msi1 is an active participant in post-translational control in healthy nerve tissue, while p70S6K1 plays a role in tumor angiogenesis.¹³³ The mutually elevated levels of these proteins at reduced levels of miR-128 cover key units in GBM oncogenesis.

DECREASED LEVELS OF miR-132

An epigenetic target is the gene encoding the p120RasGAP protein.¹⁴⁰ This protein has the ability to ontogenically activate the Ras cascade. miR-132 is also associated with tumor angiogenesis and progression.¹⁴¹

DECREASED LEVELS OF miR-137 AND miR-124

These two miRs are closely related and often their levels vary in parallel. Under their control are the CDK6, Msi1 and Cox-2 coding genes.^{133,142} An increase in their levels with correlating decreased miR-137 and miR-124 results in enhanced tumor proliferation.

DECREASED LEVELS OF miR-326

Under its control are the genes encoding Notch1/2 and PKM2.¹⁴³⁻¹⁴⁵ It is assumed that miR-326 is located in a loop with a reciprocal negative feedback connection with Notch1. Elevated levels of PKM2 in turn are related to the effect of Warburg, in which tumor cells produce ATP by glycolysis followed by cytosolic fermentation of lactic acid.^{146,147}

DECREASED LEVELS OF miR-483-5P

An epigenetic target is the gene coding for ERK1 and MAPK3, a key in Ras and BRAF pathways of proliferation. Decreased levels of miR-483-5p are directly related to the increased proliferative capacity of tumor cells.^{148,149}

DECREASED LEVELS OF miR-491-5P

An epigenetic target is the gene coding for MMP-9.¹⁵⁰ As a result of an increase in MMP-9 levels in a correlating decrease in miR-491-5p levels, leads to an increased invasion of healthy brain tissue.¹⁵¹

DECREASED LEVELS OF OTHER miRS

Often detected, but with a still unclear role in the processes of gliomagenesis are miR-139-5p, miR-181b, miR-218 and others.⁷

Another group of miRs exhibits quantitative variability. Such relative and dynamic changes are encountered in some of the following miRs

DYNAMIC CHANGES IN THE AMOUNT OF miR-145

Decreased levels of miR-145 are directly related to an increase in the amount of protein synthesized by the suppressed genes.¹⁵²⁻¹⁵⁵ This includes transcription factors Sox-2 and OCT4.¹⁵² An increase in their amount is associated with an increase in proliferative potential and a decrease in the chemosensitivity of GBM. Decreased levels of miR-145 in turn are associated with an increase in the invasive ability of the tumor.¹⁵³

DYNAMIC CHANGES IN THE AMOUNT OF OTHER miRS

Often, dynamic changes have been observed in miR-19a, miR-26b, miR-27b, miR-106a, miR-143, miR-205, and miR-451. At this stage, their importance and role in gliomagenesis are not yet specified.⁷

Whilst an extremely large number of genetic and epigenetic changes have been shown to play a role in the genes of GBM, the importance of only a part of them in the prognosis and treatment options has however been clarified. It is on the basis of these clinically relevant indicators that some study groups have proposed classification formulas. The aim of these classifications is to optimize the healing process and to invest in the most effective healing approach in the presence of certain mutations in tumor cell genotype.

Most well-established GBM genetic classification models are centered, around the highest rate of change, and those with the clearest role, such as mutations affecting EGFR, CDKN2A, PTEN, PI3K, p53 and NF1 coding genes, and other factors such as the age of the patient and the correlating survival in these cases.

One of the first attempts for such a classification was made by Phillips and his team in 2006.⁵⁹ They distributed a total of 76 cases of GBM in three groups with proneuronal, proliferative and mesenchymal characteristics. An analysis of the results obtained shows that:

PRONEURONAL GBM

Found predominantly in younger individuals (average age less than 40 years) and is with the longest

survival period for this study group. In the proneuronal type, genotypically no alterations appeared in the number of chromosomes and no changes were observed in the PNET and EGFR coding genes.⁵⁹ According to the authors, the leading role in oncogenesis here are the dysregulated processes of neurogenesis, as a key place for the Notch pathways, key to the embryogenesis of the nervous system.⁵⁹

PROLIFERATIVE GBM

Found predominantly in older individuals (average age over 50 years) and with a shorter survival period. In the proliferative type, genotypically trisomy 7 and LOH 10 are detected, together with a loss of PTEN and amplifications in EGFR.⁵⁹ According to the authors, the dysregulated processes of cell proliferation, crossing at the level of AKT, have a leading role in oncogenesis for this type.⁵⁹

MESENCHYMAL GBM

Again, characteristically found in older individuals (average age over 50 years) and also has a shorter predicted survival period. The mesenchymal type, genotypically also has trisomy 7 and LOH 10, loss of PTEN and frequent amplifications in EGFR.⁵⁹ According to the authors, the dysregulated processes of cell proliferation also play a role here, but the processes of tumor angiogenesis are also key.⁵⁹

Verhaak and his team also classified GBM based on genetic changes and patient outcome.²¹ The results achieved by them and the classes based on them show a similarity to the Phillips classification.^{21,59} They classify a total of 170 GBM cases in four categories

PRONEURONAL GBM

Found predominantly in patients with an average age of 51.8 years. This group is characterized by amplification of PDGFRA and mutations in IDH and PI3K and loss or inactivation of p53.²¹ The mean survival rate for this group is 11.3 months. Three quarters of all sGBM according to the authors enter this subgroup.²¹

NEURAL GBM

Found predominantly in patients with an average age of 63.8 years. Various mutations with different frequencies are characteristic of this group, among which are amplifications in EGFR, loss of PTEN and p53.²¹ Also, characteristic of this group is the lack of PDGFRA amplification and the EGFRvIII mutant form of EGFR. The median survival rate for this group is 13.1 months.²¹

CLASSIC GBM

Found predominantly in patients with an average age of 55.7 years. This group is characterized by amplifications in EGFR, including EGFRvIII mutant form, loss of PTEN/LOH10 and CDKN2A/LOH9.²¹ Also, characteristic of this group are the lack of mutations in p53, IDH, RB and PDGFRA. The median survival in this group was 12.2 months.²¹

MESENCHYMAL GBM

Found predominantly in patients with an average age of 57.7 years. This group is characterized by loss of NF1/LOH17, PNET and p53.²¹ Characteristic of the group is also a complete lack of mutations affecting IDH and lack of amplification of PDGFRA. The median survival in this group was 11.8 months.²¹

In 2011, Crespo and his team divided a total of 35 GBM patients into five subclasses according to frequently observed combined changes in the chromosomal set and/or specific genes with a defined role in gliomagenesis.³² According to their data, the five different classes did not show significant differences in clinically relevant parameters such as age and survival.³² The five classes and their characteristics are:

GBM PATTERN I

Characteristic of this class are amplifications in EGFR, LOH10 and deletion of the CDKN2A/LOH9.³²

GBM PATTERN II

Typical for this class are trisomy 7, loss of CDKN2A/LOH9 and LOH10.³²

GBM PATTERN III

Typical for this class are trisomy 7, loss of CDKN2A/LOH9 or paradoxically doubling of 9q, but lack of change relative to chromosome 10.³²

GBM PATTERN IV

Typical for this class are trisomy 7 and LOH 10, without loss of CDKN2A/LOH9.³²

GBM PATTERN V

Characteristic of this class are trisomy 7 and 9 and LOH 10.³²

The divisions in separate types are relative to the study, due to the approach and selection of markers, difference in the number of cases and the possible medical and non-medical population differences.

However, there is a relative similarity between the mesenchymal and the proliferating type of Phillips, the classic version of Verhaak and pattern I in Crespo.^{19,21,32,59} Joining factors here are, in one form or another, the loss of PTEN, amplification in EGFR and loss of CDKN2A/LOH9, although there are differences in their description.

Relative similarities can be found in the pro-neuronal type of Phillips and Verhaak and pattern III in Crespo, as well as between the mesenchymal type of Verhaak and pattern II in Crespo.^{19,21,32,59} In these comparisons, however, the differences are greater and the correlation of these classes to a common denominator is questionable at best.

A multi-level approach with a broader range of markers with proven relevance and application will most likely be required to produce a single genotypical classification and validate it in practice, allowing for a comparison of clinical indicators such as mean age and survival, risk factors, ethnicity and others.

The 2016 revised WHO classification of tumors of the CNS implemented a number of the breakthroughs in molecular pathology of glial tumors, without dwelling too deep into the wide variety of detectable mutations.¹ Instead focusing only on everyday diagnostics with commercially available methods and long-established varieties, relevant to patient survival and treatment. As such, GBM were segregated into three molecular subtypes - IDH wildtype (non-mutated IDH), IDH mutants and a subset of GBM not otherwise specified (NOS), for whom IDH verification could not be carried out.^{1,156}

FUTURE DIRECTIONS

The variety of genetic and epigenetic mutations and alterations in GBM will inevitably lead to new additions to the WHO classification, based on the study groups preposition. Novel candidates for future WHO classification addition to GBM subtypes are MGMT and miR-21 mutants, together with CD133/Hes3 positive GBMsc percentage in tissue volume. The discovery of new mutations, oncogenes and the establishment of some factors already known to be present in GBM, but with a yet unspecified role will inevitably lead to new breakthroughs and possibly treatment modalities for these cases.

Treatment wise, combined surgical, chemo- and radiotherapy give the best patient results, whilst a large number of new modalities are currently undergoing testing and, whilst a large number of the will inevitably prove to have no effect of patient

survival, some of them such as viral and vaccine therapy are showing prominence.^{30,97,157-160}

On the other hand, a number of new diagnostic methodologies may move the verification process away from classical pathology with the implementation of liquid based biopsy and serum GFAP levels proving and increasingly affordable method, albeit for the time being only for patient follow up.¹⁶¹⁻¹⁶⁵

CONCLUSION

GBM and its related oncological entities have been closely related to the general knowledge of the CNS, medicine in general and cell biology since these malignancies were first described more than 200 years ago.³ A number of great leaps have been made in that time regarding the phenotypisation, genetic and epigenetic multiformity.²⁵ However, despite that, the mean survival of patients with GBM has historically remained nearly unchanged.^{106,166,167}

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Относительно понятий и анамнеза мультиформной глиобластомы – морфология, генетика и эпигенетика

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Мультиформная глиобластома (МГБ) является злокачественной опухолью IV степени согласно классификации Всемирной организации здравоохранения астроцитарной дифференциации. Так как она является одним из наиболее часто диагностированных онкологических проявлений центральной нервной системы, существует большое количество докладов, рассматривающих описание и развитие идей, связанных с данным типом опухолей.

Первый зарегистрированный случай глиомы представлен в Британском научном докладе Бернсом в 1800 году и в 1804 году - Абернети, а первое подробное гистоморфологическое описание представлено в 1865 году Рудольфом Вирховым. В 1926 году Персиваль Бэйли и Харви Кушинг создают основу современной классификации глиомов. Между 1934 и 1941 годами наиболее продуктивным учёным в области исследования глиом является Ганс-Йоахим Шерер, который устанавливает некоторые из клинико-морфологических аспектов МГБ. После появления молекулярных и генетических исследований установлено исключительное многообразие МГБ, при котором разные генотипы являются носителями одних и тех же гистоморфологических и ИГХ моделей, а также и некоторые аспекты глиомагенеза. Развитие МГБ начинается или с активации определённого типа мутации в МГБ стволовой клетке – первичная МГБ, или с медленного накопления отдельных мутаций, без наличия определённой мутации, активирующей процесс – вторичная МГБ.

Знания в области МГБ тесным образом связаны с общими медицинскими знаниями о ЦНС, так как эти злокачественные образования описаны более двухсот лет назад. За это время произошёл большой скачок в науке как в области знаний о ЦНС, так и в области общих знаний в медицине.