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Review Article

A review of gliomas-related proteins. Characteristics of potential biomarkers

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Abstract: Brain tumors are one of the most commonly diagnosed cancers of the central nervous system. Of all diagnosed malignant tumors, 80% are gliomas. An unequivocal diagnosis of gliomas is not always simple, and there is a great need for research to find new treatment options and diagnostic approaches. This paper is focused on the glioma-related protein profiles as compared to healthy brain tissue, which is reflected in multiple correlations between biological aspects that influence proliferation, apoptosis evasion and the invasiveness of neoplastic cells. The work presents the possibilities of facilitating clinical practice with proteomic biomarkers, which offer a wider diagnostic spectrum and reduce the margin of mistake in histopathological or imaging diagnostic methods. In fact, many changes in the body's homeostasis can be overlooked due to the lack of symptoms or their non-specificity. Nevertheless, a single marker has limited reliability in distinguishing a particular tumor subtype, since the increased or decreased level of the protein of interest may differ between the stages or locations of the tumor. Moreover, the correlations between proposed proteins - presented in this paper - may help clinicians to choose the most optimal therapy, and estimate its effectiveness, or indicate new therapeutic targets affecting disrupted biochemical pathways.

Keywords: GBM, proteomics, biomarkers, glioma, biochemistry

Introduction

Gliomas are the most common primary brain and spinal cord tumors which contribute to a high mortality rate in patients [1]. The current classification of gliomas depends on the correct histopathological assessment based on the grading and subtypes of the tumor [2]. World Health Organization (WHO) classification of the central nervous system tumors divides glioma into four grades of advancement based on cell activity and aggressiveness. Grade I is considered as the mildest form correlated with low risk and the possibility of surgical resection depending on tumor localization. It typically occurs in children, less commonly in adults, in the cerebellum, brainstem, and rarely in the cerebral hemispheres. Grade I gliomas are characterized by low-grade growing and are relatively benign. Grade II gliomas are well-differentiated, nevertheless, slow-growing tumors with better prognosis for the patients than grade III and IV diffuse gliomas, which are undifferentiated or anaplastic. Moreover, higher grade gliomas are malignant and are burdened with a worse prognosis [3]. Grade II gliomas include astrocytoma, oligodendroma and mixed oligoastrocytoma. These tumors typically occur in patients between the age of 20 and 50, and are mainly localized in the cerebral hemispheres. Grade II gliomas may recur and progress into more aggressive higher-grade tumors. Grade III gliomas are more aggressive and their growth rate is higher than that of lower-grade gliomas, which makes complete resection difficult. Grade III includes anaplastic astrocytoma, anaplastic oligodendroma and anaplastic mixed oligoastrocytoma. Grade IV glioma i.e. glioblastoma multiforme (GBM) is considered the most aggressive and most common primary brain tumor that possesses the ability to quickly spread and invade other parts of the brain, making complete surgical removal very difficult. In many cases, relapse and proliferation often occur after surgery and chemotherapy treatment. Based on the molecular analysis, we can identify four subtypes of GBM, i.e. classical, mesenchymal, proneural and neu-

ral. Nevertheless, gliomas can be classified by cell type and its shared histological features, but not necessarily their origin, like astrocytomas, oligodendrogliomas and ependymomas, or by its localization, the infratentorial, the supratentorial or the pontine tumors. Glioma's diagnosis is based on four standard methods: magnetic resonance imaging (MRI) with sensitivity of detection lower than 90% and limited possibility of subtype differentiation [4], a neurological examination, and invasive procedures for tumor subtype determination - biopsy or surgical resection to perform genetic analysis [5]. Considering that all currently used diagnostic methods are limited in their own way, we should aim towards the least invasive and the most specific ones based on new technologies which enable the improvement of diagnostics, especially early detection, and provide information on the resumption or effectiveness of treatment. The introduction of additional tests, e.g. based on biochemical results or validated biomarkers, can significantly improve the effectiveness of cancer detection and treatment.

In glioma research, the most common samples used in experimental procedures are tissue and serum samples of postsurgical patients. Nevertheless, the latest scientific reports suggest an important role of extracellular vesicles (EVs) in the biological processes of cancer, including glioma. EVs are found in tissues and various body fluids, such as serum, cerebrospinal fluid, urine, etc. They play an important role in intercellular communication and modulation of the microenvironment to alter immune response [6]. For example, in gliomas, EVs can modulate the expression of the class II major histocompatibility complex (MHC II) molecules on the surface of dendritic cells, like α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid receptor, on the surface of cortical neurons [7]. Moreover, they can play a diagnostic role because they are carriers of various types of metabolites or proteins.

This paper is focused on the glioma-related proteins. We present the proteins that may be used as biomarkers in glioma diagnostics and divide them into groups based on their uppermost function like proliferation ability, migration ability, as well as mitochondrial or immunology pathway affiliation.

To the present day, many biochemical interactions influencing the biological activity of glioma - especially in the advanced stage - have been described. Gliomas are highly invasive tumors, especially the malignant forms [8]. Invasiveness or migration in tumors is based on the detachment of malignant cells from the tumor mass, which is caused due to decrease or loss of molecules responsible for intercellular adhesion, which allows the tumor to overcome barriers of the extracellular matrix and spread itself into surrounding tissues. The invasiveness of glioblastoma is promoted by a highly proliferative phenotype, similarly to other malignancies. The malignancy of gliomas is caused by the loss of, among others, cell cycle inhibitors and increased signalling from the multiple growth factor receptors (e.g. epidermal growth factor receptor - EGFR and platelet-derived growth factor receptor alpha - PDGFRα in gliomas) that act through downstream effectors to exert a positive effect on the regulation of the cell cycle [9]. Disturbed increased expression of both the ligand and the receptor in glioma suggests that there is a correlation with the autocrine or paracrine loop that enhances cell signalling [10, 11] leading to tumor cell growth and adhesion, especially in advanced stage (stage IV). In glioblastoma cells, there is a positive correlation with the stage of advancement, both of them, growth receptors and cell-adhesion receptors, activate focal adhesion kinase (FAK), a cytoplasmic non-receptor tyrosine kinase (nRTK), which is a major positive regulator of cell-cycle progression [12, 13]. FAK acts by inhibiting expression of $p27^{kip1}$ and also by increasing extracellular signal-regulated kinase (ERK) activity and cyclin D1 transcription [14].

Scientific reports indicate a very invasive nature of gliomas associated with excessive activity of cell-adhesion receptors which are members of the integrin family [15], the ephrin family [16] and the CD44 family [17]. Excessive activity of integrin receptors (e.g. $\alpha_5\beta_3$ and $\alpha_5\beta_5$) interfering with the cytoskeleton, promotes tumor proliferation and invasiveness [18] as does ephrin family members, which also promote cell invasion, specifically Ephrin-B3 ligand and the EphB3 receptor [19]. Moreover, immune evasion mechanisms via alteration in membrane proteins allow tumors to escape immune surveillance and remodulate the microenvironment to support tumor progression and development.

Signalling molecules in glioblastoma cells, e.g. tyrosine kinases and adapter molecules, play

an important role in the spread of invasive signalling, while regulation of glioma cell survival, migration and invasion is controlled by molecules like phosphatidylinositol 3,4,5-trisphosphate 3-phosphatase (PTEN) and phosphatidylinositol 3-kinase (PI3K) [20]. PTEN is known for negative regulation of tumor migration, but malignant gliomas may suffer from the loss of it [20]. On the contrary, PI3K is responsible for positive regulation of tumor migration and invasion of glioma cells [20]. Previously mentioned tyrosine kinase FAK, may promote migration and invasive character of the glioma cells, just like adaptor molecules that originate from Crk-associated substrates (CAS) family, such as p130CAS and HEF1 [21, 22].

Nonetheless, mutations in mitochondrial genes are common in cancer cells, despite not inactivating mitochondrial energy metabolism, tumors can reshape its bioenergetic and biosynthetic state modulating signals responsible for transduction pathways and transcriptional circuits. Alterations in tumor cells' mitochondria can impair or alter stress response and wound healing to support tumorigenesis.

Seeing gliomas as malignant and fatal diseases, there is a high demand for extensive brain tumor research in the aspects of treatment and diagnosis. The eventual discovery of biochemical pathways' alterations to aid therapeutics or to serve as biomarkers offering help in early detection of homeostasis irregularity would be beneficial for both patients and physicians. This paper proposes the most promising biomarkers and points out their place in biochemical pathways. Further discovery of protein alterations can be of benefit to the future research of therapeutics in targeted medicine.

Methods and results

We searched the NCBI and PubMed databases (the last search was performed on December 15th, 2020) for articles describing the relevance of glioma biomarkers in tumor diagnostics. Using the search phrases: "gliomas biomarkers" and "gliomas biomarkers proteomics", in NCBI we found 34485 and 4029 records, respectively, while in PubMed we found 9733 and 260 records, respectively. Due to the lack of insightful information on the relevance of the retrieved articles for this review, each record was inspected manually, and only articles on gliomas biomarkers oriented in proteomics were selected. Finally, 145 articles were included in this review.

Discussion

Gliomas proliferation proteins

The tumor is a mass of tissue formed by the accumulation of cells with abnormal metabolism due to mutations. In gliomas, mutations in EGFR, PDGFRα and PTEN lead to the activation of protein kinase B or Akt (PKB/Akt), which leads to stimulation of the mTORC-1 pathway, responsible for the stimulation of the protein metabolism essential for cell proliferation. Nevertheless, there are more mechanisms responsible for gliomas' cell proliferation, like RTK/Ras/ERK signalling stimulation or telomerase alterations. This publication proposes a number of proteins which expression is disturbed in gliomas and which may act as disease markers.

EGFR, EGFRvIII and correlating proteins

Mutation in the EGFR gene is usually accompanied by overexpression of EGFRvIII which is present in 30% of GBM. Through quantitative analysis of protein expression and tyrosine phosphorylation, Johnson et al. [23] concluded that with overexpression of EGFR and EGFRvIII (**Figure 1**) we can expect elevated levels of other proteins that combined represent a prognostic for poor survival in gliomas (**Table 1**), like S100A10 (p11), major vault protein (MVP), guanylate-binding protein 1 (GBP1) and carbonic anhydrase III (CAIII) [23]. S100A10 belongs to calcium-binding proteins that have been implicated in cancer progression in the breast [24] and bladder cancer [25], but the functional role of the protein is not well understood. Moreover, MVP overexpression has been found in malignant brain tumors compared with non-malignant brain tissues [26]. The MVP has also been suggested to be associated with the acquisition of resistance to chemotherapeutic agents in lung cancer [27, 28]. At the same time, GBP1 is a large Guanosine-5'-triphosphate (GTP)-binding interferon-inducible protein that belongs to the dynamin family [29]. Overexpression of GBP1 is correlated with elevated EGFR expression in GBM, mediation of MMP (matrix metalloproteinases) 1 expression and cell inva-

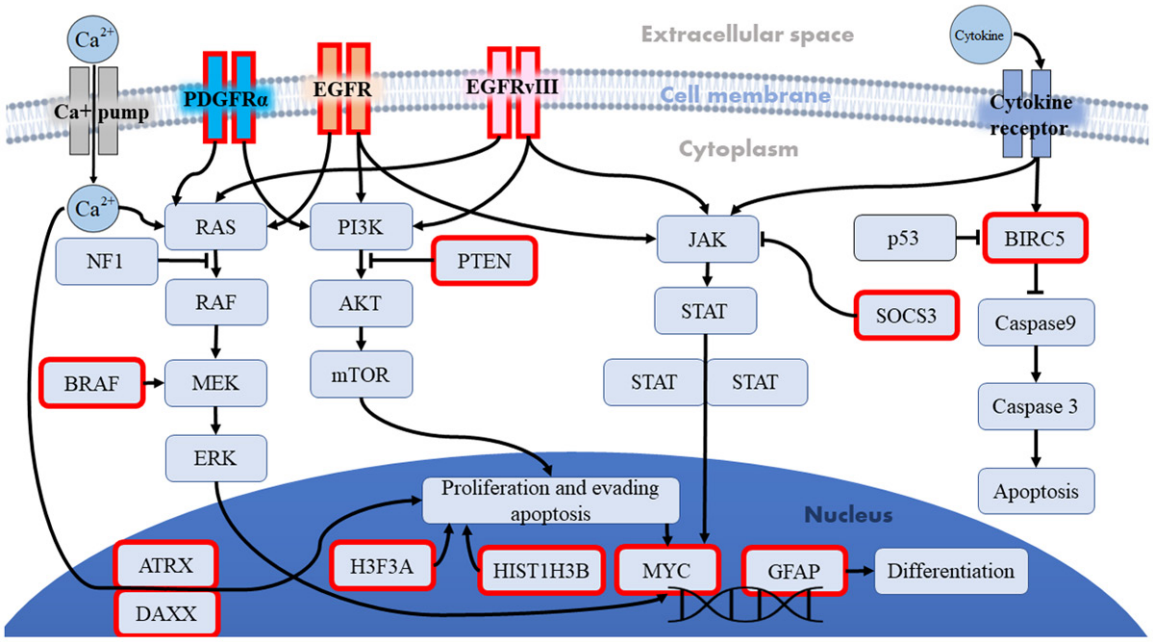

Figure 1. Pathways affecting glioma cell proliferation. Marked proteins were proposed as glioma biomarkers, which affect the most basic pathways responsible for cell proliferation. Both, mutated EGFR and EGFRvIII, are overexpressed in glioma cells, affecting MAPK/ERK, PI3K/AKT/mTOR and JAK-STAT pathways by modulating them. Moreover, decreased levels of PTEN inhibitor affect PI3K/AKT/mTOR pathway, while elevated levels of BRAF affect MAPK/ERK pathway. Elevated levels of PDGFRα receptor protein modulate MAPK/ERK and PI3K/AKT/mTOR pathways. SOCS3 interacts with JAK-STAT pathway by direct inhibition of the catalytic domain of JAK. Increased levels of SOCS3 lead to pathway impairment and promotion of neovascularization and tumorigenesis. Increased levels of BIRC5 protein disrupt the caspase cascade, leading glioma cells to avoiding apoptosis. ATRX and DAXX are encoding two subunits of a chromatin remodeling complex required for H3.3 incorporation at pericentric heterochromatin and telomeres. Presence of H3F3A/ATRX-DAXX mutations is associated with alternative lengthening of telomeres. Overexpression of c-Myc is associated with metabolism aberrations leading to uncontrolled proliferation, growth, and survival of tumor cells. High expression of GFAP significantly affects growth and cell division.

sion in glioma cells [30]. Similarly, overexpression of CAIII increases the mobility of cells and promotes, for example, the invasiveness of hepatocellular carcinoma [31]. The high heterogeneity of glioblastoma may cause problems with detecting EGFRvIII in tissue, but using EV from serum may contribute to detecting the protein (EGFRIII) and its use for diagnostic purposes [7].

In the research presented by Wang et al. [32], expression of EGF-like domain multiple 7 (EGFL7) was associated with the promotion of glioma cell proliferation while the EGFL7 knockdown resulted in its effective suppression. Moreover, expression was higher in EGFR-positive tumor tissues, which makes EGFL7 highly associated with EGFR and prognosis (**Table 1**). The EGFL7, besides being a potential therapeutic target of glioma, can also play a role as a potential diagnostic biomarker.

Protein capicua homolog (CIC protein) and BRAF

The hyperactive receptor tyrosine kinase (RTK)/Ras/ERK pathway is observed in glioma. The increased activity of the pathway is associated with the capicua (CIC) homolog protein, which activates the genes of the receptor [33]. The CIC protein mutations do not occur in glioblastomas, but in 1p19q-co-deleted oligodendrogliomas they occur in approximately 70% of cases [34-37]. However, the CIC-S (short) isoform is considered to be more important in tumorigenesis, and loss-of-function mutation is presumed to be present in oligodendrogliomas [38-40]. Nevertheless, the molecular mechanisms that overlook CIC regulation by the Ras/ERK pathway and its potential involvement in glioblastoma remain unknown. Bunda et al. [33] showed, that in 30 GBM tumor samples, CIC protein levels were substantially reduced or

Table 1. Glioma biomarkers

Biomarker	Biomarker level	Glioma Grade/Subtype	N	Molecular Correlation	Testing material	Validation	References
Glioma cells proliferation							
EGFRvIII protein	Elevated	Primary GBM, pediatric brainstem glioma	n = 139 patients [23] n = 8 tumor xenografts [23]	Upregulation of PI3K pathway	Tissue, plasma, CSF	Validated	[23]
EGF-like domain multiple 7 (EGFL7)	Elevated	Primary GBM, secondary GBM	n = 200 samples [32] from 200 patients [32]	EGF-EGFR-angiogenesis axis	Tissue	Validated	[32]
CIC protein	Absent in higher grade, higher in lower-grade	Oligodendromas, astrocytomas	n = 30 samples from 30 patients [33]	Downstream of RAS/MAPK pathway	FFPE Tissue	Not validated	[33]
H3.1/H3.3 histone	n/d	Pediatric diffuse intrinisic pontine gliomas, pediatric non-brainstem GBM, pediatric high grade gliomas, adult GBM	n = 86 samples [43] n = 48 patients, 784 samples [44]	Selective gene regulator/telomeres lengthening/stability	FFPE Tissue	Validated	[43, 44]
ATRX/DAXX	n/d	Pediatric GBM, grade II gliomas, oligoastrocytomas, grade III gliomas, secondary GBM, primary GBM	n = 48 patients, 784 samples [44]	Telomeres lengthening	FFPE Tissue	Validated	[44]
PDGF proteins family	Elevated	Secondary GBM, low grade gliomas,	n = 34 samples [57] n = 237 samples [142]	Regulation of embryonic development, cell proliferation, survival and chemotaxis	Tissue, whole blood	Not validated	[57, 142]
^{V600E}B-RAF	Elevated	Brainstem gangliogliomas, pleomorphic xanthoastrocytoma, pilocytic astrocytoma, anaplastic astrocytoma, pediatric grade II-IV tumors	n = 20 tissues from 20 patients and HEK293T cell culture [41]	Activation of RAS/RAF/MEK/ERL kinase pathway	Tissue	Validated	[41]
TETR protein	Elevated in adults primary glioblastoma multiforme, n/d in oligodendromas	Adults Primary GBM, Oligodendromas	n = 1230 samples, 60 different glioma types [60]	Upregulation of telomerase expression	Tissue	Not validated	[60]
YKL-40	Elevated in high-grade gliomas	Anaplastic glioma, GBM	n = 343 patients [65] n = 1740 samples [65]	Mediates activation of AKT1 signaling pathway	Serum, Tissue	Not validated	[65]
c-MYC	Elevated	Oligodendrogliomas/oligoastrocytomas, astrocytomas (grade II), anaplastic astrocytomas, GBM, low-grade gliomas, medulloblastoma	n = 158 samples [67]	Transcription factor	Serum	Not validated	[67]
PTEN	Decreased	GBM, anaplastic astrocytomas	n = 5 × 10^4 cells U87MG cell line [143]	PI3K/AKT/mTOR pathway regulation	Tissue	Not validated	[143]
S100A8	Elevated	GBM	n = 61 samples [75] n = 518 patients [78]	Ca^{2+} signaling	Serum, tissue	Validated	[75, 78]
S100A9	Elevated						
Fetuin-A (alpha-2-HS-glycoprotein)	Elevated	GBM, high-grade astrocytoma	n = 2 cell lines LN229 and U-138MG [80]	Inhibition of ectopic calcification	Tissue	Validated	[81]
SOCS3	Elevated	GBM	n = 540 patients [82]	Cytokine signaling/Neovascularization	Tissue	Not validated	[82]
Nucleophosmin (NPM1)	Elevated	Astrocytoma	n = 60 samples U87MG and A172 cell lines [83]	Apoptosis suppression	Cell lines	Not validated	[83]

Ferritin Light Chain (FTL)	Elevated	GBM	n = 20 samples from 20 patients and 3 human glioblastoma-derived cell lines, U251MG, A172 and U87MG [91]	Iron storage, cell proliferation, angiogenesis, immunosuppression	Tissue, cell lines	Not validated	[91]
Survivin	Elevated	GBM	n = 144 patients data from Chinese Glioma Genome Atlas and n = 6 patients and two cell lines HEB and LN299 [93]	Inhibitor of apoptosis	Genome RNA sequencing data, tissue, cell lines	Validated	[93]
GFAP (GFAP-δ isoform)	Elevated	Grade II and grade III astrocytomas, GBM.	n = 126 serum samples from 80 patients [145]	growth and cell division	Serum	Validated	[145]
Gliomas cells migration proteins							
CXCR4	Elevated	GBM	n = 18 from 2 cell lines HF2303 and GL26-Ci [115] n = 90 samples from 60 patients [116]	Cell migration	Tissue	Not validated	[115, 116]
Cathepsin D	Elevated	GBM	n = 87 [117]	aspartic-type endopeptidase activity	Tissue, Serum	Not validated	[117]
Gliomas mitochondrial pathways							
Lactate dehydrogenase A (LDHA)	Elevated	GBM	U87 and U251 cell lines [122]	Catalyzes the conversion of pyruvate to lactate and is considered to be a key checkpoint of anaerobic glycolysis	Cell lines	Not validated	[122]
Gliomas immunology							
Mutant-p53	Elevated	Astrocytic tumors	n = 48 patients, 784 samples [44]	Alternative lengthening of telomeres, tumor suppressor, induces growth arrest of apoptosis, negatively regulates cell division	Tissue	Not validated	[44]
IL-13Rα2 (Interleukin-13 receptor alpha 2)	Presence	GBM	n = 274 patients, 343 samples [133]	Invasiveness of tumor cells	Tissue	Validated	[133]
CD133/CD44	Elevated	GBM	n = 25 mice xenographs [138]	Cell growth and proliferation	Tissue	Not validated	[138]

GBM - glioblastoma multiforme, CSF - Cerebrospinal fluid.

absent in comparison to lysates derived from non-neoplastic brain tissue, but in the majority of the lower-grade gliomas the levels of CIC protein were elevated.

Alike the CIC protein, the Serine/threonine-protein kinase (BRAF) protein can also activate the RAS/RAK/ERK kinase pathway [41]. In non-cancerous cells, the BRAF protein is responsible for signalling within cells (**Figure 1**) that are involved in directing their growth [42]. The increased expression of the BRAF protein commonly found in tumors [41] in combination with the overexpression of the CIC protein can be used to classify the glioblastoma stage (**Table 1**). Moreover, the increased level of the BRAF protein and the decreased level of the CIC protein may be an interesting direction in the search for a new therapeutic path, especially in patients with acquired resistance to BRAF inhibitor (BRAFi) treatment.

Histone H3 alterations (H3F3A and HIST1H3B)

In high-grade gliomas in children, approximately 80% of diffuse mediastinal glioma cases and 20% of extracerebral glioblastoma cases have mutations in the H3F3A and HIST1H3B genes, which code for H3.3 and H3.1 histones [43, 44] (**Figure 1**). The performed genome-wide studies suggest, that the identified changes in the H3 histone seem to occur only in high-grade pediatric gliomas [43]. This suggests the possibility of using histones to predict the advancement of cancer in children (**Table 1**).

Alpha-thalassemia/mental retardation X-linked (ATRX)

The transcriptional regulator ATRX is associated with histone proteins, especially with H3.3, and is involved in chromatin remodeling, which is required for the incorporation of histone into pericentric heterochromatin or telomeres [45-49]. The development of GBM is positively correlated with the presence of mutations in the ATRX gene (**Table 1**), which lead to disturbances in the synthesis of the ATRX protein [44]. There is also a documented association between the ATRX and death-domain associated protein (DAXX) gene mutations [44] (**Figure 1**), IDH1 mutations [50] and TP53 mutations [44]. Schwartzentruber et al. [44] found that TP53 mutations show strong correlation with alternative lengthening of telomeres. DAXX forms a heterodimer with ATRX (DAXX-ATRX), and participates in H3.3 recruitment to DNA [45, 51]. Altered ATRX-DAXX are specific to pediatric GBM [44]. ATRX mutations occur in pediatric GBM [44]. Mutations can also be found in secondary and primary GBM [50, 52]. So far, no mutations in ATRX genes have been found in oligodendroglioma [52].

Platelet-derived growth factor receptor alpha (PDGFRα)

Mutations in the platelet-derived growth factor receptor alpha (PDGFRα) genes have been found in low-grade gliomas and in secondary GBM [53]. PDGFRα is a receptor that is involved in cell proliferation, survival and chemotaxis (**Figure 1**). Depending on the context, it promotes or inhibits cell proliferation and cell migration. Overexpression of PDGFRα has been found mainly in lower-grade gliomas as well as in secondary GBM [54-56]. Scientific studies indicate that tumor cells express PDGF-A, -B and PDGFRα, while surrounding endothelial cells express PDGF-B and PDGFRα, suggesting that stimulation of glioma development is autocrine as well as paracrine [57, 58]. Nevertheless, the expression of PDGF ligands differs in different grades of gliomas. PDGF-A is expressed in all grades, whereas PDGF-B is expressed only in high-grade gliomas [59], what suggests that PDGF-B may be involved in grade progression of gliomas (**Table 1**).

Telomerase reverse transcriptase (TERT)

Mutations of telomerase reverse transcriptase (TERT) are rarely present in pediatric primary GBM, whereas in adult primary GBMs they appear frequently [60], what allows us to presume that due to high levels of TERT mRNA and observed telomerase activity in adults [61] the levels of the mutated protein are elevated. Upregulation of mutated TERT elevates pathological expression of telomerase, enabling tumor cells to maintain sufficient telomeres length and prolonging cell proliferation. In addition, TERT mutations are correlated with methylation aberrations and epigenetic changes in histones, which can affect gene expression by altering the chromatin state from a closed, inactive state to an open, actively transcribed state [62]. Elevated levels of TERT are not exclusive to gliomas nor brain tumors and appear also in the urinary tract and liver tumors.

Nevertheless, changes in TERT protein concentrations can effectively facilitate the classification and prognostication of brain tumors [60] (**Table 1**).

Chitinase-3-like protein 1 - CHI3L1 (YKL-40)

Chitinase-3-like protein 1 (CHI3L1), also known as YKL-40, is responsible for cell proliferation, differentiation, angiogenesis, inflammation, tissue remodeling and apoptosis [63] by inhibiting Fas expression through the phosphorylation of PKB/Akt [64]. The research of Iwamoto et al. [65] indicates that YKL-40 is a valid serum biomarker for high-grade gliomas, like anaplastic glioma or glioblastoma, and can be used as an independent prognostic factor or as an aid in prognosis of the longitudinal alterations in tumor burden measured with MRI scans (**Table 1**).

c-Myc oncoprotein (MYC)

Deregulation of the c-Myc oncoprotein is common among diverse malignant human tumors with poor prognosis [66]. Glioma cancer stem cells express higher levels of c-Myc (**Table 1**) that is required for its proliferation, growth, and survival [66] (**Figure 1**). Nevertheless, c-Myc is associated with aberrant metabolism, but the prognostic impact of this oncoprotein remains unclear [67]. In a study by Wang et al. [68], loss of c-Myc abolished xenograft formation by glioma stem cells, accentuating a key role of this proto-oncogene in glioma cancer stem cell maintenance. It is suggested that c-Myc mutations are correlated with IDH1 mutation, which helps mediate the malignant transformation of IDH1 mutant gliomas [67]. Evaluation of c-Myc protein levels by Odia et al. [67] suggests, that its overexpression is associated with IDH1 and strong p53 co-expression.

Phosphatase and tensin homolog (PTEN)

PTEN is a common tumor suppressor present in many human cancers, e.g. brain, lung, breast, or prostate cancer. Furthermore, decreased expression or mutation in PTEN genes is associated with advanced gliomas [69] (**Table 1**). Rasheed et al. [70], was the first to point out the implicated correlation of PTEN mutations with high-grade adult gliomas. The occurrence of mutation in the PTEN gene product causes inhibition of the PI3K/AKT/mTOR pathway (**Figure 1**), leading to uncontrolled cell proliferation [71]. Mutation of PTEN protein is observed in GBM, anaplastic astrocytomas and not was observed in lower-grade glioma [71].

S100A8/S100A9

Proteins S100A8 and S100A9 are mainly associated with the calcium economy, namely with the opening and closing of Ca^{2+} channels [72]. In GBM, S100A8 and S100A9 proteins are elevated in both serum and tissue [73-76] (**Table 1**). Moreover, it has been reported that both of these proteins are frequently co-expressed, which is co-regulated [77]. Research by Popescu et al. [73] show, that S100A9 and S100A8 proteins may act as prognostic markers for gliomas. On the contrary, Arora et al. [78] show, that elevated levels of S100A8 and S100A9 are upregulated in GBM as compared to grade III glioma tissues, while serum testing revealed that only S100A8 can serve as a discriminant marker.

Alpha-2-HS-glycoprotein (fetuin-A)

The major physiological role of the Fetuin-A is the inhibition of ectopic calcification [79]. In a study by Nangami et al. [80], the authors suggest, that tumor-derived fetuin-A promotes growth, motility, and invasive potential of glioblastoma cells (**Table 1**). These authors presume, that ectopic fetuin-A is synthesized by a panel of high-grade astrocytoma tumor cells. They created two subclones with fetuin-A knocked down by ~50% and ~90%, and demonstrated a reduction of motility and invasive capacities in GBM cell lines. Moreover, due to autocrine or paracrine uptake of fetuin-A, inhibition of senescence signalling pathway occurs, which is necessary to initiatedegradation of p53 [81].

Suppressor of cytokine signaling 3 (SOCS3)

Suppressor of cytokine signaling 3 (SOCS3) is a member of eight molecules (SOCS1-7 and CIS) responsible for signal transduction and activation of transcription protein (STAT) through direct interaction with the catalytic domain of Janus kinases (JAKs) in the JAK-STAT pathway (**Figure 1**). SOCS3 is also correlated with cullin5-RING E3 ligase (CRL5) [82]. Moreover, elevated expression levels of the substrate-binding SOCS3 in the CRL5 complex are correlated

negatively with Von Hippel-Lindau tumor suppressor (VHL) protein levels contributing to the higher angiogenesis [82]. Thus, Zheng et al. study considers increased expression levels of SOCS3 to be related with high levels of vascular endothelial growth factor A (VEGFA), which are especially elevated in glioblastomas during neovascularization and may be utilized during postsurgical prognostics in therapeutic response towards angiogenesis inhibitors [82] (**Table 1**). Moreover, increased expression of SOCS proteins, may negatively affect the signaling cascade of the JAK-STAT pathway, creating a negative-feedback loop, which prevents prolonged cytokine signaling and results in chronic inflammation with proteome aberrant proliferation and tumorigenesis (**Figure 1**).

Nucleophosmin (NPM1)

A multifunctional chaperone - nucleophosmin (NPM1) plays an important role in cancer development due to its diverse functions, including intracellular transport, ribosome biogenesis, duplication of centrosomes, chromatin remodeling, mRNA splicing and apoptosis [83]. Elevated levels of NPM1 protein have been observed, among others, in breast [84], colon [85], stomach [86], thyroid [87], bladder [88], prostate cancer [89] and gliomas [83]. Holmberg Olausson et al. [83], performed immunostaining that showed significantly higher intensity in grade IV gliomas in comparison to grade I gliomas, however, it showed no significant change in the intensity when they compared grade I and grade II or grade I and grade III gliomas [83] (**Table 1**).

Ferritin light chain (FTL)

Recent studies have demonstrated, that ferritin may not only be the primary iron storage protein, but also be essential to cell proliferation, immunosuppression and angiogenesis [90]. In tumors, ferritins are composed of two distinct functional subunits, ferritin light chains (FTL) and ferritin heavy chains (FHL) [91]. However, Wu et al. [91] revealed, that only FTL is closely associated with the survival of glioblastoma patients. Moreover, expression levels of FTL were elevated in high-grade gliomas in comparison to low-grade gliomas. Additionally, in case of patients with downregulated FTL, overall survival and disease-free survival were higher [91] (**Table 1**). In addition, an increased level of FTL has been detected in the plasma of glioblastoma patients [92].

Survivin (BIRC5)

Survivin belongs to the inhibitors of apoptosis (IAP) family [93] and is responsible for the regulation of cell-cycle progression, induction of chromosomal instability and apoptosis inhibition by binding to caspase-3/7 (**Figure 1**) in the G2/M phase [94-97]. It is strongly expressed in a majority of tumors (e.g. lung, ovarian, breast, prostate and colon cancer) and its elevated levels can be observed during embryonic development, whereas it is absent in healthy differentiated tissues [98] (**Table 1**). Moreover, expression of Survivin is associated with tumor grade and might be a prognostic factor in gliomas [97].

Glial fibrillary acidic protein (GFAP)

Glial fibrillary acidic protein (GFAP) is an intermediate filaments providing mechanical support to cells, which are mostly detectable in astrocyte cells of the central nervous system (CNS) [99]. The activity of GFAP expression has a significant effect on various properties of the astrocyte cells, such as growth and cell division [100] (**Figure 2**). Nevertheless, while GFAP expression is a biomarker for astrocyte maturity, its decreased levels may result in cellular dedifferentiation in brain tumor tissue [101, 102] (**Table 1**). Moreover, GFAP expression is considered to decrease with higher tumor grade, but on the contrary, levels of specific GFAP isoforms, like GFAP-δ isoform, increase its amount, which has been identified in glioblastoma cells [102]. A study by Sereika et al. [103] indicates, that GFAP expression in grade II and grade III astrocytoma is considerably higher in reference to human control.

Gliomas cells migration proteins

Invasion of glioma cells most likely requires degradation of the extracellular matrix, and to achieve that several protease families, like cathepsins, serine protease, MMP or a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS) family of metalloproteases, exhibited their usefulness [104-106]. In gliomas, protease activity is based on localization in specific regions of the tumor cell membranes. For example, the binding of MMP-2 to integrin $\alpha_5\beta_3$ on the cell surface, enhances pro-

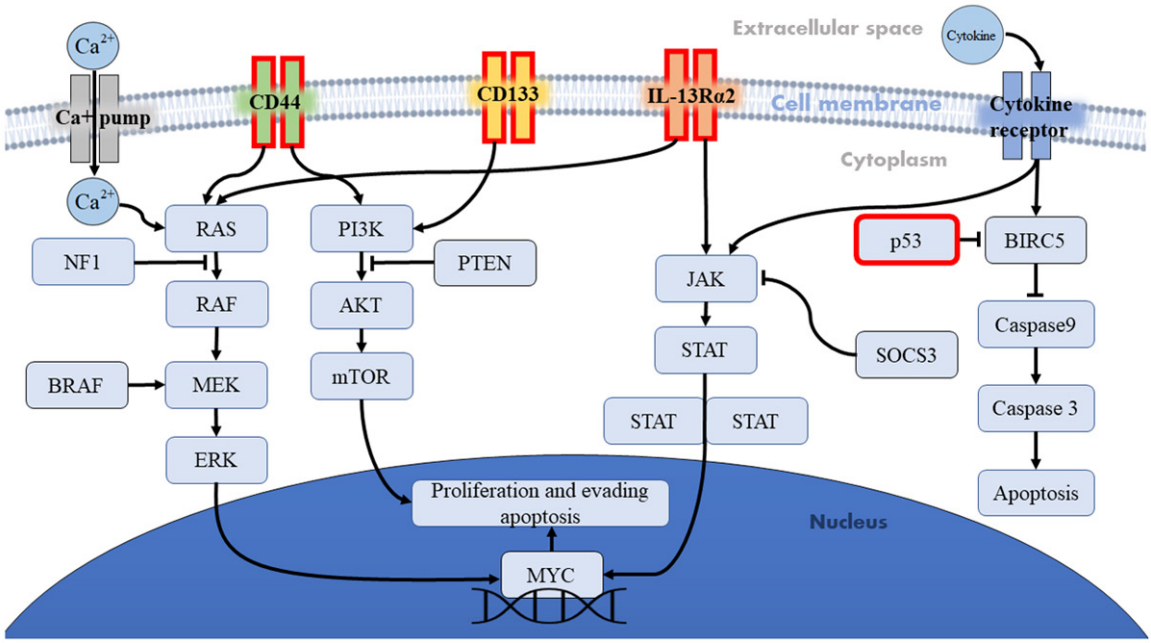

Figure 2. Pathways for glioma immunology interactions. Marked proteins were proposed as glioma biomarkers, which affect the most basic pathways responsible for cell immunology. MAPK/ERK and PI3K/AKT/mTOR pathways are over-modulated by CD44 overexpression, but only the latter is also affected by CD133 overexpression. Moreover, MAPK/RAS and JAK-STAT signaling pathways are modulated by the presence of IL-13Rα2. Elevated levels of mutated p53 proteins, not correlated with the mentioned pathways, are responsible for inhibition of cell apoptosis.

teasome activity [107]. The same goes for urokinase, which is a serine protease. Urokinase expression increased in glioblastoma (grade IV glioma) promotes invasion, while downregulation of expression of its receptor inhibits glioblastoma invasion [105, 108-110].

CXCR4

The C-X-C chemokine receptor type 4 (CXCR4) transduces a signal by regulating intracellular calcium ion levels and enhancing mitogen-activated protein kinase (MAPK)1/MAPK3 activation [111]. Moreover, it is involved in the AKT signaling cascade [112] and plays a role in cell migration, e.g. during wound healing [111]. Increased expression of CXCR4 signaling is associated with directional perivascular invasion of glioma cells [113] (**Table 1**). A study conducted by Yadav et al. [113], present primary cultures of human glioma stem cells (HF2303) and mouse glioma (GL26-Cit) that exhibited significant migration towards human (HBMVE) and mouse (MBVE) brain microvascular endothelial cells, which was then inhibited by knock-down of CXCR4. Studies report that overexpression of CXCR4 is common for many glioblastoma cell lines and also indicates a correlation with sensitivity to CXCL12 of vascular origin, which stimulates their migration toward vasculature [114, 115]. CXCR4 has already been proposed as a non-exclusive molecular marker for high-grade gliomas by Stevenson et al. [116].

Cathepsin D

Another protein involved in cell migration is cathepsin D, which has been reported as functionally important in the process of tumor angiogenesis and invasion in malignant progression of gliomas [117]. Significantly elevated levels of protein expression in high-grade gliomas in comparison to low-grade gliomas imply, that it could be a potential differentiating and prognostic molecular marker for aggressive gliomas [118, 119]. Nevertheless, cathepsin D has also been reported to be overexpressed in the carcinoma cells of the breasts and other organs with a high risk of relapse [120, 121]. In their research, Fukuda et al. [117] proposed cathepisn D as a biomarker in high-grade gliomas with high relapse possibility. Multivariate analysis of research outcomes confirmed that cathepsin D could be used as an independent predictor for short survival (**Table 1**).

Mitochondrial pathways proteins in gliomas

Mitochondria are responsible for diverse cellular functions, such as, cellular energy metabolism, redox signaling, regulation of ion homeostasis, and cell death. Frequently observed dysfunctions in various malignancies, including gliomas, may encompass genomic mutations in mtDNA, altered metabolism (Warburg effect), structural abnormalities, glycolysis phosphorylation over oxidative phosphorylation, enhanced reactive oxygen species generation, or abnormal apoptotic machinery of isocitrate dehydrogenase (IDH) enzyme.

Lactate dehydrogenase A (LDHA)

Lactate dehydrogenase A (LDHA) is an enzyme that plays a key role in anaerobic glycolysis, which is responsible for increased glucose uptake and lactate production in tumor cells. Overexpression of LDHA has already been reported in several cancers [122]. Research performed by Di et al. [122] showed, that in high-grade glioma samples (grade III and grade IV) expression levels of LDHA were significantly higher than in low-grade gliomas (II grade), and up-regulated in comparison to normal tissues, which may indicate oncologic role in the glioma progression (**Table 1**). Knock-down of LDHA in breast cancer [123], oesophageal squamous cell carcinoma [124], hepatocellular carcinoma in xenografts [125], pancreatic cancer [126] or renal cell carcinoma [127], is responsible for impairment of tumor proliferation. Moreover, knock-down of LDHA performed by Di et al. [122], on glioma cell lines revealed, that expression levels of cyclin D1 and Bcl-2 decreased, while poly (ADP-ribose) polymerase (PARP) cleavage and Bax increased, indicating growth inhibition of glioma cells and induction of apoptosis. Furthermore, LDHA knock-down leads to downregulation of the expression of MMPs, VEGF and VE-Cadherin, which impairs cell migration and invasion *in vitro* [122].

Immunology aspects in gliomas

Impaired antitumor immunity and impaired systemic immunity are exhibited in patients with glioblastomas; which, respectively, rely on local cellular immunity mediated by the Th1 subset of helper T cells, and on systemic humoral immunity, which is mediated by the Th2 subset of helper T cells [89]. Moreover, patients tend to exhibit a low number of circulating T-cells, which makes them vulnerable to viral infections, impaired cytotoxic T-cell reactions and abnormally delayed-type hypersensitivity [128]. Mechanisms involved in the immunosuppressive effect may be demonstrated both locally and systemically. Starting with multiple genetic pathway alterations, like PI3-kinase/PTEN, through down-regulation or low levels of expression of MHC class I, to upregulation of anti-apoptotic proteins, such as the survivin protein, which concludes that tumor microenvironment is characterized through its immunosuppressive nature [89].

Cellular tumor antigen p53 (mutant-p53)

The p53 is a tumor suppressor and transcription factor, which induces growth arrest or apoptosis - depending on the physiological circumstances and cell type, and which is also involved in cell cycle negative regulation as a trans-activator. Deregulation of p53 is considered as one of the factors in GBM proliferation, migration, invasion, evasion of apoptosis (**Figure 2**), and stemless cancer cells [129]. Mutations in p53 coding gene TP53 are one of the most common in tumors. Most TP53 alterations are missense mutations in the DNA binding domain, which leads to inhibition of transcription factor activity [129]. Mutant p53, which has a carcinogenic potential, has been overexpressed in GBM [130] (**Table 1**). Increased expression of mutated p53 is caused due to the disruption of the negative feedback loop of mouse double minute 2 homolog (MDM2), also known as E3 ubiquitin-protein ligase MDM2. Wild-type p53 is regulated by the E3 ubiquitin ligase MDM2 [130]. In conclusion, a gain of function mutation in p53 is associated with enhanced proliferation, invasion, migration, and resistance to chemotherapy [130-132]. Nevertheless, the presence of TP53 mutation was correlated with H3F3A and ATRX-DAXX mutations which Schwartzentruber et al. [44] found strongly associated with alternative lengthening of the telomeres. Moreover, Liu et al. [52] correlated TP53 with ATRX, IDH1 and IDH2 mutations, indicating their specificity to astrocytic tumors and implicating that a combination of these alterations can contribute to the neoplastic growth in diffuse astrocytomas in adults.

Interleukin-13 receptor alpha 2 (IL-13Rα2)

Cancer-associated receptors - interleukin-13 receptor alpha 2 (IL-13Rα2) and EGFRvIII, are commonly overexpressed in human GBM [133] (**Table 1**). IL-13Rα2 is presumed to induce invasiveness of GBM cells without affecting their proliferation [133]. Moreover, IL-13Rα2 is possibly associated with EGFRvIII [133]. Overexpressed receptors display high affinity to IL-13, which is associated with epithelial tissue repair, which is mediated through the autocrine release of EGF and the subsequent activation of EGFR [134]. IL-13/IL-13Rα2 interactions do not activate the JAK/STAT6 pathway, and IL-13Rα2 is known/considered as a decoy receptor of IL-13 [135]. Cytoplasmic domain of IL-13Rα2 binds to EGFRvIII, which upregulates the tyrosine kinase activity and activates the STAT3 and RAS/MEK/ERK pathways (**Figure 2**). Moreover, IL-13Rα2 is undetectable in healthy brain cells, which makes it an important tool in the diagnosis of glioblastoma [133].

CD133/CD44

CD133 is a human cell membrane glycoprotein antigen that can be found in normal and malignant tissues, and to this day it has been investigated as an extracellular biomarker for cancer cells [136]. It also plays an important role in cell growth, proliferation and the pathophysiology of growing tumors [137]. In a study presented by Brown et al. [138], patients with glioblastoma had higher expression of CD133, which was associated with proliferation and invasiveness of the GBM. Moreover, the authors found a correlation between CD133 and CD44 presence in glioblastoma stem cells, which suggests that a differential expression of CD133 and CD44 is a prediction marker for radiotherapy response [138]. CD44 is a ligand of hyaluronic acid (HA), which is a major component of the extracellular matrix [139, 140]. While elevated levels of CD133 promote cell proliferation, the CD44 is responsible for higher invasiveness [141]. Nevertheless, the expression of both, CD133 and CD44, are correlated with the proliferative or invasive state of glioblastoma cells [138] (**Table 1**; **Figure 2**).

Summary

The clue of this paper is to bring closer proteins being candidates for minimally invasive diagnostic markers which would increase the level of comfort for glioma patients and would help to relieve medical staff from unnecessary and costly neurosurgical operations. Moreover, generating a larger portfolio of high confidence tumor-characteristic proteins with functional relevance to specific type or subtype of glioma is important for further development of reliable diagnostics. Currently, the diagnosis of gliomas is based primarily on imaging tests such as MRI. To date, there is no effective diagnostic method for the early stage of this cancer. In addition, gliomas treatment can be also a serious problem due to the stage of advancement (IV stage) as well as due to their proliferation or very frequent relapses. The use of additional diagnostic tools, e.g. evaluation of the expression of proteins characteristic to gliomas, could facilitate their diagnosis, as well as indicate new therapeutic targets, treatment effectiveness or predict their recurrence.

It's highly unlikely for a single biomarker to be sufficient to effectively detect glioma progression, postoperative recurrence and survival outcome. The use of combined proteomics biomarkers may provide a completely improved diagnostic method, relapse prediction, and targeted therapy possibilities for glioma patients. Moreover, the facilitation of combined proteomics biomarkers distinguishing type and subtype of glioma in preoperative diagnostics may advise the best surgical approach and the most appropriate postoperative treatment guidance for physicians. Thus, there is a need for further proteomics investigations aiming to improve current diagnostics, which will raise the effectiveness of physicians and reduce the eventual chances of incorrect treatment selection. Potential biomarkers presented in this paper may improve glioma diagnostics, however, most of them have not been validated. Therefore, their further experimental evaluation on a large cohort of patients is needed before eventual clinical application.

Future directions for gliomas biomarkers facilitation in standard diagnostics procedures should concentrate on comparative proteomics, based on analysis of proteome changes in response to disease stage and development. Basing on the currently available literature, the most promising protein identifications in gliomas are provided through liquid chromatography with tandem mass spectrometry (LC-MS/

MS). However, proteomic identification aspects in LC-MS/MS are a wide and maybe promising topic for another publication. Moreover, the most reliable approach should take into account multi-omics, for example combining the results from proteomic and metabolomics analyzes, which will facilitate the diagnosis or prognosis of glioblastoma. By expanding the range of possible biomarkers and their interactions, we will enable the discovery of new, more effective targeted therapies with a wider and more effective range of action.

Disclosure of conflict of interest

None.

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