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REVIEW

Protein tyrosine phosphatases in glioma biology

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Abstract Gliomas are a diverse group of brain tumors of glial origin. Most are characterized by diffuse infiltrative growth in the surrounding brain. In combination with their refractive nature to chemotherapy this makes it almost impossible to cure patients using combinations of conventional therapeutic strategies. The drastically increased knowledge about the molecular underpinnings of gliomas during the last decade has elicited high expectations for a more rational and effective therapy for these tumors. Most studies on the molecular pathways involved in glioma biology thus far had a strong focus on growth factor receptor protein tyrosine kinase (PTK) and phosphatidylinositol phosphatase signaling pathways. Except for the tumor suppressor PTEN, much less attention has been paid to the PTK counterparts, the protein tyrosine phosphatase (PTP) superfamily, in gliomas. PTPs are instrumental in the reversible phosphorylation of tyrosine residues and have emerged as important regulators of signaling pathways that are linked to various developmental and disease-related processes. Here, we provide an overview of the current knowledge on PTP involvement in gliomagenesis. So far, the data point to the potential implication of receptor-type (RPTPδ, DEP1, RPTPμ, RPTPζ) and intracellular (PTP1B, TCPTP, SHP2, PTPN13) classical PTPs, dual-specific PTPs (MKP-1, VHP, PRL-3, KAP, PTEN) and the CDC25B and CDC25C PTPs in glioma biology. Like PTKs, these PTPs may represent promising targets for the development of novel diagnostic and therapeutic strategies in the treatment of high-grade gliomas.

Keywords Signal transduction · Tyrosine phosphorylation

Abbreviations

BBB	Blood–brain barrier
CDK	Cyclin-dependent kinase
DSPs	Dual-specificity PTPs
EGF	Epidermal growth factor
EGFR	Epidermal growth factor receptor
EGFRvIII	EGFR variant III
Eya	Eyes absent
FNIII	Fibronectin type III
GBM	Glioblastoma multiforme
HPV	Human papillomavirus
JNK	Jun *N*-terminal kinase
LEOPARD	Lentigines, electrocardiogram abnormalities, ocular hypertelorism, pulmonic stenosis, abnormalities of genitalia, retardation of growth, and deafness
MKPs	MAP kinase phosphatases
MMPs	Matrix metalloproteases
PDGFR	Platelet-derived growth factor receptor
PI3K	Phosphatidylinositol-3-kinase
PIP_3	Phosphaditylinositol-3, 4, 5-triphosphate
PRL	Phosphatase of regenerating liver
PTEN	Phosphatase and tensin homolog on chromosome 10

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PTK	Protein tyrosine kinase
PTN	Pleiotrophin
PTP	Protein tyrosine phosphatase
Rb	Retinoblastoma
VEGF	Vascular endothelial growth factor

Introduction

Like in many other cell types, accumulation of genetic damage in glial (precursor) cells may ultimately lead to transformation into tumor cells. The World Health Organization (WHO) classifies the resulting gliomas in many different histological subtypes and in four different malignancy grades [88]. Astrocytomas, oligodendrogliomas and mixed oligoastrocytomas are the most common glioma types. Most of these tumors are characterized by diffuse infiltrative growth in the surrounding brain parenchyma which precludes curative treatment by surgery or radiotherapy alone, and together with their relative resistance towards conventional chemotherapy this places these tumors among the most intractable human malignancies [24]. For the most frequent of these gliomas, i.e. glioblastoma multiforme (GBM), only 10% of the glioblastoma patients survive 5 years post-diagnosis when receiving combined chemo- and radio therapy as opposed to 2% for radiation treatment alone [74, 137]. Ependymomas are quite rare and are traditionally thought to originate from the ependymal cells lining the ventricular walls in the brain and the central canal in the spinal cord.

A more detailed insight in the molecular etiology of these gliomas may open up new ways to combat these tumors. Multiple studies towards that end, including cytogenetic analyses, but also genome-wide microarray expression screens, have been performed and important players have been identified. They mainly converge on aberrant growth factor signaling and deregulation of cell cycle control, processes that exploit the phosphorylation of proteins on tyrosine residues [17, 43, 106]. This reliance on protein tyrosine kinase (PTK) activity urges for a closer look on the role that is played by protein tyrosine phosphatases (PTPs), their enzymatic counterparts (Fig. 1), in glioma biology. The PTP enzyme family has emerged as an important regulator of developmental and disease-related signaling pathways [143], and multiple members are directly linked to malformation syndromes and tumorigenesis [54, 107]. So far, a systematic review on the role of PTPs in gliomagenesis is lacking. Here, following a brief discussion of the aberrant signaling pathways in glioblastomas, we will introduce the general features of the PTP family before presenting detailed information on PTP involvement in glioma biology. The PTP enzymes discussed may represent entry points for development of novel diagnostics and therapies in the treatment of high-grade gliomas.

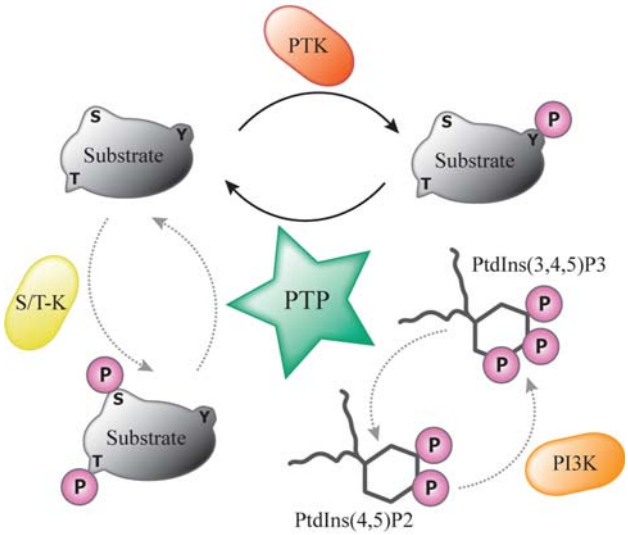

Fig. 1 Reversibility of signaling pathways by virtue of protein tyrosine phosphatase activity. The opposing actions of PTK and protein tyrosine phosphatase (PTP) enzymes provide the cell with a functional diad that regulates the activity of the mutual substrates through phosphorylation of tyrosine (Y) residues in a reversible manner. Note that phosphorylation itself may well regulate the activity of PTKs and PTPs themselves. Therefore, PTPs do not simply repress or undo PTK activity; they may synergize or cooperate in situations where tyrosine phosphorylation boosts PTP activity or dephosphorylation activates the PTK. Some PTPs have a so-called dual specificity; in addition to their activity towards phosphotyrosine they are also able to dephosphorylate serine (S) and/or threonine (T) residues in protein substrates that have been phosphorylated by serine/threonine kinases (S/T-K). A subset of these dual-specific PTPs, most notably the tumor suppressor protein PTEN, even demonstrate the potential to dephosphorylate phospholipid substrates like phosphatidylinositol-3,4,5-triphosphate (PtdIns(3,4,5)P3) that is produced by phosphatidylinositol-3-kinase (PI3K)-mediated phosphorylation of PtdIns(4,5)P2 (phosphatidylinositol-4,5-bisphosphate)

Affected processes in gliomas

The sequential changes that transform glial (precursor) cells into tumor cells fit well with the cancer cell hallmarks encountered in many other tumor systems [52]. First, cancer cells have acquired the ability to be self-sufficient in providing growth signals while reducing their sensitivity to growth-inhibitory signals. The molecules and pathways involved in gliomas include alterations in Ras and PI3K (phosphatidylinositol-3-kinase) signaling pathway components, which regulate proliferation, survival and differentiation. Especially, genes encoding the receptor PTKs for epidermal growth factor (EGFR) and platelet-derived growth factor (PDGFR) are frequently mutated,

and also alterations in the fibroblast growth factor (FGFR) and hepatocyte growth factor/scatter factor (cMET) receptor PTK genes have been documented [17]. Proteins involved in the subsequent signaling downstream of these PTK receptors have been linked to gliomagenesis as well (Fig. 2). Mutations in two tumor suppressor genes, NF1 and PTEN (*P*hosphatase and *ten*sin homolog on chromosome *10*), are found in a considerable portion of glioblastomas and also genetic changes in Akt and Ras have been documented [17]. The involvement of PTEN and other PTP family members will be described in more detail later on.

Secondly, glioma cells tend to evade apoptosis and senescence. The TP53 gene, encoding a key regulator of cell cycle progression, DNA repair, cellular senescence, apoptosis and angiogenesis [152], is frequently inactivated at an early stage in gliomagenesis. Alternatively, other important players that affect p53 functioning, e.g. the p53 activator p14ARF or the negative p53 regulators MDM2 and MDM4 (Fig. 2) are deleted or amplified in gliomas, respectively. In addition, glioma cells may exploit several other mechanisms to evade apoptosis, including abrogated PI3K signaling (Fig. 2), genetic alterations in death receptor and mitochondria-dependent pathways via Bcl2-like-12 [135, 136], and inactivation of the retinoblastoma (Rb) tumor suppressor pathway (Fig. 2). The Rb pathway controls the cell cycle entry step into the DNA replication phase [46]. Many of the involved proteins are genetically altered in GBMs: the CDK4 and CDK6 genes are often amplified, while Rb is deleted or mutated in ~11% of the glioblastomas [17]. Normally, continued proliferation of somatic cells leads to senescence due to successive shortening of chromosome ends, the telomeres [14]. High-grade gliomas bypass telomere shortening, hence senescence, either by restoring embryonal telomerase activity [128] or by exploiting a telomere maintenance mechanism that involves recombination-based interchromosomal exchanges of DNA segments [55].

Thirdly, gliomas elicit angiogenesis and invade surrounding tissues. GBMs are among the most highly vascularized solid tumor types [66] and this may be due to mutations in the key glioma genes PTEN and EGFR that feed into the HIF1α pathway [68]. HIF1α is a transcription factor that normally accumulates under hypoxic conditions and then activates factors involved in angiogenesis and cell survival [127], including the vascular endothelial growth factor (VEGF) and VEGF receptor families (Fig. 2). In glioma specimens, this activation may be independent of hypoxia [110] and often gives rise to abnormal microvasculature that results in thrombosis and microhemorrhages,

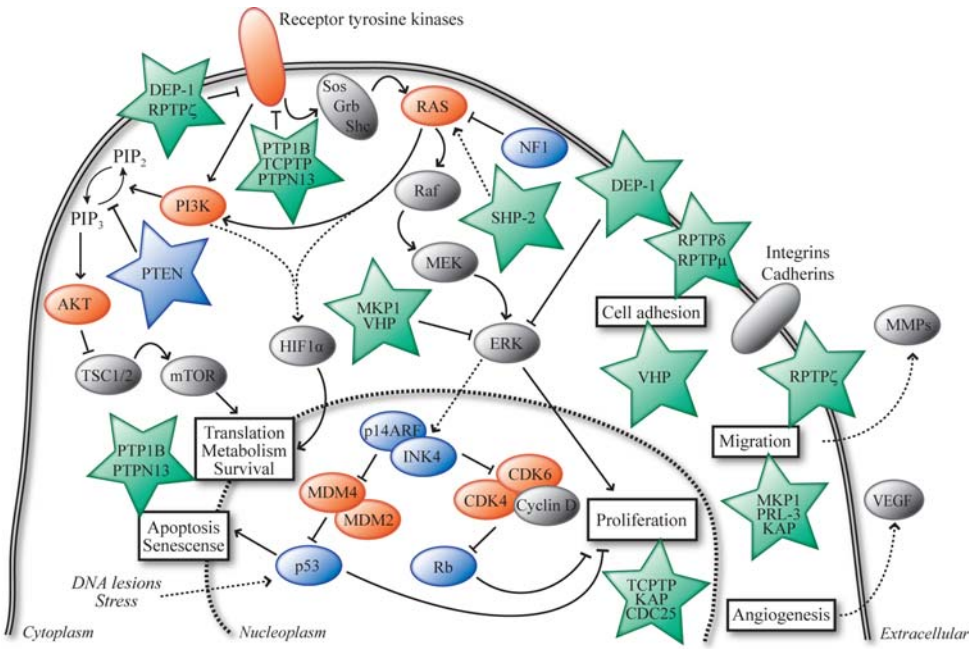

Fig. 2 Interplay of PTP signaling and the major pathways affected in glioblastomas. The Ras/PI3K, p53 and Rb signaling pathways, which are often altered in glioblastomas, are shown in a cellular context. For simplicity, only major factors that are described in the text are depicted. Proteins shown in *vermillion* are frequently hyperactive in gliomas (due to amplification/mutation) while proteins in *blue* are frequently hypoactive or even inactive (as a result of mutation/deletion). The (*mostly green*) *asterisks* represent the receptor-type and non-transmembrane PTPs (protein names are used) that are discussed in the text and in Table 1, and the ways how they feed into the Ras/PI3K, p53 and Rb pathways and affect cellular processes (*boxed text*) is depicted. *Arrows* indicate interactions that result in stimulation, lines ending with a *perpendicular bar* indicate inhibitory interactions. *Dashed lines* reflect indirect interaction pathways. *PIP2* phosphatidylinositol-4,5-bisphosphate, *PIP3* phosphatidylinositol-3,4,5-triphosphate

paradoxically causing hypoxia and eventually tumor necrosis. 'Dispersion' of glioma cells in the surrounding brain tissue is distinct from the invasion and metastasis as displayed by other tumors [24], but still many parallels exist. Like in epithelial tumors, several integrins, including αvβ3, are upregulated in gliomas [82]. In addition, the expression of the N-cadherin cell adhesion molecule and its associated protein β-catenin is increased at the borders of GBMs [149]. In addition, the levels of matrix metalloproteases (MMPs) and non-MMP proteases, instrumental in degrading surrounding extracellular matrix, have been reported to be elevated in gliomas [146]. Low-grade gliomas usually have normal protease levels [153, 157], but still display an invasive phenotype, suggesting that increased protease activity is not required for glioma dispersal.

Protein tyrosine phosphatases

Reversible tyrosine phosphorylation of proteins (Fig. 1) plays an important role in the regulation, proliferation and differentiation of cells and the development and function of tissues and organisms [143]. The exploitation of this signaling mechanism to drive gliomagenesis is reflected in the altered activities of PTK growth factor receptors and their downstream effectors that have been observed in tumor specimens (as depicted in Fig. 2) and warrants a closer look on the role of the catalytic opponents of PTKs, the PTPs.

There are 107 genes in the human genome that belong to the PTP superfamily of enzymes and, based on the sequence homology of their catalytic domains and these have been categorized into four different classes [6]. Class I comprises 38 so-called 'classical' PTPs, i.e. enzymes that exclusively dephosphorylate phosphotyrosine residues, as well as 61 dual-specificity PTPs (DSPs). As suggested by the name, DSPs can also dephosphorylate phosphoserine and phosphothreonine residues, and some even display a preference for phosphatidylinositol phosphates and mRNAs as substrates [115]. The 38 classical PTPs can be further subdivided into transmembrane, receptor-like (RPTPs) and non-receptor-type PTPs [54]. In the human genome, there is only a single Class II gene (ACP1). It encodes the low-molecular weight PTP, termed LMPTP, that is specific for phosphotyrosine residues [117]. Class III comprises three CDC25 homologs that dephosphorylate tyrosine and threonine residues within cyclin-dependent kinases (CDKs), which participate in cell cycle regulation [120]. Class IV consists of the eyes absent (Eya) proteins, which recognize phosphorylated tyrosine, or dual serine and tyrosine residues and function as transcriptional regulators [65]. Recently, Eya was shown to dephosphorylate tyrosine phosphorylated histone H2AX, thereby regulating the recruitment of pro-apoptotic and/or DNA repair factors to sites of DNA damage [27, 78].

Each PTP class is believed to originate from a distinct ancestral gene and as such the clear similarity in the dephosphorylation mechanism they exploit provides an impressive example of convergent evolution. A common feature of the PTP classes I, II and III is the PTP signature motif (H/V)C(X)R(S/T) in their catalytic domain [138]. The cysteine residue is essential for catalytic activity; the target phosphate group is transferred from the substrate onto this catalytic site cysteine, producing a thiol intermediate, and is subsequently released via hydrolysis [8]. The Eya Class IV phosphatases use a slightly different mechanism, in which aspartate instead of cysteine plays a crucial role in a metal-dependent reaction. Outside the catalytic domain, PTPs are very diverse in their structure. Multiple additional protein domains, such as protein–protein interaction or phospholipid-binding motifs, help to diversify their functions (Fig. 3).

PTPs in tumorigenesis

Because multiple PTKs have been identified as proto-oncogenes, it was initially believed that many PTPs might be rapidly uncovered as tumor suppressors. However, it turned out that there is a considerable redundancy with regard to PTP functioning. Furthermore, PTPs may not simply oppose PTK actions but, as some kinases are (auto)inhibited by phosphorylation, could also act in synergy. Thus, next to some tumor suppressors, the PTP superfamily also harbors proto-oncogenes [107]. Before turning to the involvement of PTPs in gliomagenesis, the evidence implicating PTPs in other tumors will be summarized.

In fact, PTEN represents the only PTP that can unambiguously be termed a tumor suppressor, i.e. the gene is frequently deleted or mutated in tumor specimens [70]. Ironically, it is not PTEN's protein dephosphorylation capacity, but its ability to dephosphorylate D3-phosphoinositosides—and thereby dampen PI3K-Akt signaling—that is crucial for maintaining tissue homeostasis [90, 102]. Several other PTP genes are deleted or mutated in cancer tissues as well, but the frequency is usually quite low and causal relationships often have not been assessed. A screen encompassing 87 out of the 107 human PTP genes revealed mutations for six of them, all encoding classical PTPs (PTPRF, PTPRG, PTPRT, PTPN3, PTPN13 and PTPN14) in 26% of the colon cancer samples analyzed [154]. Alterations in these genes were also identified in lung, breast and gastric cancer samples, but at an even lower frequency. For PTPRT, the most frequently mutated PTP

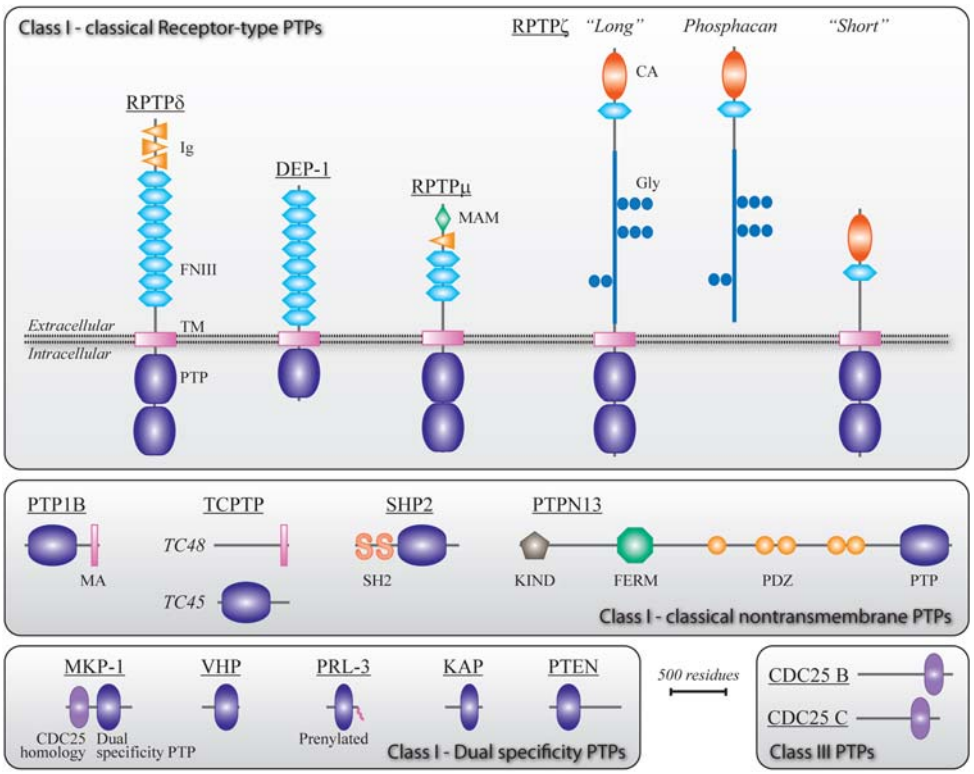

Fig. 3 Domain structure of the PTP superfamily members implicated in glioma biology. Schematic representations of class I transmembrane receptor type and intracellular 'classical' PTPs are given in the upper and middle part of the figure, respectively. The lower part shows the class I dual-specific phosphatases and the class III CDC25 family members. Thus far, class II and class IV type PTPs have not been implicated in gliomagenesis. Alternative splicing of genes PTPRZ and PTPN2 leads to expression of three variants of RPTPζ [87] and two of TCPTP [60], respectively. PTP protein names are used here (Table 1), and isoform names are in *italics*. Protein domain names and acronyms are indicated and the curly tail in PRL-3 represents its C-terminal prenylation. *CA* carbonic anhydrase-like domain, *FERM* band 4.1/ezrin/radixin/moesin homology domain, *FNIII* fibronectin type III repeat, *Glyc* glycosylation sites encoded within PTPRZ exon 12, *Ig* immunoglobulin-like repeat, *KIND* kinase non-catalytic C-lobe domain, *MA* membrane-associated domain, *MAM* meprin/A5-protein/PTPμ homology domain, *PDZ* PSD-95/discs-large/ZO-1 homology domain, *PTP* catalytic protein tyrosine phosphatase domain, *SH2* Src homology 2 domain, *TM* transmembrane domain. *Drawings* are to scale (*bar* corresponds to 500 amino acid residues)

out of these six, growth suppressive activity was indeed demonstrated in cell transfection experiments, underscoring the relevance of this PTP in cell growth regulation [154]. The majority of cancer-related PTPRT mutations affects the extracellular domain that mediates homophilic cell–cell interactions, suggesting that mutation of this phosphatase supports tumor migration [159]. The signaling pathways that are regulated by PTPRT remain to be disclosed, but recently the signal transducer and activator of transcription 3 (STAT3), that plays an important role in a variety of hematopoietic malignancies and solid tumors [158], was identified as a PTPRT substrate [163]. Extensive sequence analysis screens have also revealed genetic alterations in some other classical PTP genes (PTPRJ, PTPN6, PTPRO, PTPN1), implicating these as potential tumor suppressors [107].

As stated above, some PTPs might even function as oncogenes. Currently, the only PTP gene for which this has been demonstrated is PTPN11 that encodes the classical PTP SHP2 [20]. SHP2 (Fig. 3) is normally in an inactive conformation due to an intramolecular interaction of its N-terminal SH2 domains with the catalytic PTP domain at its C-terminus. SHP2 mutations as observed in hematological malignancies and some solid tumors disrupt this interaction, thereby constitutively activating the phosphatase [85, 141]. Then, this synergizes with growth factor and cytokine stimuli that run via the Ras-ERK, AKT and STAT5 signaling routes [99], all pathways that have important roles in growth, proliferation and survival. How exactly SHP2 is stimulating these ligand-gated signaling pathways, i.e. which specific targets it dephosphorylates, remains controversial, but the dephosphorylation and consequent activation of Src family kinases is a likely scenario [20]. Indications that other PTPs also have oncogenic potential are more indirect. Several classical PTP genes are overexpressed in human cancers, including PTPRA, PTPRH, PTPRF, PTPN1, PTPN6 and PTPN7, but these may reflect homeostatic adaptation to enhanced kinase activities [107].

Further studies are needed to address the contribution of these PTPs in tumor development in a more direct way.

Linking PTPs to glioma biology

It has also been investigated whether PTPs are relevant players in glioma development. Indeed, 15 out of the 107 PTP genes are implicated in some way. In Table 1, the observational data on these PTPs and gliomagenesis are summarized and on the following pages, their involvement is discussed in more detail (in the subheadings first the official gene name and between brackets the common protein name will be given). Undoubtedly, the number of studies and the fraction of PTPs that are involved in gliomagenesis will increase in the coming years. However, it is to be expected that genome-wide microarray datasets will only make a limited contribution to this, due to the very low expression levels of most PTP genes; hence, more PTP-focused approaches are required.

PTPRD (RPTPδ)

RPTPδ, a cell adhesion molecule-like RPTP with fibronectin type III (FNIII) and immunoglobulin-like (Ig) repeats in its extracellular domain (Fig. 3), is mainly expressed in brain. Mouse model studies revealed its importance in hippocampal learning and memory [145]. PTPRD is located on chromosome 9p23–24.1, a genomic region that is often lost during the progression from low- to high-grade gliomas of the astrocytoma and oligodendroglioma types [61]. Two recent studies on GBMs report focal homozygous deletions at the PTPRD locus that do not impart surrounding genes [130, 150]. Also, missense or nonsense mutations in the PTPRD gene or hypermethylation of the PTPRD promoter were frequently encountered [130, 150], and the loss of RPTPδ expression predicts for poor prognosis in these patients [150]. PTPRD mutations and deletions are also common among other tumors [29, 31, 125, 133]. In melanomas and lung carcinomas, these mutations are distributed all over the PTPRD gene. The alterations that were detected in GBM samples more locate to the RPTPδ extracellular part than to the intracellular PTP domains [130, 150]. The re-introduction of functional RPTPδ in GBM cell lines harboring PTPRD mutations or deletions leads to reduced proliferation and an increase in apoptotic cells [130]. Transfection experiments pointed to STAT3 as an RPTPδ substrate [150] and, interestingly, aberrant activation of STAT3 is commonly observed in GBM specimens [116]. Thus, RPTPδ has a tumor suppressor function in a variety of tissues. In glial cells, this activity may require its putative cell adhesion potential as well as phosphatase activity (Fig. 2).

PTPRJ (DEP-1)

PTPRJ encodes the transmembrane protein DEP-1 that consists of a single intracellular PTP domain and eight FNIII repeats in its long extracellular part (Fig. 3). DEP-1 is able to counteract the signaling of several RTKs, including PDGFR, VEGFR2 and MET [77, 108, 139], pointing to a role as tumor suppressor (Fig. 2). Indeed, it was shown to negatively regulate cellular growth [69]. In glioma cells, DEP-1 is instrumental in the growth-inhibitory effect of somatostatin by dephosphorylating and inactivating the MAP kinase ERK [93, 94]. DEP-1 expression is detectable in only a subset of gliomas and expression levels correlate well with somatostatin's antiproliferative effects [93, 94]. Not much is known about possible alterations in the PTPRJ gene in glioma specimen. Thus far, an amplification of the chromosome 11p11.2 region, which contains the PTPRJ gene, has been detected in an angiocentric glioma [114]. Angiocentric gliomas are grade I tumors that contain features of both astrocytic and ependymal differentiation [88]. PTPRJ amplification would not correspond with a suggested tumor suppressor function for DEP-1 but, since only one case has been described, clearly more angiocentric glioma samples need to be studied before conclusions can be drawn.

PTPRM (RPTPμ)

The cell surface receptor RPTPμ is a homophilic cell–cell adhesion molecule expressed in neuronal, glial and endothelial cells (Fig. 3). RPTPμ not only forms an adhesive contact itself, but it also regulates cell adhesion by dephosphorylating components of the cadherin–catenin complexes. In addition, the rigidity of the extracellular part of the molecule is thought to dictate the location of this phosphatase in cell–cell spacings [7] in line with a role for this PTP in cell contact signaling processes. When compared with normal brain tissue and low-grade astrocytomas, full-length RPTPμ protein expression is lost specifically in GBM [15]. To investigate whether this influenced cell adhesive and migratory characteristics, RPTPμ knockdown experiments were performed in a GBM cell line. Reduced RPTPμ levels resulted in morphological changes and an increased migration in vitro, and in a mouse xenograft model of intracranially injected GBM cells RPTPμ knockdown caused morphological heterogeneity in the grafts [15]. These data put forward RPTPμ as a 'migration suppressor' with regard to the diffuse infiltrative growth pattern observed in human gliomas (Fig. 2). A more recent study revealed that the RPTPμ downregulation in GBM results from proteolytic breakdown which releases an active PTP fragment in the cytosol [16]. Interestingly, both overexpression of RPTPμ and shRNA-mediated

Table 1 Overview of protein tyrosine phosphatases associated with glioma biology

Gene[a]	Protein (synonyms)	Chromosomal location	Alteration	Glioma type	WHO grade	Model system	References
Classical class I PTPs (8 out of 38 genes)							
PTPRD	RPTPδ	9p23–p24.3	Del/Mut	OD, AC	II, III and IV	CM	[61, 130, 150]
PTPRJ	DEP1 (CD148, RPTPη)	11p11.2	11p amp[b]	AG	I	CM	[114]
PTPRM	RPTPμ	18p11.2	LOE	GBM	IV	CM	[15]
PTPRZ	RPTPζ	7q31.3	OE	GBM	IV	CM	[147]
PTPN1	PTP1B	20q13.1–13.2	Act	GBM	IV	PCL + TG	[4]
PTPN2	TCPTP (MPTP, PTP-S)	18p11.3–11.2	Dephosph EGFRvIII	GBM	IV	CL	[73]
PTPN11	SHP2 (SH-PTP2, Syp, PTP1D, PTP2C, SH-PTP3)	12q24.1	Mut[b]	OD	II	CM	[91]
PTPN13	PTPN13 (PTP-BAS, FAP-1, PTP1E, RIP, PTPL1, PTP-BL)	4q21.3	OE	GBM	IV	CM	[39]
Dual-specific class I PTPs (DSPs, 5 out of 61 genes)							
DUSP1	MKP-1 (3CH134, PTPN10, erp, CL100/HVH1)	5q34	DR	GBM	IV	CL + Etop	[86]
			OE			CL + DM	[84]
DUSP26	VHP ('similar to RIKEN cDNA 0710001B24')	2q37.3	DR	GBM	IV	CM	[140]
PTP4A3	PRL-3	8q24.3	OE	Gliomas	II, III and IV	CM	[75]
CDKN3	KAP	14q22	Ab splicing	Prim GBM	IV	CM	[161]
PTEN	PTEN (MMAC1, TEP1)	10q23.3	Mut / Del / Epigenetic	Prim and sec GBM	IV	CM	[22, 35, 43, 76] and references therein
Class III PTPs (2 out of 3 genes)							
CDC25B	CDC25B	20p13	OE	AC, GBM	III, IV	CM	[104]
CDC25C	CDC25C	5q31	DR	GBM	IV	CL + AM	[44]

Genes are listed in the order used in Alonso et al. [6]

Note that thus far no PTPs from classes II (LmPTP) and IV (Eya) have been implicated in glioma biology

Ab aberrant, *Act* activation, *AG* angiocentric glioma, *amp* amplification, *AC* astrocytoma, *AM* ansamycin, *CL* cell line, *CM* clinical material, *Del* homozygous deletion, *Dephosph* dephosphorylates, *DM* dexamethasone, *DR* down-regulated, *Etop* etoposide, *GBM* glioblastoma, *LOE* loss of expression, *Mut* mutation, *OD* oligodendroglioma, *PCL* primary cell line, *prim* primary, *Sec* secondary, *TG* troglitazone

[a] Some PTP genes give rise to multiple protein isoforms

[b] Found in one patient only

reduction of the RPTPμ intracellular fragments suppressed migration and growth factor-independent survival of glioblastoma cells. Apparently, decisions in glioma cells on proliferation versus cell death or adhesion versus migration are dependent on the relative levels of full-length RPTPμ and RPTPμ intracellular domain. Importantly, application of a peptide inhibitor of RPTPμ phosphatase activity also resulted in a reduction of glioma cell migration [16], warranting further studies towards RPTPμ targeted therapeutics.

PTPRZ (RPTPζ)

The classical PTP gene that currently has the strongest links with gliomagenesis is PTPRZ, which encodes RPTPζ [80]. Originally, the cDNA was cloned by two different groups, who termed the encoded protein PTPζ [79] and RPTPβ [83], respectively. This is causing quite some confusion in the literature, also because the name RPTPβ is nowadays linked to the protein encoded by the gene PTPRB [6]. As a result of alternative splicing, PTPRZ encodes three variants that may have different roles in glial differentiation (Fig. 3). Long and short transmembrane RPTPζ isoforms are present in glial precursor cells. In more mature glia, a secreted version called phosphacan is expressed, which lacks the PTP part and consists of the RPTPζ extracellular domain [18]. Pleiotrophin (PTN) has been identified as a ligand for RPTPζ [89]. It induces cell migration, at least in part by binding and clustering RPTPζ, and thereby inhibiting its phosphatase activity [42, 96]. Fibroblasts that overexpress PTN acquire a transformed phenotype suggesting that PTN may function as an oncogene [21]. In line with this, several carcinoma patients showed increased PTN levels in both serum and tumor material [131]. PTN is overexpressed in GBM tissues as well [147] and may exert an oncogenic effect through the inactivation of RPTPζ.

The role of RPTPζ in glioma development is as yet unclear. PTPRZ overexpression in tumor material is correlated with increased malignancy [101, 147]. Some other cancer variants also display increased PTPRZ expression [38]. Although in normal adult brain it is mainly phosphacan that is expressed, all three PTPRZ isoforms can be found in gliomas. Knockdown of RPTPζ leads to a decrease in GBM growth, both in vitro and in vivo [148], but the mechanism that may explain this growth advantage resulting from RPTPζ overexpression remains unclear. After all, excess of RPTPζ would be expected to function as a potential PTN scavenger, thus neutralizing PTN's oncogenic abilities. The tumor-promoting effect of RPTPζ may be explained by mechanisms independent of PTN, for instance through the effects of other RPTPζ ligands that include growth factors, extracellular matrix proteins and neuronal cell adhesion molecules [111]. Neuronal adhesion molecule binding by RPTPζ is thought to influence neuron–glial cell interactions and cell migration, e.g. by promoting transcriptional activity of NFκB [87] which is implicated in the integration of signals involved in adhesion and migration. In addition, a recent study revealed that the endothelial integrin $\alpha_v\beta_3$ not only interacts with both PTN and RPTPζ, but in doing so mediates the stimulatory effect of PTN on cell migration and angiogenesis [97]. Thus, the overexpression of RPTPζ may provide an advantage for GBM cells by promoting their migration, even on endothelial cell tracks [142]. Alternatively, because proteolytic cleavage involving MMPs and presenilin/γ-secretase was shown to produce an RPTPζ intracellular fragment that displays nuclear localization [23], even more direct effects at the transcriptional level should be considered. Finally, altered RPTPζ levels have a bearing on neurotrophic signaling pathways in view of the recent identification of tropomyosin-related kinase A, TrkA, a nerve growth factor receptor that is highly expressed in the developing nervous system, as an in vivo RPTPζ substrate [129]. Also because high RPTPζ levels were reported in oligodendrogliomas as opposed to (oligo)astrocytomas within the grade II gliomas [49], a further evaluation of RPTPζ's contribution to gliomagenesis is warranted.

PTPN1 (PTP1B)

The cytoplasmic, ER membrane-associated phosphatase PTP1B (Fig. 3) is overexpressed in several tumors, including mammary and ovary carcinomas, but it is unclear as yet whether it should be viewed as a potential oncogene or a tumor suppressor [107]. PTP1B can act as a positive regulator of Ras signaling, partly by modulating p120RasGAP levels [33] and it is also able to activate the oncogene protein Src [11]. Importantly, the elimination of PTP1B activity in MMTV-neu induced mammary tumors in mice significantly delayed tumor growth and prevented lung metastasis, whereas PTP1B overexpression in mammary tissue led to spontaneous breast cancer development [9, 67]. In contrast, PTP1B effectively inhibits signaling of several oncogenic tyrosine kinases [50], while inactivation of the gene in TP53 knockout mice accelerates the spontaneous development of lymphomas [32].

In gliomas, no amplification of the PTPN1 gene has been found [118]. However, PTP1B may well be of relevance for glioma therapy. The treatment of tumor cells derived from a primary GBM patient with troglitazone led to PTP1B activation and subsequent dephosphorylation of STAT3, a negative regulator of Fas-mediated apoptosis that controls anti-apoptotic FLIP and Bcl-2 protein levels [4]. Thus, PTP1B activity may facilitate at least one way of

tumor cell death. It should be noted, however, that most recently it was found that STAT3 not only functions in transcription regulation in the nucleus in response to cytokine and tyrosine kinase oncoprotein signaling, but that in addition it is required in mitochondria for the alterations in energy metabolism that support Ras-dependent malignant transformation of cells [47, 155]. Reasoning along these lines, PTP1B activity could potentially counteract STAT3s moonlighting activity in mitochondria and in this way hamper the glioma cell's adaptation to a more glycolytic, hypoxic growth state (Fig. 2). Taken together, depending on the cell type, PTP1B has distinct functions, but current data are more in favor of a tumor suppressive rather than an oncogenic role in GBM. Investigations on PTP1B as a drug target [162] principally relate to diabetes [34], and several inhibitors have been tested clinically.

PTPN2 (TC-PTP)

TC-PTP is an intracellular PTP that is ubiquitously expressed and that is highly similar in amino acid sequence to PTP1B (Fig. 3). As a consequence, these PTPs have different as well as overlapping substrates and thus may fulfill complementary as well as redundant roles in health and disease [34]. Alternative splicing of PTPN2 transcripts leads to two protein isoforms; a 48 kDa variant localized at the endoplasmic reticulum and a 45 kDa variant, TC45, that lacks the hydrophobic C-terminus [19, 28, 100]. TC45 is usually found in the nucleus but upon proper stimuli it can also reside in the cytoplasm. Interestingly, TC45 causes a reduced proliferation of U87MG glioblastoma cells that are engineered to express the glioma-associated truncated protein EGFRvIII when compared with normal U87MG cells [73]. This might well be caused by inhibition of ERK and PI3K signaling due to direct dephosphorylation of EGFRvIII (Fig. 2). Injection of TC45- and EGFRvIII-overexpressing U87MG cells in the brains of nude mice revealed that also in vivo TC45 expression leads to reduced growth of EGFRvIII-expressing tumors [73]. Although no altered TC45 activity levels in gliomas have been reported to date, the potential of TC-PTP to counteract EGFRvIII activity in vivo may be of therapeutic value.

PTPN11 (SHP-2)

So far, PTPN11 is the only PTP that was proven to function as an oncogene in certain tumors [20, 107]. It contains two Src homology type 2 (SH2) domains that function as phosphotyrosine-binding domains (Fig. 3). Activating germline PTPN11 mutations are found in patients with Noonan syndrome, a developmental disorder characterized by an increased risk of malignancies. Somatic mutations that activate PTPN11 occur in several types of hematologic malignancies, most notably juvenile myelomonocytic leukemia. The role of SHP-2 in RAS/ERK signaling (Fig. 2) is thus well established in tumor development. Germline mutations that impair phosphatase activity and turn PTPN11 into a dominant-negative mutant are causative of LEOPARD (*l*entigines, *e*lectrocardiogram abnormalities, *o*cular hypertelorism, *p*ulmonic stenosis, *a*bnormalities of genitalia, *r*etardation of growth, and *d*eafness) syndrome, which also predisposes to the development of cancers such as myelodysplastic syndrome, acute myelogenous leukemia or neuroblastoma. It remains an intriguing conundrum why Noonan and Leopard syndrome mutations result in partly similar pathologies despite their quite opposite effects on SHP2 catalytic function [45].

The expression of SHP-2 in the U87MG GBM cell line resulted in increased AKT phosphorylation upon EGF stimulation [156], underscoring that SHP-2 also facilitates growth factor signaling in glial cells. PTPN11 mutations in gliomas are rather uncommon [64, 91] but other components in the RAS/PI3K pathway, like EGFR, NF1 and RAS, are genetically altered in the majority (88%) of GBMs [17]. Only a single PTPN11 mutation, in a grade II oligodendroglioma patient, has been described thus far [91]. This missense mutation in the SH2 domain of SHP-2 promotes its phosphatase activity and thus resembles the Noonan syndrome type of activating mutations. Although PTPN11 can display oncogenic behavior in other tumor types, and plays an important positive role in Ras signaling in gliomas as well, it does not represent a specific target in these tumors.

PTPN13 (PTPN13)

The large cytosolic PTP PTPN13 (Fig. 3) appears to be endowed with tumor suppressive as well as oncogenic potential [2]. Support for a tumor suppressive role comes from mutation screens in colon, breast, lung and ovarian cancer specimens [119, 154] and our finding that high-risk human papillomavirus (HPV) protein E6-induced degradation of PTPN13 in squamous epithelial cells contributes to oncogenic transformation [132], at least in part by augmenting the Ras/Erk signaling pathway. In line with this, PTPN13 inactivating mutations and enhanced Erk activity was detected in HPV-negative head and neck squamous cell carcinomas [56]. Contrasting with the above, several studies have pointed to a tumor-promoting activity of PTPN13. The PTPN13 gene is a target for the transcription regulator fusion protein EWS-FLI1 and the resulting overexpression of PTPN13 in Ewing's sarcoma cells boosts cell growth and motility [1]. Furthermore, PTPN13 expression in a variety of tumors provides the cancer cells with a survival mechanism, by inhibiting

Fas-induced apoptosis [51]; and, finally, PTPN13 may be instrumental in tumor cell survival through its interactions with p75NTR, TRPM2 and IκBα, all proteins that modulate cell stress signaling [2].

PTPN13's link to FAS-induced apoptosis appears relevance for glioma biology (Fig. 2). FAS is a death receptor that, upon activation by its ligand, induces caspase cascades leading to cleavage of proteins and apoptosis. PTPN13 attenuates FAS receptor cell surface levels by inhibiting the export of the FAS receptor from intracellular stores to the cell membrane [62]. PTPN13 expression is specifically upregulated in GBM tissues [39] and knockdown of PTPN13 in GBM cell lines indeed results in increased FAS-mediated apoptosis. In addition, PTPN13 directly interacts with and dephosphorylates FAS in a FAS ligand-dependent manner, thereby reducing the ability of glioma cells to undergo FAS-mediated apoptosis [39]. Hence, PTPN13 might play a role in the aforementioned apoptosis resistance that is displayed by gliomas and that complicates their treatment with chemo- and radiotherapy.

DUSP1 (MKP-1)

Dual-specificity MAP kinase phosphatases (MKPs) are capable of dephosphorylating phosphotyrosine as well as phosphothreonine residues of MAP kinases and thus influence important cellular processes such as proliferation, differentiation, apoptosis and survival [115]. MKP-1 (Fig. 3) is induced by growth factors and dephosphorylates the MAP kinases JNK (Jun N-terminal Kinase), p38 and ERK1/2. The apoptosis-inducing effect of the chemotherapeutic drug etoposide in a glioma cell line was shown to be PKCδ-dependent, involving the ubiquitin-mediated degradation of MKP-1 and resulting in increased ERK1/2 phosphorylation [86]. Likewise, MKP-1 levels are decreased when glioma cells are treated with cadmium, another apoptosis-inducing compound that also leads to increased MAP kinase phosphorylation [72]. On the other hand, the inhibitory effect of dexamethasone and rosiglitazone on glioma cell invasiveness rather depends on an increase in MKP-1 levels in glioma cells [63, 84]. Thus, both anti-apoptotic and anti-migratory aspects are to be considered for MKP-1 as a potential target in glioma therapy (Fig. 2).

DUSP26 (VHP)

The gene DUSP26 is expressed in brain and retina. It encodes VHP (Fig. 3), a dual-specificity phosphatase with unclear function. VHP has been implicated in MAP kinase dephosphorylation and in upregulation of cell–cell adhesion [140]. The latter is the result of VHP's ability to dephosphorylate Kap3, a subunit of the KIF3 motor complex that is involved in the transport of cadherin/catenin components from intracellular vesicles to the cell membrane at sites of cell–cell contact. If VHP promotes cell–cell adhesion, a process that is lost in diffusively infiltrating gliomas, one may expect impaired VHP activity in GBM material. Indeed, in eight out of nine cases, a quantitative PCR analysis of mRNA levels showed that DUSP26 transcript levels were decreased in GBM patient samples when compared with normal brain tissue [140]. This may be taken as evidence that VHP is an important regulator of cellular adhesion in glial cells (Fig. 2) and urges for studies involving additional samples and functional read-outs. In anaplastic thyroid cancer samples, however, DUSP26 expression levels were found to be upregulated. The DUSP26 overexpression stimulated the growth of these cells, most likely through the dephosphorylation of p38 and thus inhibition of p38-mediated apoptosis, whereas it had little effect on Erk1/2 MAP kinases [160]. This would rather point to DUSP26 as being an oncogene.

PTP4A3 (PRL-3)

Phosphatase of regenerating liver (PRL) enzymes is unique in the PTP family because of their C-terminal CAAX prenylation motif (Fig. 3). Not much is known about the nature of their substrates [115]. In dividing cells, PRLs are located at the mitotic spindle, but in interphase cells they are membrane associated. It is conceivable that this cell cycle-dependent localization confines PRL access to substrates. Several studies tie PRL members to oncogenic events such as angiogenesis, cell invasion, motility and metastasis [122], and proposed modes of action include stimulation of Src, Rho or PI3K signaling pathways. The PRL-3 protein was found to display a conspicuous expression pattern during gliomagenesis. In normal brain tissue and grade I gliomas, no PRL-3 is detectable, whereas grade II gliomas display low PRL-3 levels. In high-grade glioma tissues strong PRL-3 expression is observed [75]. Interestingly, the PRL-3 levels correlate with that of several matrix metalloproteinases that are instrumental in the proteolytic degradation of the extracellular matrix, suggesting that PRL-3 is associated with glioma invasion (Fig. 2).

CDKN3 (KAP)

KAP was identified as a cell cycle regulating protein because of its ability to dephosphorylate Cdk2, thereby inhibiting G1-S phase progression [48, 53]. KAP also binds two other cell cycle regulators, Cdk3 and cdc2, but it remains to be determined whether these also serve as KAP substrates. It therefore came as a surprise that astrocytomas

display increased CDKN3 messenger levels that correlate well with increasing malignancy grade and decreased patient survival [161]. A closer examination revealed that in primary GBM tissues CDKN3 transcripts are spliced differently, leading to the expression of a dominant-negative KAP variant. Thus, the aberrant splice variant interferes with normal KAP functioning and, as a consequence, increases the Cdk2-dependent proliferation of GBM cells (Fig. 2). The reduction in KAP activity also has a bearing on the migration of glioma cells, but this reflects KAP phosphatase-dependent regulation of cdc2 protein levels and hence cdc2-dependent cell motility [161].

PTEN (PTEN)

The paradigm of PTP involvement in glioma development is PTEN. PTEN is a dual-specificity phosphatase (Fig. 3) and is thus able to dephosphorylate phosphorylated serine, threonine and tyrosine residues in vitro, with a preference for extremely acidic substrates [103]. Germline mutations in PTEN give rise to a whole series of seemingly unrelated syndromes including Cowden disease, an autosomal dominant disorder characterized by multiple hamartomas and predisposition to breast, thyroid and endometrial carcinomas [36]. Intriguingly, it is PTEN's capability to dephosphorylate phosphaditylinositol-3,4,5-triphosphate (PIP_3) [90] (Figs. 1, 2) that appears most relevant in vivo and has turned PTEN into the second-most inactivated tumor suppressor protein in human cancers [70]. Key in this notion was a missense mutation in a Cowden patient, which disrupted the phosholipid phosphatase activity of PTEN but did not affect its protein phosphatase activity [102]. Thus, PTEN counteracts PI3K by preventing the PIP_3-mediated recruitment of the serine/threonine kinase Akt to the cell membrane. As a consequence, Akt will not be activated by a submembranous kinase and will not be able to phosphorylate its many target proteins that stimulate cellular growth, proliferation and survival (Fig. 2).

Ample reports, from its discovery onwards [134], have documented PTEN inactivation, either by mutation (homozygous) deletion or through epigenetic mechanisms, in high-grade gliomas [43]. Mice lacking PTEN expression in astrocytes show an increased proliferation of these cells [41]. In addition, PTEN loss contributes to the angiogenic process featured in high-grade gliomas via upregulation of VEGF transcript levels [113]. Several members of the JNK family show increased levels in PTEN-deficient glioma cells as well, resulting in the simultaneous upregulation of the JNK and PI3K pathway that feed into cellular processes such as proliferation, survival, DNA repair and apoptosis [151]. Intriguingly, in a recent study, the microRNA miR-26a was disclosed as a direct regulator of PTEN expression: it appeared to be frequently amplified in human glioma specimens with monoallelic PTEN loss, and miR-26a-mediated PTEN repression-enhanced tumor formation in a murine glioma model [58]. This epigenetic mechanism for PTEN downregulation in glioma corroborates the Akt signaling pathway as a major Achilles' heel in the development of these tumors (Fig. 2). For further details on PTEN involvement in gliomagenesis, we refer to recent dedicated reviews [22, 35, 76].

CDC25B and CDC25C

The human class III PTP subfamily comprises three CDC25 variants that are all involved in cell cycle regulation [120]. They positively regulate different stages of mitosis, and are often found upregulated in human cancers, where they cause aberrant cell cycle regulation and genetic instability [13]. CDC25B (Fig. 3) has been linked to glioma progression based on its high expression in WHO grades III and IV astrocytomas when compared with the levels in lower grade tumors, and may serve as a prognostic marker in astrocytoma patients [104]. Also, CDC25C may have bearing for glioma biology as revealed by experiments involving the potential anticancer antibiotic ansamycin. Ansamycin inhibits the activation of Hsp90 and thus results in degradation of Hsp90 target proteins and ultimately to cell cycle arrest and apoptosis [57, 71, 95]. Ansamycin treatment of glioma cell lines resulted in the downregulation of CDC25C and Cdc2 levels, both proteins that are involved in G2–M transition [44]. In lung cancer cell lines, a similar effect was observed [126]. CDC25C downregulation, therefore, could explain the ansamycin-induced cell cycle arrest and apoptosis observed in glioma cell lines. Future experiments will have to reveal whether a similar effect on CDC25C can be exploited for glioma treatment in vivo. All three CDC25 proteins have been targets for pharmaceutical drug discovery, but no inhibitors have so far been tested clinically.

PTP signaling significance in glioma biology

The above illustrates that several PTPs are involved in gliomagenesis, whereas the contribution of other PTPs is as yet hypothetical (Table 1; Fig. 2). Especially, the results obtained with permanent glioma cell lines should be interpreted with care, since these model systems only partially represent the molecular and pathological characteristics of glial tumors.

A number of PTPs appear frequently mutated in glioma tumor specimens, providing strong evidence for a causal contribution to gliomagenesis. PTEN is inactivated by mutation, deletion or gene silencing in a large portion of these tumors, and several recent reviews are dedicated to its

involvement in gliomagenesis [3, 22, 35, 76]. Also PTPRD is located in a region that is often deleted in astrocytomas (including GBMs) and oligodendrogliomas, suggestive of an important role for PTPRD in glial cell functioning. PTPRD-deficient mice, however, while presenting neuropathological symptoms [145], do not display increased glial tumor susceptibility. Genomic alterations in glioma samples have also been detected for PTPRJ and PTPN11, but since this concerns single cases it remains uncertain whether these mutations play a role in gliomagenesis or are merely the consequence of genetic instability in these tumors. The precedent of PTPN11 activating mutations in leukemias speaks in favor of SHP-2 as an oncogenic protein in sporadic gliomas. The status of PTPRJ as a cancer susceptibility gene [121] could as yet not be backed by knockout studies; DEP-1-deficient mice did not show an increased tumor incidence, not even in colon [144].

Several PTPs have been linked to gliomagenesis based on the stage-specific changes in their messenger and/or protein expression levels. So far, it remains unclear by which mechanism such PTP level changes are brought about and whether the observed changes are functionally relevant in an in vivo tumor setting. The changes in the availability of crucial transcription factors or in the accessibility of PTP gene regulatory sequences through epigenetic mechanisms may play a role at the transcriptional level, but also factors that impinge on mRNA and/or protein stability may post-transcriptionally modulate PTP levels and favor tumor growth. In line with this, small compounds, such as etoposide, ansamycins and cadmium induce the specific degradation of certain PTPs and result in reduced proliferation and increased apoptosis in glioma cell models. A clinically relevant hallmark of gliomas is their very infiltrative growth pattern. Therefore, PTPs that are known or suspected to be involved in adhesion and migration of cells deserve special attention. Three of the PTP genes that display altered expression levels in the highly malignant GBM subtype have been linked to cellular adhesion: PTPRD, PTPRM and DUSP26 (Table 1). Also, PTPRZ, DUSP1, PTP4A3 and CDKN3, all implicated in the control of cell migration, demonstrate aberrant expression levels in GBM specimens (Table 1). It is tempting to speculate that these alterations contribute to the adhesive and migratory changes of glioma cells (Fig. 2).

Confounding issues in glioma research

So far, the acquired insight into the molecular mechanisms underlying gliomagenesis has not yet resulted in markedly improved treatment modalities for GBM patients. Several reasons may account for this, including the often extensive and diffuse infiltrative growth in the brain parenchyma, the difficult 'druggability' of this tumor type due to the blood–brain barrier (BBB), and the lack of easily accessible and clinically relevant glioma model systems for research purposes. For instance, most glioma cell models do not recapitulate the diffuse infiltrative growth pattern upon introduction in the mouse brain [25, 37, 112]. Furthermore, neither the amplification of EGFR, which is found in approximately 50% of the GBM patients, nor the expression of EGFRvIII is present in most GBM cell lines [10, 105, 109]. The use of short term, primary cultures does not solve the problem because significant genetic alterations have been found after only a small number of passages in glioma cultures [30, 81]. To create research models that better recapitulate GBM features, including diffuse infiltrative growth, xenograft models have been developed through orthotopic (the tissue from which the tumor originated) implantation of (primary) glioma cells into immune-suppressed or immune-deficient mice [5, 25, 40]. A drawback of these xenograft models is that grafts usually lack accurate angiogenesis and that contributions by the immune system cannot be considered [37]. The use of genetically modified animal models that spontaneously develop gliomas, therefore, seems a powerful approach [5, 59] and quite recently the generation of a mouse GBM model in a region- and cell type-specific manner using intracerebral lentiviral transduction was reported [92].

However, even in such powerful models, the BBB, which regulates the composition of the central nervous system interstitial fluid by allowing low-molecular weight and lipid compounds to pass while at the same time restricting access of water-soluble compounds and macromolecules, may well hamper the diffusion of chemotherapeutic agents to glioma cells [98]. Consequently, progress in drug discovery for glioblastoma treatment has been slow. DNA-alkylating agents lomustine and carmustine were first marketed over 30 years ago, while temozolomide is a more recent addition in the same drug class [124, 137]. New insights into glioma's molecular drivers have led to the approval by the FDA, in an accelerated review early 2009, of the use of bevacizumab (avastin) against refractory GBM. In addition, a number of clinical trials are ongoing or planned. Table 2 lists currently approved and experimental drugs for glioblastoma. Their mode of action is rather diverse and given the number of compounds that target PTKs or their downstream effectors one may expect PTP targeting drugs to enter the pipeline in the near future.

The potential therapeutic and diagnostic use of PTP signaling pathways in gliomas

Glioma patients are still facing a very poor prognosis and, in view of the limited durability of surgical and local

Table 2 Approved and experimental drugs for glioblastoma

Drug name	Mode of action	Status	Notes
Lomustine	Alkylating agent	Marketed	
Carmustine	Alkylating agent	Marketed	Also sold as slow-release polymeric wafer system under Gliadel®
Temozolomide	Alkylating agent	Marketed	Prodrug, indicated for newly diagnosed glioblastoma multiforme
Bevacizumab (Avastin)	Anti-VEGF	Approved in 2009	
Nimotuzumab	Anti-EGFR	Phase 3	
TM601	Tumor cell binder, antiangiogenic	Phase 3 planned	Synthetic form of the scorpion venom peptide chlorotoxin; also as radiolabelled formulations
MPC-6827 (Azixa)	Microtubule-destabilizing agent	Phase 2	
CDX-110	EGFRvIII vaccine	Phase 2	
Cotara	131I-radiolabelled mAb conjugate	Phase 2	
XL184	RTK inhibitor	Phase 2	Targets Met, VEGFR2, Kit, Flt-3 and Tie-2
TLN-4601	Peripheral benzodiazepine receptor (PBR) ligand	Phase 2	Inhibitor of the RAS-mitogen-activated protein kinase (MAPK) pathway
CYT997	Vascular targeting agent and tubulin inhibitor	Phase 2	
BSI-201	PARP-1 inhibitor	Phase 2	
Banoxantrone (AQ4 N)	Topoisomerase inhibitor and DNA intercalator	Phase 2	Prodrug, activated by hypoxia
ICT-121	CD133 peptide vaccine	Phase 1	Trial planned 2010
ICT-107	Dendritic cell-based vaccine	Phase 1	Uses patient-derived, specifically primed dendritic cells
MP-470	Multiple TRKi and Rad51 DNA repair inhibitor	Phase 1	

BioWorld® Today (AHC Media LLC), Thomson Pharma® IDdb, Pharmaprojects, Company and NIH websites

Experimental treatments are usually tested in combination with approved therapies

This table shows that more recently developed compounds are targeting specific signaling pathways rather than the general DNA damaging effect of the earlier drugs

irradiation treatments and small number of applicable drugs (Table 2), research efforts aim at the identification of novel targets. PTPs that are linked to glioma development and progression thus represent potential starting points in glioma diagnostic and therapeutic strategies. A prime candidate is of course the PTEN tumor suppressor that is so frequently inactivated in GBM. To overcome this loss of function, the PI3K pathway needs to be suppressed and several inhibitors of PI3K signaling are being evaluated for clinical use. Rapamycin is a widely used drug that inhibits mTOR, a downstream target of AKT [12]. Unfortunately, a recent phase I clinical trial revealed that rapamycin treatment leads to increased AKT phosphorylation in PTEN-deficient GBM patients, probably due to the relief from a negative feedback loop created by mTOR [26]. This indicates that PI3K signaling should be targeted more upstream to become useful in anti-glioma strategies.

Apoptosis resistance of gliomas provides yet another hurdle on the road towards effective therapies against these tumors. Several PTPs have been associated with apoptosis signaling pathways in gliomas (Fig. 2), which potentially makes them therapeutic targets. For instance, the finding that in glioma cell lines the anti-diabetic and anti-inflammatory drug troglitazone activates PTP1B and, as a consequence, downregulates the anti-apoptotic FLIP and Bcl2 proteins [4] urges for a follow-up in in vivo glioma models. Likewise, compounds that specifically inhibit PTPN13, the negative regulator of FAS-mediated apoptosis in glioma cell lines [39], may enhance the sensitivity of glial tumor cells to undergo apoptosis, e.g. following radio- or chemotherapy.

Targeting of gliomas via the blood stream implies successful transfer over the BBB, an obstacle that prevents adequate effect of many agents in diseases of the central nervous system. In the design of small compound inhibitors for glioma-relevant PTPs, one therefore has to take the BBB into account. Likewise, the exploitation of (monoclonal) antibodies, nowadays common agents to fight cancer growth, to specifically target glioma cells in the brain is limited by the BBB [123]. To circumvent this problem, antibodies that for example inhibit EGFR and VEGFR signaling might be injected directly intracerebrally.

A promising start for the application of PTP-directed antibodies in glioma therapies was obtained using a monoclonal antibody against the extracellular domain of the short RPTPζ transmembrane isoform [38]. When coupled to the cytostatin saporin, the antibody killed U87MG glioma cells in vitro and it significantly delayed in vivo tumor growth of a U87MG xenograft. As mentioned before, such cell-based models do not recapitulate all pathobiological features of gliomas and the therapeutic potential of this approach needs further investigation. Irrespective, these results urge for further studies on the use of monoclonal antibodies against receptor-type PTPs as tumor-directed agents in glioma therapies. In addition, in view of the often altered expression levels for several of the PTPs discussed here in GBM specimens when compared with normal glial tissue, the assessment of PTP expression levels in tumor tissue may well serve to refine GBM staging, aid in the design of combinatorial treatment protocols and/or support the monitoring of treatment responses.

Concluding remarks

Ample evidence indicates an important role for PTPs in development and progression of tumors, including gliomas. Alterations in multiple PTP genes and their products have been noted in gliomas. However, careful assessment of their exact functional relevance in glioma biology is needed. Functional studies on PTP signaling in other tumor systems will of course be of value but, in view of the unique growth and dispersion characteristics of gliomas, studies using tumor models that faithfully mimic glioma biology are mandatory. This will ultimately allow a better validation of glioma treatment modalities and enable improvement in the poor prognosis glioma patients still face today.

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