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REVIEW

Opposite Interplay Between the Canonical WNT/β-Catenin Pathway and PPAR Gamma: A Potential Therapeutic Target in Gliomas

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Abstract In gliomas, the canonical Wingless/Int (WNT)/β-catenin pathway is increased while peroxisome proliferator-activated receptor gamma (PPAR-γ) is downregulated. The two systems act in an opposite manner. This review focuses on the interplay between WNT/β-catenin signaling and PPAR-γ and their metabolic implications as potential therapeutic target in gliomas. Activation of the WNT/β-catenin pathway stimulates the transcription of genes involved in proliferation, invasion, nucleotide synthesis, tumor growth, and angiogenesis. Activation of PPAR-γ agonists inhibits various signaling pathways such as the JAK/STAT, WNT/β-catenin, and PI3K/Akt pathways, which reduces tumor growth, cell proliferation, cell invasiveness, and angiogenesis. Nonsteroidal anti-inflammatory drugs, curcumin, antipsychotic drugs, adiponectin, and sulforaphane downregulate the WNT/β-catenin pathway through the upregulation of PPAR-γ and thus appear to provide an interesting therapeutic approach for gliomas. Temozolomide (TMZ) is an antiangiogenic agent. The downstream action of this opposite interplay may explain the TMZ-resistance often reported in gliomas.

Keywords WNT/beta-catenin pathway · PPAR gamma · Glioma · STAT3 pathway · PI3K/Akt pathway · NSAID · Curcumin

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Introduction

Glioma is the most frequent primary brain tumor, and accounts for ∼ 30% of all central nervous system (CNS) tumors. They diffusely infiltrate into the surrounding normal brain tissue [1]. Glial cells contain multipotent tumor stem cells that have the potential to transform into normal neural progenitor cell variants [2, 3]. Gliomas are named according to the origin of the cell type with which they share histological characteristics. In the 2016 World Health Organization (WHO) classification, gliomas are classified into astrocytoma, oligoastrocytoma, oligodendroglioma, and glioblastoma based on histology, and each is further subdivided based on isocitrate dehydrogenase mutation status [4]. They have traditionally been categorized by the WHO grading system into grades I to IV based on their histological aggressiveness features [4]. Grade I and II gliomas are slow-growing and less aggressive whereas grade III and IV gliomas are malignant tumors characterized by a high proliferation rate (grade III) and angiogenic activity (grade IV). Low- and intermediate-grade gliomas (grades II and III) evolve inexorably to anaplastic transformation with a dismal prognosis, but over a very variable period of time. Malignant gliomas, considered to be the most frequent malignant brain tumors [5–7], account for 80% of these tumors [1] and are the most fatal human cancers [8, 9]. Patients with grade IV

glioblastoma present the most aggressive form with a median overall survival of 15 months [10]. Despite considerable improvements in surgical resection and radiotherapy, as well as immune and gene therapy, the prognosis of glioblastoma is still dismal [11]. Thus, it is crucial to probe the underlying molecular mechanisms involved in the development of gliomas.

In numerous tissues, activation of the canonical Wingless/Int (WNT)/β-catenin pathway induces inactivation of peroxisome proliferator-activated receptor gamma (PPAR-γ), while PPAR-γ activation induces inhibition of the canonical WNT/β-catenin pathway [12–17]. In arrhythmogenic right ventricular dysplasia/cardiomyopathy, osteoporosis, bipolar disorder and schizophrenia, and certain neurodegenerative diseases [18] such as Alzheimer's disease [19, 20], the WNT/β-catenin pathway is downregulated while PPAR-γ is upregulated. Conversely, in cancers [21–23], type 2 diabetes [24], and certain neurodegenerative diseases such as amyotrophic lateral sclerosis [25, 26], age-related macular degeneration [27, 28], multiple sclerosis, Huntington's disease, and Friedreich's ataxia, WNT/β-catenin signaling is upregulated while PPAR-γ is downregulated [18].

WNT/β-catenin, a determining factor in the evolution of numerous cancers [29–31], is upregulated in gliomas compared to normal brain, while PPAR-γ is downregulated [32, 33]. Activation of the WNT/β-catenin pathway plays a major role in the evolution of gliomas [34], cell proliferation [35], inhibition of apoptosis [36], and cell invasion [37].

PPAR-γ is expressed at low levels in the CNS and is present in neurons, astrocytes, oligodendrocytes, and microglia [38–41]. In many pathophysiological states, PPAR-γ activation induces inhibition of the WNT/β-catenin pathway [42–44]. The anti-inflammatory properties of PPARγ agonists may partly explain their beneficial therapeutic effects. PPAR-γ agonists diminish activation of the WNT/β-catenin pathway and represent a promising therapeutic target for glioma patients [21]. Several potential treatments for gliomas may operate through this interplay, such as non-steroidal anti-inflammatory drugs (NSAIDs), curcumin (Cur), antipsychotic drugs, adiponectin, sulforaphane (SFN), and basic leucine zipper ATF-like transcription factor 2 (BATF2).

The opposite interplay between the WNT/β-catenin pathway and PPAR-γ and its interactions with potential treatments in gliomas are reviewed here.

The Canonical WNT/β-Catenin Pathway

The WNT pathway has been implicated in numerous processes such as embryogenesis and the maintenance of neuronal homeostasis in adulthood [45–48]. Carcinogenesis involves the dysregulation of this pathway [35–37].

The WNT ligands are lipid-modified glycoproteins [49] secreted by both neurons and immune cells in the CNS [50]. They stimulate intracellular WNT signaling. In the presence of one of the 19 members of the WNT family [51], frizzled (FZD) and low-density lipoprotein-related receptors 5 and 6 (LRP5/6) receptors are activated. Then, the complex binds disheveled (DSH) and AXIN and inhibits glycogen synthase kinase 3 beta (GSK-3β) activity. β-catenin accumulates in the cytosol and then is translocated to the nucleus for binding to T-cell factor/lymphoid enhancer factor (TCF/LEF). This leads to the transcription of WNT-target genes, such as cyclin D1, c-Myc, PDK1 (pyruvate dehydrogenase kinase 1), and MCT-1 (monocarboxylate lactate transporter-1).

However, β-catenin is phosphorylated by GSK-3β in the absence of WNT ligands. β-catenin complexes with the GSK-3β/APC (adenomatous polyposis coli)/AXIN destruction complex and then is degraded by the proteasome.

Dikkopf-1 (DKK1) is an antagonist of WNT signaling [52]; it binds to LRP5/6 co-receptors and inhibits WNT signaling [53]. The β-catenin/TCF complex regulates DKK1 transcription *via* a negative feedback loop [54].

Secreted FZD-related proteins (SFRPs), a family of five glycoproteins, and WNT inhibitor protein (WIF) inhibit the WNT pathway upstream [53]. WIF acts as a WNT antagonist and tumor suppressor [17]. SFRPs and WIF-1 play major roles in development and tissue homeostasis. Their expression is downregulated in cancers [55].

GSK-3β is a major regulator of the WNT pathway [56]. It is a neuron-specific intracellular serine-threonine kinase which regulates several processes such as inflammation, neuronal polarity, and cell membrane signaling [57–59]; it inhibits the cytosolic stabilization and nuclear migration of β-catenin; and it is an inhibitor of the WNT/β-catenin pathway. Its dysregulation has been reported in several pathological disorders, including tumorigenesis [59]. The phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) pathway regulates the expression of GSK-3β [60].

Peroxisome Proliferator-Activated Receptor Gamma

The ligand-activated transcriptional factor PPAR-γ belongs to the nuclear hormone receptor superfamily. It is expressed in different cell types, including adipose tissue,

muscle, brain, and immune cells; it activates the expression of many genes and regulates glucose homeostasis, insulin sensitivity, lipid metabolism, immune responses, cell fate, and inflammation [13, 32]; and it is abundantly expressed in adipose tissue and at lower levels in heart, skeletal muscle, and liver [61]. PPAR-γ is expressed at a low level in the CNS in neurons, astrocytes, oligodendrocytes, and microglia [62]; its expression is mainly localized in the microglia and astrocytes; and it plays a major role in the inflammatory response [63]. The PPAR-γ agonists, thiazolidinediones (TZDs), improve insulin sensitivity in peripheral tissues [64] and ameliorate glucose tolerance in type 2 diabetes [65], as well as acting on the promoters of the glucose transporter and glucokinase in pancreatic β-cells and the liver. PPAR-γ also plays an important role in regulating cardiovascular rhythms by controlling circadian variations of blood pressure and heart rate through Bmal1 [66, 67]. PPAR-γ modulates the expression of several genes involved in inflammation, and regulates the activity of inflammation-related transcription factors such as nuclear factor-kappa B (NFκB) [68].

Interplay Between the Canonical WNT/β-Catenin Pathway and PPAR-γ

Several studies have shown a direct interaction between PPAR-γ and β-catenin [43, 69, 70]. The TZD agonists of PPAR-γ (troglitazone, thiazolidinedione, rosiglitazone, or pioglitazone) downregulate β-catenin transcription. This transcription is induced by β-catenin in a PPAR-γ-dependent manner [43, 44, 71]. The β-catenin inhibition by PPAR-γ agonists occurs at the post-transcriptional level. The functional interaction between PPAR-γ and β-catenin involves the binding domain of the TCF/LEF factors of β-catenin. Likewise, this interaction involves a binding domain of β-catenin in PPAR-γ [42]. Many studies have described the antagonism between PPAR-γ signaling and the β-catenin pathway in several tissues [44, 71]. Similarly, PPAR-γ inhibits the WNT/β-catenin pathway [44] and osteoblastogenesis but induces adipogenesis [72].

Inhibition of the WNT/β-catenin pathway increases PPAR-γ transcription. Overexpression of AXIN inhibits WNT signaling in pre-adipocytes and the cells differentiate into adipocytes. PPAR-γ with the canonical WNT/β-catenin pathway regulates the molecular switching between osteoblastogenesis and adipogenesis. PPAR-γ agonists appear to be potential therapeutic candidates during the fibrosis process by inhibiting the WNT/β-catenin pathway [73–75].

Arrhythmogenic right ventricular cardiomyopathy shows activation of PPAR-γ and inhibition of the WNT/β-catenin pathway [69, 76]. In transgenic mice, inhibition of the canonical WNT/β-catenin pathway by plakoglobin or γ-catenin induces the cardiomyopathy phenotype. This causes fat accumulation in cardiomyocytes and ventricular arrhythmias [69]. Plakoglobin (or γ-catenin) has similarities to β-catenin [36]; it competes with β-catenin leading to inhibition of the transcription factors TCF/LEF [77–79]. Thus, the removal of TCF/LEF1 factors induces adipogenesis and stimulates the phenotype of this human cardiomyopathy [69, 76, 80].

The Canonical WNT/β-Catenin Pathway in Gliomas

Hyper-activation of the canonical WNT/β-catenin pathway is associated with glioma development and malignant progression [81–83], invasion [84], prognosis [85], inhibition of cell differentiation, and an invasive phenotype [33, 86] (Fig. 1).

The expression of WNT1 is higher in gliomas than in normal brain, and its overexpression is considered to be an independent prognostic factor for glioma patients [82]. Overexpression of WNT1 and WNT3a in glioma stem cells (GSCs) has been shown in the malignant transformation and progression of high-grade gliomas [87, 88].

WNT3a and the cytosolic/nuclear β-catenin ratio are associated with a worse prognosis in malignant gliomas [81, 89]. WNT2 and WNT5 are also overexpressed in gliomas. The knockdown of WNT2 by siRNA in human U251 glioma cells inhibits proliferation and invasion, and induces apoptosis [89, 90].

Moreover, the expression of β-catenin is positively correlated with the progression of gliomas [82, 83, 85, 90, 91] and is considered to be a prognostic marker for malignancy [82, 83]. The nuclear accumulation of β-catenin is responsible for the malignant progression, and its protein levels are correlated with malignancy and the expression of the Cyclin D1 and c-Myc genes [26, 83, 92].

The WNT/β-catenin pathway induces the transcription of genes implicated in cell proliferation, c-Myc (through glutaminolysis, nucleotide synthesis, and LDH-A activation) and Cyclin D (through G1) [93–96]. Indeed, the transcription of WNT-target genes is preceded by the cytosolic accumulation and nuclear translocation of β-catenin [81, 84]. The WNT target gene c-Myc drives glutaminolysis [94, 97] and induces glutamine uptake into the cell and mitochondria to promote the synthesis of aspartate [96]. Both c-Myc and HIF-1α (hypoxia-inducible factor-1 alpha) stimulate PDK1 and LDH-A [98]. PDK1, a key regulator of glycolysis by phosphorylating the pyruvate dehydrogenase (PDH) complex, inhibits the conversion of pyruvate into acetyl-CoA in mitochondria, and then LDH-

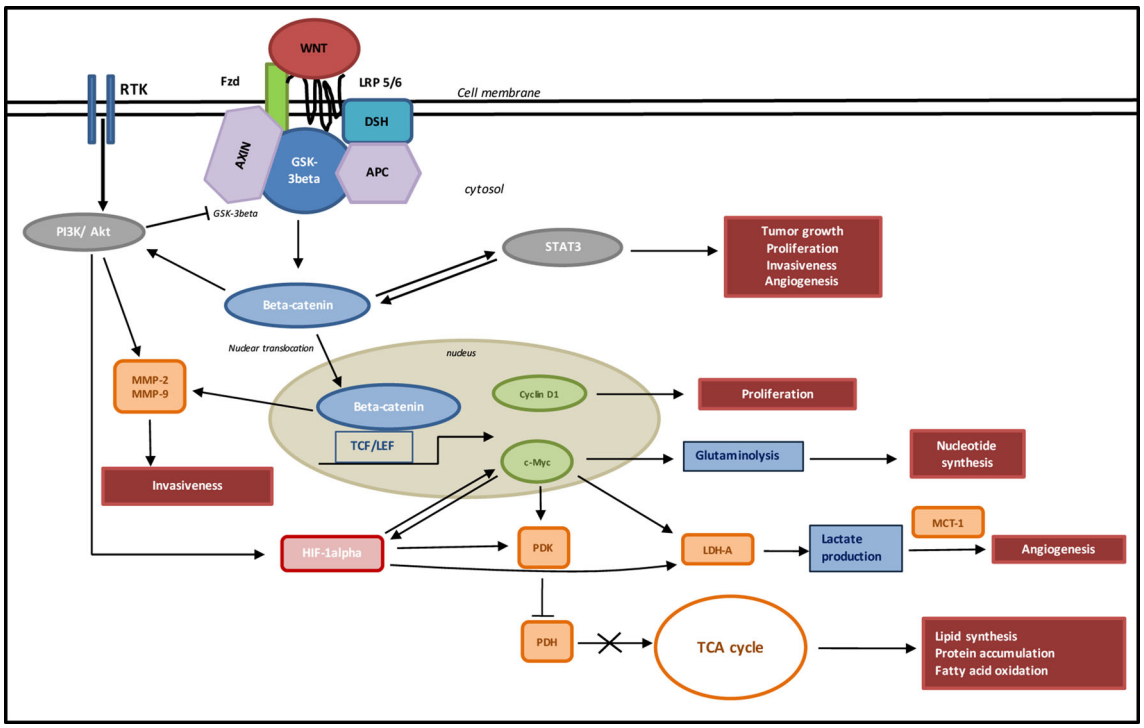

Fig. 1 Role of WNT/beta-catenin signaling in gliomas. When the canonical WNT/β-catenin pathway is upregulated, binding of WNT to FZD leads to activation of DSH, which recruits the destruction complex to the plasma membrane. AXIN binds to the cytoplasmic tail of LRP5/6. WNT also binds LRP5/6. This initiates LRP phosphorylation and DSH-mediated FZD internalization. Activation of DSH leads to the inhibition of GSK-3β, which further reduces the phosphorylation and degradation of β-catenin. The β-catenin degradation complex AXIN/APC/GSK-3β is inactivated with the recruitment of AXIN to the plasma membrane. β-catenin phosphorylation is inhibited. Then, β-catenin accumulates into cytosol and translocates to the nucleus to bind the TCF–LEF co-transcription factors. This induces the canonical WNT-response gene transcription (c-Myc, cyclin D, PDK1, and MCT-1). The STAT3 signaling pathway upregulates the expression and transcriptional activity of β-catenin; in gliomas STAT3 is a tumor aggressiveness factor. In gliomas, overexpression of EGFR (a receptor tyrosine kinase: RTK) stimulates the PI3K/Akt pathway. PI3K/Akt signaling leads to the phosphorylation of GSK3β that leads to the nuclear translocation and stabilization of β-catenin. In the same way, the WNT/β-catenin pathway stimulates EGFR in gliomas. Akt signaling increases MMP-2 and MMP-9 activity, which induces the invasion of malignant cells into healthy brain near the glioma. Akt signaling induces HIF-1α (hypoxia-inducible factor-1 alpha), which stimulates PDK1. Overexpression of WNT/β-catenin also stimulates PDK1. PDK1 and Myc induce lactate dehydrogenase A (LDH-A), and cytosolic pyruvate is shunted into lactate through activation of LDH-A. Overexpression of MCT-1 exports lactate to the extracellular space. Lactate production activates angiogenesis. c-Myc-induced glutaminolysis supports mitochondrial integrity and the production of aspartate, and results in nucleotide biosynthesis. c-Myc and cyclin D stimulate the proliferation of gliomas.

A converts the pyruvate into lactate in cancer cells [99]. PDH is considered to be a potential mediator to reduce glioblastoma growth [100]. Activation of PDK1 induces angiogenesis [101, 102] and promotes neovascularization [103]. Angiogenesis is also induced by lactate produced through the activation of LDH-A [104]. Furthermore, high-grade gliomas have high rates of glycolysis and lactate production correlated with a high level of MCT-1 expression [105].

The nuclear translocation of β-catenin regulates the expression of matrix metalloproteinases (MMPs) [33, 106]. Many studies have reported the overexpression of MMPs in cancer cells, including glioma cells [107]. MMP-2 and MMP-9 induce the invasion of malignant cells into healthy brain near the glioma and their expression is positively correlated with tumor progression [108].

In contrast to other cancers, studies have shown no mutation at GSK-3β phosphorylation sites [109, 110], and truncation of APC has not been associated with gliomagenesis [41]. These reports suggest that unbalanced ligand/antagonist expression may deregulate the different pathways involved in tumor progression. Indeed, WNT antagonists appear to be repressed in glioblastomas [33]. Tumor suppressor WIF-1 expression decreases with malignancy in astrocytomas [41]. Primary *de novo* glioblastomas are associated with hypermethylation of the FZD-related protein (SFRP) promoters whereas secondary glioblastomas present hypermethylation of the promoter of the LRP antagonist DKK1 [109]. As regards glioma progression, hypermethylation of WNT pathway inhibitor genes, like SFRP and DKK1 in malignant astrocytic gliomas [109] and WIF-1 in glioblastomas, has been reported [38, 111].

PPAR-γ in Gliomas

PPARs control gene expression involved in adipogenesis, lipid metabolism, inflammation and metabolic homeostasis [112]; they have been found in developing and adult brain tissues [113]. Activation of the PPAR pathway plays a role in determining the viability of neurons in the developing midbrain [114]. PPAR-γ expression has been described in many cancers including colon, lung, bladder, breast, duodenum, and thyroid [115–121]. In gliomas, the cell-cycle is stopped in G0/G1 phase [122–124], and the proportion of cells entering S-phase is reduced by PPAR-γ agonists [123, 124]. Likewise, decreased c-Myc levels and Cyclin D1 have been detected upstream of the S-phase transition when PPAR-γ agonists are used [124, 125].

In gliomas, PPAR-γ agonists reduce local tissue invasiveness [125–127]. MMP-2 and MMP-9 expression is correlated with tumor progression [108]; they are down-regulated after treatment with pioglitazone [125–127]. Pioglitazone, a PPAR-γ agonist, reduces β-catenin expression without changing its cellular localization [125, 128]. Reducing β-catenin expression could contribute to inhibiting the evolution of gliomas from a low to a high grade. High-grade gliomas show over-expression of β-catenin compared to low grade gliomas [129].

PPAR-γ agonists induce apoptosis by reducing cellular viability. This effect is mediated by a BAX (BCL2-associated X protein)-dependent pathway. BAX is upregulated after activation of PPAR-γ [123, 125–128, 130, 131]. Treatment with TZDs leads to apoptosis of glioma cells in a concentration-dependent fashion associated with cell-cycle arrest, while sparing normal primary astrocytes [122, 123, 125–128, 130, 131]. PPAR-γ agonists downregulate SOX2 (SRY-Box 2) [132]. SOX2, a stemness gene, maintains pluripotency in stem cells and inhibits neural differentiation while it is overexpressed in brain tumor-initiating cells. PPAR-γ agonists also increase the expression of N-cadherin, a neural differentiation marker [131]. Activation of the PPAR-γ pathway can regulate the differentiation of neural stem cells [133, 134].

Catalase is involved in the inhibition of reactive oxygen species (ROS) and possesses a PPAR genomic binding site [135]. The anti-cytotoxic effects of PPAR-γ agonists are partially mediated by enhanced redox reactions in glioma cells [135]. Activation of PPAR-γ transcription upregulates catalase activity in normal astrocytes and rat cell models. But this upregulation is not found in the C6 glioma cell line. This is abolished in cells transfected with a dominant-negative PPAR-γ construct [135].

Interactions Between β-Catenin Signaling and PPAR-γ Agonists Through STAT3 Signaling in Gliomas

Signal transducer and activator of transcription 3 (STAT3) stimulation has been implicated in many cancers, such as breast cancers, acute leukemia, colon cancers, and gliomas. The STAT3 pathway is involved in the regulation of proliferation [136], tumor growth, invasiveness, migration [137], and angiogenesis [138]. High levels of STAT3 signaling have been found in brain tumor-initiating cells [139]. In gliomas, STAT3 is a transcriptional factor necessary for mesenchymal transformation and tumor aggressiveness [140].

The biologically active phosphorylated STAT3 is mediated by EGFR and cytokine receptor in gliomas [141]. Phosphorylated STAT3 is regulated through multiple WNT/β-catenin-induced signaling pathways, such as (1) JAK/STAT signaling induced by EGFRs that bind to epidermal growth factors and by the stimulation of cytokine receptors that bind to the ligands interleukin (IL)-6, leukemia inhibitory factor, and EGF [142], (2) EGFR/PI3K/Akt/mTOR (mammalian target of rapamycin) signaling, and (3) WNT/β-catenin target gene transduction c-Myc *via* HIF-1α stabilization [22]. WNT/β-catenin-induced STAT3 signaling activates transcription of the target genes Bcl-2, Bcl-xl, and ki-67 [143], and *via* HIF-1α activation, the WNT/β-catenin target genes cyclin D1 and c-Myc in a positive feedback loop [22].

Inhibition of STAT3 arrests glioma cell growth, invasion, migration, differentiation, and cell cycle progression [144–146]. Several studies have shown that PPAR-γ agonists induce growth arrest and apoptosis in glioblastoma cells in culture without affecting primary astrocytes, and inhibit expansion and proliferation of $CD133^+$ GSCs by inhibition of the EGF-induced JAK/STAT pathway [122, 147]. Troglitazone, a TZD PPAR-γ agonist, is considered to be an antagonist of STAT3 signaling [148]. In glioma cells, PPAR-γ agonists inhibit STAT3 signaling through the reduction of phosphotyrosine 705 STAT3 [149]. Inhibition of STAT3 proteins by PPAR-γ agonists underlies the inhibition of upstream tyrosine kinase 2 or its direct effect on STAT3 protein [119], or the activation of negative regulators, such as suppressor of cytokine signaling or SHP-1 proteins in GSCs [150].

PPAR-γ agonists can act on the WNT/β-catenin pathway by inhibiting STAT3 signaling (Fig. 2). Indeed, inhibition of STAT3 downregulates several critical signaling pathways in malignant glioma cells, including the PI3K/Akt and WNT/β-catenin pathways, as well as the transcription of RTKs [144], and results in downregulation of the expression of the WNT-target genes cyclin D1 and

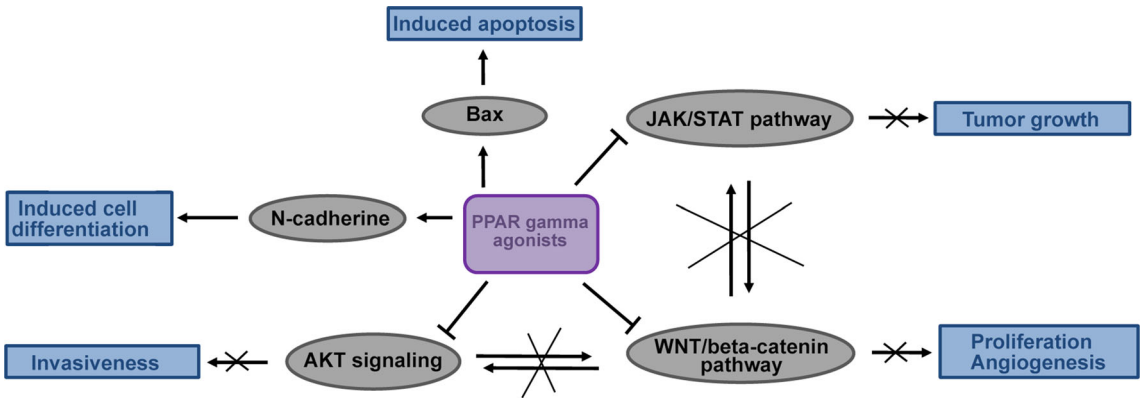

Fig. 2 Potential effects of PPAR gamma agonists in gliomas: inhibition of the JAK/STAT pathway, then reduced tumor growth; inhibition of the WNT/β-catenin pathway, then proliferation and angiogenesis; inhibition of Akt signaling, then reduced invasiveness; activation of N-cadherin, then cell differentiation; activation of BAX, then apoptosis. Activation of PPAR-γ agonists may play major negative roles in regulating the progression and proliferation of gliomas.

c-Myc, leading to the death of glioma cells [149]. Furthermore, the downregulation of β-catenin signaling in malignant gliomas is associated with a decrease of phosphorylated Akt and STAT3 levels [152], supporting the idea that the β-catenin/TCF4 (transcription factor 4) complex directly binds to the STAT3 gene promoter [151]. The STAT3 pathway is regulated by a plausible opposite interplay between PPAR-γ agonists and the WNT/β-catenin pathway.

Interactions Between β-Catenin Signaling and PPAR-γ Agonists Through EGFR/PI3K/Akt Signaling in Gliomas

The WNT/β-catenin pathway stimulates the activation of RTKs in gliomas [22]. Overexpression of EGFRs occurs in 30%–70% of primary glioblastomas [153]. EGFRs are the most common RTKs aberrantly overexpressed in glioblastomas involving EGFR gene amplification [154] and are major key regulators of the migration, differentiation, apoptosis, proliferation, and survival of glioblastoma cells by binding PI3K/Akt [155–158].

The actions of the PI3K/Akt pathway are multiple in cancer cells with increasing cell proliferation, cell survival and cell migration [159–161]. Moreover, Akt signaling increases MMP-2 and MMP-9 activity in cancer cells and then participates in the invasiveness [60].

The NF-κB proteins, a ubiquitous transcription factor family that mediates immune and inflammatory responses, are also activated by overexpressed EGF, and/or its mutationally-activated EGFR in gliomas, *via* numerous dysregulated signaling pathways, such as the PI3K/Akt, mTORC2, and IKK (IκB kinase) pathways [162–164]. Allelic loss of PTEN (phosphatase and tensin homolog protein), a tumor suppressor that negatively regulates PI3K activity and inhibits Akt signaling, occurs in many gliomas, and the lack of PTEN expression enables Akt to remain active and activate NF-κB [163, 164]. NF-κB activation subsequently induces the expression of NF-kB target genes promoting proliferation, tumor growth, and cell survival by anti-apoptotic responses [163, 164]. The increase of NF-κB activity in glioblastoma is correlated with the astrocytic tumor grade [164]. Peptidyl-prolyl-isomerase 1 (Pin1) enhances NF-κB signaling while the inhibitor of growth protein 4 (ING4) inhibits NF-κB activity [163, 164]. The protein kinase CK2 (casein kinase 2) positively regulates both the STAT3 and NF-κB signaling pathways [163]. STAT3 signaling is activated by NF-κB-driven IL-6 cytokines [163]. CK2 activates STAT3 signaling through activation of the JAK/STAT, Akt/mTORC, and Akt/EZH2 (a methyltransferase) signaling pathways [163]. CK2 activates NF-κB signaling directly *via* p65, and by activating the Akt/mTORC and IKK signaling pathways, and the inhibition of IκB [163]. MAPK (mitogen-activated protein kinase) signaling positively regulates both NF-κB and STAT3 signaling [163].

PI3K/Akt pathway signaling induces the activation of HIF-1α and protects against ROS, which activate PDK1 and then inhibit PDH [165]. Inhibition of PDH results in shunting of the TCA cycle and the conversion of pyruvate into lactate by activated LDH-A, leading to angiogenesis and aggressiveness [166].

The EGFR/PI3K/Akt pathway activates Pin1 that induces the isomerization of phosphorylated PKM2 (pyruvate kinase M2) [158], and facilitates the nuclear translocation of acetylated PKM2, which reduces its activity and targets PKM2 towards lysosome-dependent degradation [167]. Acetylated PKM2 participates in cell growth in gliomas by promoting glucose metabolism [168]. Nuclear PKM2 binds nuclear β-catenin that activates the c-Myc-mediated expression of glycolytic enzymes, such as the

glucose transporter, LDH-A, PDK1, and PKM2 in a positive feedback loop [169]. Activated PKM2 directly stimulates growth factor receptors to promote cell division and tumor growth [170, 171].

The WNT/β-catenin pathway stimulates EGFR in gliomas [153]. Moreover, in glioma cells the inhibition of β-catenin signaling reduces stimulation of the β-catenin-induced EGFR/PI3K/Akt pathway [152]. Likewise, activation of the PI3K/Akt pathway directly stimulates β-catenin signaling [160] by inhibiting the activity of GSK-3β [60]. Furthermore, inhibition of the PI3K/Akt pathway by the PI3K inhibitor LY294002 decreases β-catenin/TCF activity in glioma cells [172]. Treatment with indomethacin-loaded lipid-core nanocapsules activates GSK-3β expression by inhibiting Akt signaling and then leads to decreased β-catenin levels in C6 glioma cells [173]. A positive interplay between the WNT/β-catenin pathway and PI3K/Akt signaling has been reported in gliomas [174].

Few studies have demonstrated the antagonistic role of PPAR-γ on the EGFR and PI3K/Akt pathways in glioma cells. However, ciglitazone, a TZD PPAR-γ agonist, induces apoptosis by downregulation of Akt activity, inducing mitochondrial membrane potential collapse [175] (Fig. 2). This leads to a plausible opposite interplay between PPAR-γ agonists and the WNT/β-catenin pathway through the EGFR/PI3K/Akt signaling. Moreover, in glioma cells, PPAR-γ activation increases the expression of PTEN, enabling Akt to remain inactive while decreasing the expression of cyclooxygenases-2 (COX-2), leading to lower the COX-2-induced conversion of arachidonic acid into prostaglandin E2 (PGE2), suggesting that PTEN likely acts as a negative regulator to COX-2 expression. [176]. COX-2 protein is overexpressed in all glioma types whereas normal glial cells do not express it. Increasing levels of COX-2 expression and prostaglandin E2 are associated with cell proliferation, invasion, and angiogenesis, and apoptosis inhibition, and the COX-2 expression level is positively correlated with glioma grade [177]. Furthermore, an aberrant positive feedback interaction between the COX-2/PGE2 and WNT pathways stimulates the self-renewal and proliferation of GSCs [178]. WNT signaling underlies GSC identity directly through COX-independent WNT signaling, and indirectly through COX/PGE2-dependent WNT signaling [178].

The Opposite Interplay Between the WNT/β-Catenin Pathway and PPAR-γ: A Potential Therapeutic Target in Gliomas

A Therapeutic Target for Non-steroidal Anti-inflammatory Drugs

NSAIDs reduce nuclear β-catenin levels and induce its degradation [179]. NSAIDs such as sulindac, exisulind, and celecoxib decrease β-catenin levels and then inhibit the transcriptional activity of the β-catenin/TCF/LEF complex [180]. Aspirin inhibits glioma cell proliferation and invasion by decreasing β-catenin/TCF transcription [181], arrests the glioma cell-cycle at G0/G1 and decreases invasion and tumor growth by reducing β-catenin/TCF activity [129, 181]. Moreover, NSAIDs inhibit the invasion of glioma cells *in vitro* by dephosphorylating Akt signaling and decreasing MMP-2 gene expression [60, 182].

NSAIDs inhibit COX-2 [183]. NSAIDs such as the COX-2 selective inhibitors potentiate the effects of TMZ by acting as PPAR-γ agonists in high-grade gliomas [184]. However, NSAIDs may have COX-independent anti-carcinogenic effects through the involvement of PPAR-γ [185, 186]. Indeed, NSAID effects are mediated by PPAR-γ [187, 188], and prostaglandins or their metabolites may be ligands of PPAR-γ [189].

NSAIDs may act as PPAR-γ agonists while inhibiting the WNT/β-catenin pathway, highlighting the crosstalk between these two pathways (Fig. 3).

A Therapeutic Target for Curcumin

Cur, a diferuloylmethane derivative, is a polyphenol derived from a turmeric orange pigment. It is highly lipophilic, poorly hydrophilic, and stable at acidic pH [190]; it has many effects on tumor cells, such as anti-inflammatory, antioxidant, pro- and anti-apoptotic, anti-angiogenic, cytotoxic, and autophagic actions; and is an effective inhibitor of proliferation, migration, invasion, and viability by inducing apoptosis or autophagy of glioma cells [191–194]. Cur acts on numerous signaling pathways in glioma cells by downregulating proliferative and survival signaling pathways such as PI3K/Akt, NFκB, COX-2, STAT-3, c-Myc, Cyclin D1, Bcl-2, Bcl-xL, and Ki, downregulating invasiveness and angiogenesis signaling pathways such as MMPs and MAPK, and upregulating apoptosis or cell-cycle arrest signaling pathways such as ING4, p53, p21, Bax, and caspases [191–194] (Fig. 3).

Cur interacts with several signaling pathways including STAT3 and PPAR-γ [195, 196].

Cur administration decreases activity of the STAT3 pathway and leads to attenuated glioma growth [197]. The

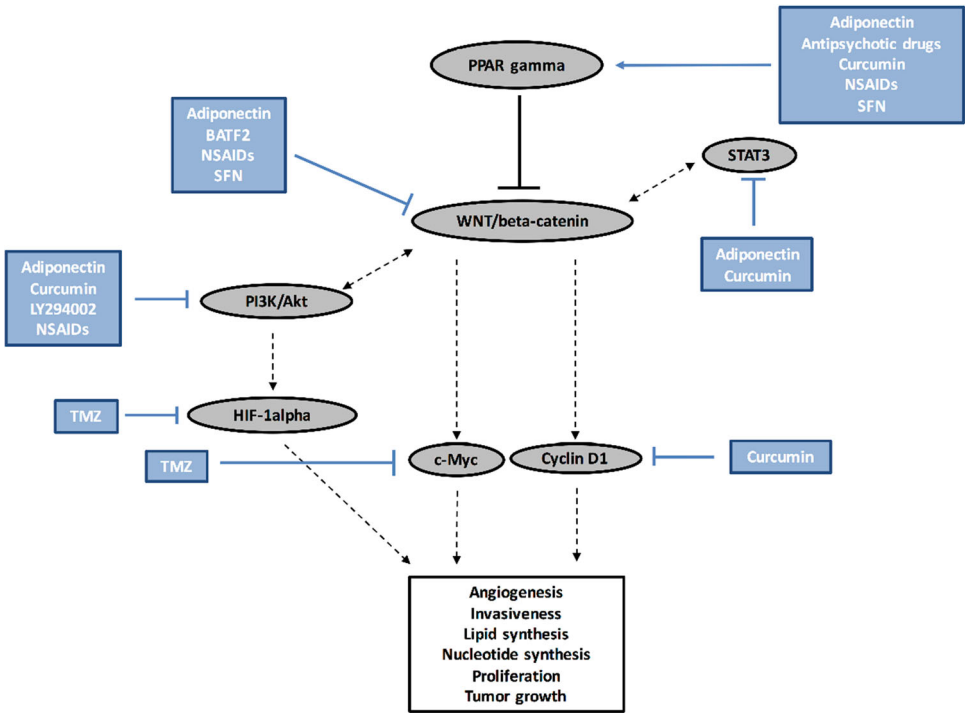

Fig. 3 Different actions and interactions of potential treatments for gliomas with the opposite interplay between the WNT/beta-catenin pathway and PPAR gamma.

mechanism by which Cur activates PPAR-γ is not yet fully understood, but Cur can be considered a ligand of PPAR-γ and may directly bind PPAR-γ receptors [198]. Through the activation of PPAR-γ, Cur can repress both EGFR activation and cyclin D1 expression, a WNT target gene, to inhibit tumor growth [199].

Moreover, Cur treatment increases the mRNA level of GSK-3β in DAOY medulloblastoma cells and suppresses the WNT/β-catenin signaling pathway [200]. Autophagy in glioma cells is induced by Cur by inhibiting the PI3K/Akt/mTOR pathway [201]. By inhibiting the WNT/β-catenin pathway, Cur decreases cyclin D1 expression and then participates in the repression of the development and proliferation of gliomas [200].

Cur, a ligand of PPAR-γ, may act directly on the WNT/β-catenin pathway or indirectly on EGFR signaling and the STAT3 pathway to reduce glioma progression (Fig. 3).

A Therapeutic Target for Antipsychotic Drugs

Several antipsychotic drugs such as olanzapine, chlorpromazine, quetiapine, and risperidone have inhibitory effects on cancers [202]. These drugs downregulate β-catenin signaling and modulate Ca^{2+} homeostasis in the CNS [203]. Olanzapine, a D2/5-HT2 antagonist, inhibits the WNT/β-catenin pathway in gliomas [204]. In glioma cells, quetiapine acts as a PPAR-γ agonist and directly inhibits the WNT/β-catenin pathway [205] (Fig.3).

A Therapeutic Target for Adiponectin

Adiponectin is a pleiotropic cytokine produced by adipocytes [206]; it regulates several processes, such as glucose metabolism, lipid catabolism, insulin sensitivity, energy metabolism, and mitochondrial function [207]. In several cancers, adiponectin administration downregulates cell proliferation, cell invasion, and angiogenesis [208–210]. Low levels of adiponectin are correlated with the progression and development of malignancies [211]. Adiponectin administration inhibits the WNT/β-catenin pathway by interacting with the WNT co-activators LRP5/6. This inhibition occurs at the level of LRP6 phosphorylation and then inhibits β-catenin accumulation and the activation of target genes in a dose-dependent manner [212]. Adiponectin also decreases activity of the PI3K/Akt pathway and then attenuates the cell proliferation and development of gliomas [213] (Fig. 3).

However, adiponectin activates nuclear receptors of PPAR-γ [214], and also inhibits STAT3 signaling [215] in several diseases including cancers. In gliomas, the inhibition of both the WNT/β-catenin and PI3K/Akt pathways by adiponectin administration and the role of adiponectin as a PPAR-γ ligand in several diseases, including cancers, appear to be an interesting therapeutic target.

Temozolomide in Gliomas

TMZ is a 3-methyl derivative of mitozolomide. Survival benefits of TMZ associated with low toxicity have been

reported [216]. TMZ is considered to be the first-line anticancer drug in glioma treatment [217]; it decreases HIF-1α and c-Myc expression during the hypoxic state in gliomas [218, 219] and then impairs VEGF (vascular endothelial growth factor) secretion [220].

However, TMZ-resistance is often found in gliomas with poor responses and has a dismal prognosis [221]; GSCs appear to be insensitive to chemotherapy with TMZ [222]. GSCs show overexpression of miR-125b [223] correlated with an aberrant WNT/β-catenin pathway [224]. TMZ has no effects on the WNT/β-catenin and PI3K/Akt pathways in GSCs, two upstream pathways of HIF-1α and c-Myc [222]. STAT3 signaling is involved in the resistance to TMZ [225]. However, the association of TMZ with LY294002, a PI3K inhibitor, decreases GSC proliferation and invasion [222, 226]. The cytotoxicity of TMZ induced by inhibition of PGE2 affords only a modest survival advantage and fails to prevent glioma progression because of COX-independent WNT activation [178]. Resistance to TMZ may be explained by targeting downstream targets of the WNT/β-catenin pathway, and the combination of inhibitors of WNT and/or PI3K, such as PPAR-γ agonists, with TMZ may enhance its effects (Fig. 3).

A Therapeutic Target for Sulforaphane

SFN (1-isothiocyanate-4-methylsulfinylbutane), a member of the isothiocyanate family, is naturally found in vegetables [227, 228]. It attenuates energy metabolism, apoptosis, and enzyme detoxification in cancers [229].

In gliomas, SFN inhibits miR-21 (micro-ARN 21) expression by downregulating the WNT/β-catenin/TCF4 pathway, reducing the proliferation and migration of glioma cells [230]. Moreover, by inhibiting miR-21 expression, it potentiates the apoptotic effects of TMZ in gliomas [230]. SFN also stimulates BAX signaling and inhibits Bcl-2 and caspase activity to induce apoptosis in glioma cells [230].

In tumor cells, SFN administration also increases the expression of PPAR-γ co-activator-1α (PGC-1α) to decrease HIF-1α expression, and then attenuates tumor development [231]. By inhibiting the WNT/β-catenin pathway in gliomas and acting as an activator of PGC-1α, SFN could be a potential therapeutic approach to overcome TMZ resistance in glioblastoma treatment (Fig. 3).

A Therapeutic Target for BATF2

Basic leucine zipper ATF-like transcription factor 2 (BATF2) is considered to be a new tumor suppressor of growth and migration in glioblastoma cells by suppressing the WNT/β-catenin pathway [222]. BATF2 also inhibits angiogenesis by reducing VEGF expression, which is stimulated by both the WNT/β-catenin and PI3K/Akt pathways [232]. Currently, the interactions of BATF2 with PPAR-γ have not yet been studied but its anti-inflammatory actions [233] and its role as a WNT/β-catenin pathway inhibitor in gliomas [222] could suggest several interactions with PPAR-γ (Fig. 3).

Conclusions

Gliomas inexorably evolve into anaplastic transformation with an extremely poor prognosis in an unpredictable period. In gliomas, the canonical WNT/β-catenin pathway and PPAR-γ act in an opposite manner. The WNT/β-catenin pathway activation *via* the direct activation of the WNT target genes c-Myc and Cyclin D1 involved in glioma development, stimulates the glycolytic enzymes PDK1, c-Myc, LDH-A, and lactate production, promoting angiogenesis, aggressiveness, and a poor prognosis. The activation of PPAR-γ agonists inhibits various signaling pathways such as the STAT3 and PI3K/Akt pathways, which downregulate the WNT/β-catenin pathway, leading to decreased proliferation, invasiveness, and angiogenesis. Moreover, PPAR-γ agonists also induce the activation of N-cadherin and BAX, leading to cell differentiation and apoptosis, respectively. Activation of PPAR-γ agonists may play a major role in regulating the progression and proliferation of glioma. NSAIDs, Cur, antipsychotic drugs, adiponectin, and SFN downregulate the WNT/β-catenin pathway through the plausible upregulation of PPAR-γ. TMZ, an antiangiogenic treatment, by targeting the downstream crosstalk between the WNT/β-catenin and PPAR-γ pathways may explain the resistance to TMZ. BATF2, a novel tumor suppressor, downregulates WNT/β-catenin and inflammation but its possible effect as a PPAR-γ agonist has not yet been demonstrated and deserves future clinical studies. In gliomas, the crosstalk between WNT/β-catenin signaling and PPAR-γ through the EGFR/PI3K/Akt and STAT3 signaling pathways, provides a better understanding of the mechanisms underlying the development and progression of gliomas, and constitutes a potentially effective therapeutic target.

Compliance with Ethical Standards

Conflict of interest The authors declare that the research was conducted in the absence of any commercial or financial relationship that could be construed as a potential conflict of interest.

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