# Systems biology of Wnt signaling in glioma chemotherapy resistance: Integrating multi-omics mechanisms and emerging therapeutic vulnerabilities (Review)

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Received October 20, 2025; Accepted June 25, 2026

DOI: 10.3892/ol.2026.15769

**Abstract.** Temozolomide (TMZ) resistance remains a key clinical challenge in treating glioma and a primary cause of tumor recurrence and therapeutic failure. Beyond well-established $O^6$-methylguanine-DNA methyltransferase-mediated DNA repair, the Wnt signaling pathway, acting as a complex regulatory network, reinforces the chemoresistant phenotype through synergy with DNA repair systems and epigenetic reprogramming. The present review adopts a systems biology perspective to synthesize existing evidence, defining aberrant Wnt activation as a central integrative hub that drives TMZ resistance through a multi-tiered network. These mechanisms include enhanced DNA damage response, metabolic reprogramming, glioma stem cell maintenance and interactions with complex pathways such as PI3K/Akt and JAK/STAT. Current therapeutic strategies are summarized, ranging from small-molecule inhibitors and natural compounds to nanomedicine and cellular reprogramming, to propose treatment priorities for distinct resistance phenotypes. The present review aims to provide a reference for future translational research and the development of strategies to overcome chemoresistance in glioma.

## Contents



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*Key words:* glioma, chemoresistance, temozolomide, cisplatin, Wnt signaling pathway, systems biology, multi-omics, metabolic reprogramming, nanomedicine, glioma stem cells

## 1. Introduction

Gliomas, arising from glial cells, account for ~80% of adult malignant brain tumors (1). Among these, glioblastoma (GBM; IDH wild-type) is the most aggressive grade according to the 2021 World Health Organization Classification of Tumors of the Central Nervous System (2). Although the standard treatment plan includes surgery, radiotherapy and chemotherapy, patient survival remains poor, with a median survival time of only 12-15 months (2). Compared with other subtypes, GBM contributes to a notably higher number of years of life lost (3) and contributes to notably higher mortality rates (1). Chemoresistance to its first-line chemotherapeutic agents, such as temozolomide (TMZ), is one of the main factors posing a major barrier to prognostic advancement.

TMZ, a lipophilic alkylating agent, induces cytotoxicity by methylating DNA/RNA at guanine (N7/O6) and adenine (N3) sites, ultimately triggering G2/M phase cell cycle arrest and apoptosis (4). However, glioma cells evade these effects by mobilizing complex DNA repair pathways, including direct repair, base excision repair (BER) and mismatch repair (MMR) (5). $O^6$-methylguanine-DNA methyltransferase (MGMT) is key to direct repair, reversing $O^6$-methylguanine lesions (6), while BER and MMR deficiencies further contribute to therapeutic evasion (7,8). Crucially, recent studies have indicated that chemoresistance is not merely a consequence of isolated enzymatic alterations, but a systemic process driven by complex signaling networks (9-11).

The Wnt signaling pathway, a conserved axis, serves as a multi-functional hub in tumor development and drug resistance across various malignancies, including colorectal, non-small cell lung, liver, pancreatic and breast cancer (12-18). Previous studies underscore its role as a central orchestrator of glioma chemoresistance, promoting stemness, invasiveness and survival under TMZ stress (5,9).

The present review adopts a systems biology perspective to analyze evidence showing how Wnt signaling connects molecular, cellular and microenvironmental resistance mechanisms.

Beyond summarizing these mechanisms, the landscape of emerging therapeutic vulnerabilities will be described and a rational framework to overcome chemoresistance will be proposed, providing a reference for future clinical translation.

## 2. Role of the Wnt signaling pathway in drug resistance in glioma

*Current status of dysregulation in the Wnt signaling pathway*

*Composition of the Wnt signaling pathway*. The Wnt signaling pathway comprises two primary branches: The classical (β-catenin-dependent) and non-classical (β-catenin-independent) pathways (19,20). This axis is triggered when secreted Wnt ligands bind to frizzled (Fzd) receptors and low-density lipoprotein receptor-related protein 5/6 co-receptors, activating the intracellular signaling protein dishevelled (Dvl). In the absence of Wnt ligands, cytoplasmic β-catenin is marked for degradation by a complex comprising glycogen synthase kinase-3β (GSK-3β), adenomatous polyposis coli and axin. This complex phosphorylates β-catenin for subsequent ubiquitination and proteolysis, maintaining low cytoplasmic concentrations (21,22).

Upon activation, Dvl inhibits the degradation complex, leading to β-catenin accumulation and its subsequent nuclear import. Nuclear β-catenin operates as a transcriptional co-regulator and binds to the T cell factor/lymphoid enhancer factor family of transcription factors, which then together activate the transcription of downstream target genes, such as MYC, cyclin D1, axis inhibition protein 2 and CD44 (22). These target genes are widely involved in tumor growth, survival (23), stemness maintenance (24), epithelial-mesenchymal transition (EMT) (25,26) and drug resistance (20).

Conversely, the non-canonical Wnt pathway operates independently of β-catenin to modulate cell polarity and migration (27). The primary branches include the Wnt/planar cell polarity (Wnt/PCP) pathway and the Wnt/$Ca^{2+}$ pathway. The Wnt/PCP axis involves ligands (such as Wnt5a and Wnt11), receptors (such as Fzd, receptor tyrosine kinase-like orphan receptors 1 and 2 and related to receptor tyrosine kinase), core effector proteins (such as Vangl, prickle and Dvl) and downstream small GTPases (Ras homolog family member A, Rac family small GTPase 1 and cell division cycle 42) (28), thereby governing cytoskeletal rearrangements and directional migration (29,30). Meanwhile, the Wnt/$Ca^{2+}$ cascade triggers intracellular calcium mobilization, engaging key enzymes such as calcium/calmodulin-dependent protein kinase II, PKC and calmodulin phosphatase 1 (31) to regulate cell adhesion, motility and inflammation response in diseases (32).

*Abnormalities in the classical Wnt signaling pathway*. Hyperactivation of the canonical Wnt/β-catenin pathway is a primary driver of chemoresistance in glioma, particularly against TMZ in GBM (5,33). At the transcriptomic level, non-coding RNAs often alter this pathway to induce resistance. For instance, the m6A-mediated stabilization of circTTLL13 (34), the long non-coding RNA (lncRNA) component of mitochondrial RNA processing endoribonuclease-driven degradation of the negative regulator zinc and ring finger 3 (35), and the lncRNA MIR155 host gene/polypyrimidine tract binding protein 1 axis (36) all activate Wnt/β-catenin signaling to promote TMZ tolerance.

Aberrant protein expression also contributes to this resistant phenotype. Specifically, disabled homolog 2-interacting protein deficiency induces Wnt-dependent, autophagy-related protein 9B-mediated autophagy, a vulnerability reversible by the Wnt inhibitor LGK974 *in vivo* (28,35). Similarly, the experimental overexpression of ubiquitin conjugating enzyme E2T (UBE2T) promotes β-catenin nuclear translocation and downstream survival signaling (such as c-Myc and survivin signaling). Inhibiting UBE2T via M435-1279 or the Wnt inhibitor XAV-939 restores TMZ sensitivity (37). Furthermore, the transcription factor FOS-like 1 activates both the Wnt/β-catenin and NF-κB pathways, increasing glioma stemness and chemoresistance (38).

Epigenetically, p53 mutations in GBM downregulate miR-34a, thereby de-repressing Wnt6 and sustaining Wnt/β-catenin activation. Importantly, restoring miR-34a or directly inhibiting Wnt signaling re-sensitizes tumors to TMZ (39).

In addition to TMZ, this pathway also plays a notable role in resistance to other chemotherapy drugs. For instance, in the drug resistance model of cisplatin (DDP; a commonly used second-line chemotherapy drug used for glioma in clinical practice) (40,41), the circRNA molecule Circ_0055412 is notably upregulated and activates nuclear factor of activated T cells 3/β-catenin transcription by stabilizing capping actin protein, gelsolin-like mRNA and adsorbing microRNA-330-3p, which activates the Wnt/β-catenin signaling pathway, enhancing tumor cell sensitivity to cisplatin (42).

*Non-classical Wnt pathway*. Non-canonical Wnt signaling, particularly the Wnt/PCP branch, affects GBM evolution and recurrence. Wnt/PCP activation, together with dishevelled-associated activator of morphogenesis 1 upregulation and BRAF-MAPK signaling, induces a 'neuronal-like' state transition characterized by synaptic protein expression (including synapsin I and synaptosomal-associated protein) and enhanced tumor migration. BRAF combined with vemurafenib abrogates this transformation and synergizes with TMZ to notably extend survival in *in vivo* patient-derived xenograft models (43). Conversely, the role of the Wnt/$Ca^{2+}$ cascade in TMZ resistance remains largely unexplored. Compared with the well-documented canonical axis, these non-canonical pathways represent a key research gap in the understanding of glioma chemoresistance.

*Wnt-driven drug-resistant cell phenotypes: Stemness maintenance and metabolic reprogramming*

*Wnt/β-catenin pathway promotes chemoresistance by regulating cellular stemness*. Canonical Wnt signaling is central to sustaining the stemness of glioma stem cells (GSCs), thereby driving therapeutic resistance (Fig. 1). This intrinsic resistance in GSCs is frequently mediated by synergistic Wnt/β-catenin and Hedgehog signaling, which upregulates ATP-binding cassette (ABC) transporters (such as ABC subfamily G member 2 and P-glycoprotein) to enhance drug efflux *in vitro* (44). At the molecular level, diverse regulators converge on the Wnt axis to promote stemness maintenance. For instance, the enhancer of zeste homolog 2/heterochromatin protein 1 binding protein 3 complex epigenetically activates Wnt family member 7B to promote GSC self-renewal and TMZ resistance (45), while mutS homolog 2 (MSH2)-mediated cross-regulation

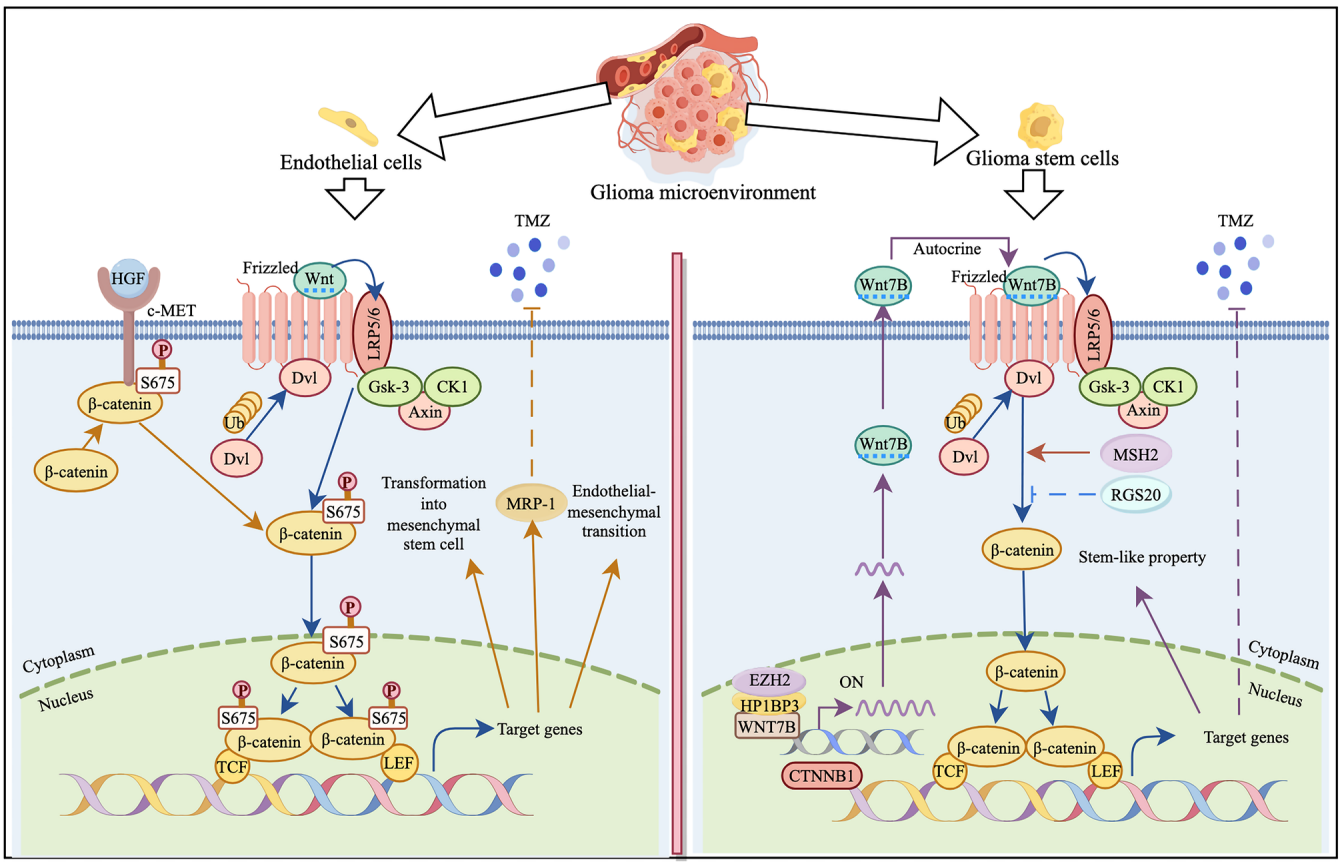


Figure 1. Microenvironment-mediated TMZ resistance through stemness activation. On the left of the image, in endothelial cells, HGF/c-met signaling phosphorylates β-catenin to drive endothelial-to-mesenchymal transition and upregulates the MRP-1 efflux pump. On the right of the image, in glioma stem cells, an autocrine Wnt7B loop (driven by EZH2/HP1BP3) and intracellular modulators (including MSH2 and RGS20) synergistically stabilize β-catenin. Together, these microenvironmental and intrinsic pathways build robust barriers against TMZ by reinforcing stem-like properties. Figure created by Figdraw. TMZ, temozolomide; Dvl, dishevelled; CK1, casein kinase 1; LRP, low density lipoprotein receptor related protein; EZH2, enhancer of zeste homolog 2; HP1BP3, heterochromatin protein 1 binding protein 3; MSH2, mutS homolog 2; RGS20, regulator of G protein signaling 20; MRP-1, multidrug resistance-associated protein 1; TCF, T cell factor; LEF, lymphoid enhancer-binding factor; c-Met, mesenchymal-epithelial transition factor; P, phosphate; Ub, ubiquitination.

of Wnt/β-catenin induces DDP resistance (46). Conversely, the loss of regulator of G protein signaling 20, an endogenous Wnt repressor, exacerbates TMZ resistance *in vivo* by removing physiological stemness constraints (47). Therefore, targeting of this pathway to eliminate stem-like properties has emerged as a potential therapeutic approach to reverse TMZ resistance, suppress tumor progression and improve patient prognosis (48-50).

Beyond intrinsic cellular mechanisms, Wnt-mediated stemness maintenance remodels the tumor microenvironment (TME) (Fig. 1). Specifically, microenvironmental Wnt signaling triggers endothelial-to-mesenchymal transition via the mesenchymal-epithelial transition factor/β-catenin axis, which upregulates multidrug resistance-associated protein 1 to confer a robust TMZ-resistant phenotype (51).

*Metabolic reprogramming mediated by Wnt/β-catenin signaling in chemoresistance*. Targeting metabolic alterations constitutes a key approach in adaptive glioma therapy, involving energy metabolic remodeling and microenvironmental responses and notably drives chemotherapy resistance (52,53) (Fig. 2C).

From a systems biology perspective, multi-omics analyses reveal that core signaling pathways, such as PI3K/Akt and Wnt/β-catenin, are coordinately upregulated as glioma malignancy progresses, collectively orchestrating metabolic reprogramming (54). Activation of the serine synthesis pathway (SSP) constitutes a defining feature of metabolic reprogramming in glioma. Inhibition of the rate-limiting enzyme phosphoglycerate dehydrogenase can markedly inhibit SSP and synergistically enhance TMZ killing of drug-resistant GBM cells in *in vivo* and *in vitro* models, by decreasing MGMT expression through downregulation of the Wnt/β-catenin signaling pathway, while simultaneously increasing reactive oxygen species levels (55).

Furthermore, fluctuations in oxygen tension within the TME regulate metabolic adaptation and resistance (Fig. 2D). Specifically, hyperoxic stress upregulates miR-1290 to inhibit phospholipase C β-1, driving β-catenin accumulation and subsequent chemoresistance. While *in vivo* preclinical models suggest that hyperbaric oxygen might compromise chemotherapy efficacy, clinical validation remains necessary (56). This oxygen-induced Wnt activation also triggers oxidative stress, further reinforcing adaptive metabolic resistance (57,58).

*Multi-pathway interaction and cross-network drug resistance regulation of the Wnt signaling pathway*. Wnt signaling does not operate in isolation; rather, β-catenin serves as an integrative hub that cross-regulates diverse oncogenic networks to orchestrate therapeutic resistance (59).

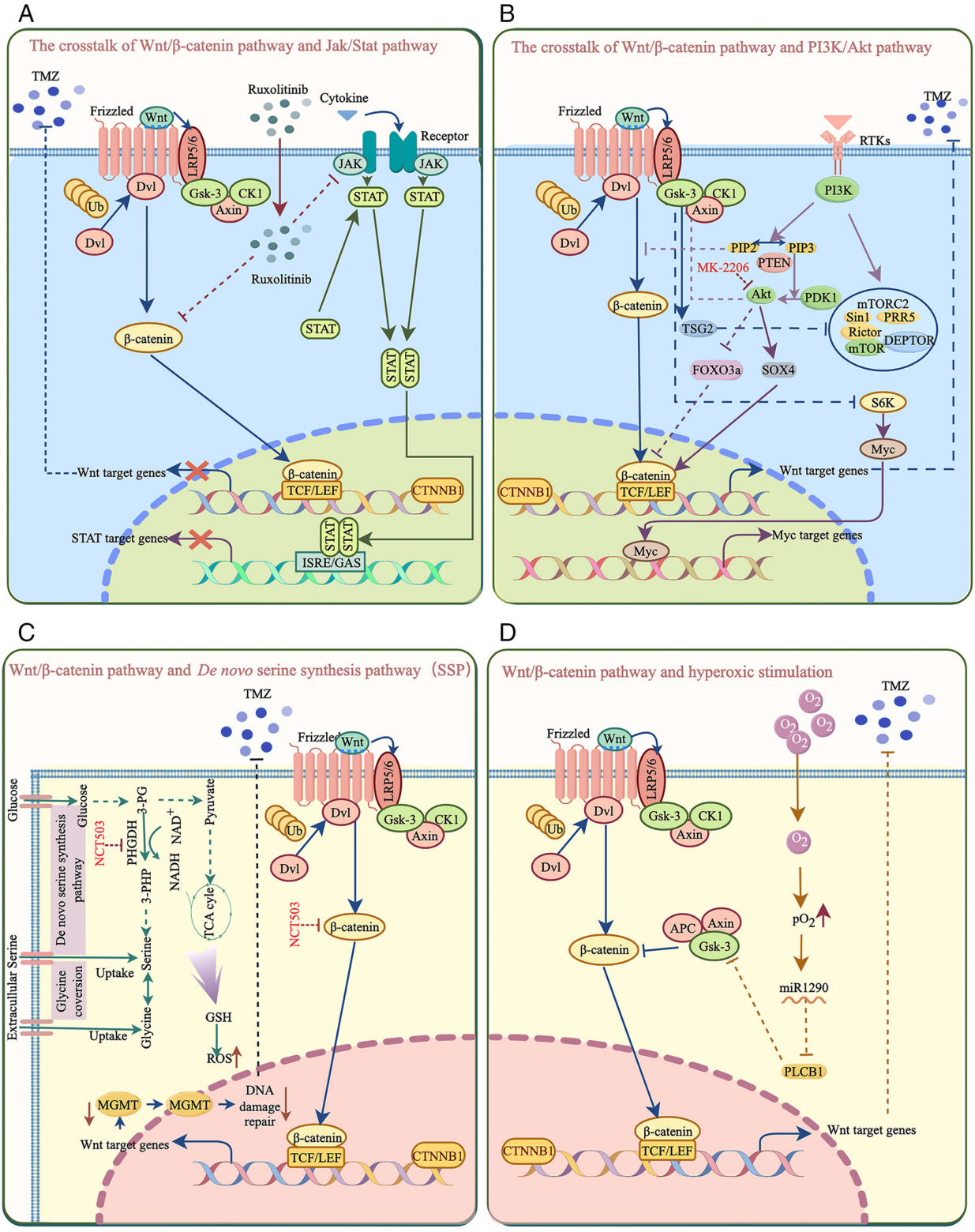


Figure 2. Abnormally activated Wnt/β-catenin signaling pathway drives chemotherapy resistance in glioma through multi-level interactions. (A) Bidirectional crosstalk between the Wnt and JAK/STAT pathways, which can be disrupted by the JAK1/2 inhibitor Ruxolitinib. (B) The PI3K/Akt axis inhibits GSK-3β to stabilize β-catenin; this process is blocked by the Akt inhibitor MK-2206. (C) Activation of the SSP enzyme PHGDH upregulates Wnt signaling, maintains MGMT expression and reduces ROS-mediated DNA damage, a metabolic resistance reversible by NCT503. (D) Hyperoxic stimulation induces abnormal β-catenin accumulation via the miR-1290/PLCB1 axis. Figure created by Figdraw. 3-PG, 3-phosphoglycerate; 3-PHP, 3-phosphohydroxypyruvate; Akt, protein kinase B; APC, adenomatous polyposis coli; axin, axis inhibition protein; CK1, casein kinase 1; CTNNB1, catenin β1; Dvl, dishevelled; Fzd6, frizzled class receptor 6; GBM, glioblastoma; Gsk-3, glycogen synthase kinase-3; GSC, glioma stem cell; GSH, glutathione; ISRE/GAS, interferon-stimulated response element/γ-activated site; Jak, Janus kinase; LRP5/6, LDL receptor-related protein 5/6; MFSD2A/Cav1, major facilitator superfamily domain containing 2A/caveolin-1; MGMT, O6-methylguanine-DNA methyltransferase; mTORC2, mechanistic target of rapamycin complex 2; NADH/NAD+, nicotinamide adenine dinucleotide (reduced/oxidized); PHGDH, phosphoglycerate dehydrogenase; PI3K, phosphoinositide 3-kinase; PLCB1, phospholipase C β1; $pO_2$, partial pressure of oxygen; PTEN, phosphatase and tensin homolog; ROS, reactive oxygen species; RTK, receptor tyrosine kinase; S6K, ribosomal protein S6 kinase; SOX4, SRY-box transcription factor 4; SSP, serine synthesis pathway; Stat, signal transducer and activator of transcription; TCA, tricarboxylic acid; TCF/LEF, T-cell factor/lymphoid enhancer factor; TMZ, temozolomide; TSG2, tumor susceptibility gene 2; Ub, ubiquitin.

*Wnt classical pathway and PI3K/Akt pathway*. The Wnt/β-catenin and PI3K/Akt/mTOR pathways synergistically drive GBM stemness and TMZ resistance via hub nodes such as GSK-3β, DEP domain-containing mTOR-interacting protein and Fzd (60) (Fig. 2A). Mechanistically, TMZ treatment inadvertently induces resistance by activating PI3K/Akt signaling, which phosphorylates GSK-3β at SER9. This phosphorylation prevents β-catenin degradation, thereby upregulating downstream Wnt target genes (61). Consequently, disrupting this axis via the pan-Akt inhibitor MK-2206 effectively reduces β-catenin transcriptional activity, suppressing GSC growth and tumor progression *in vivo* more robustly than monotherapy targeting either pathway alone (62).

*Wnt/β-catenin and STAT3 signaling pathways*. A bidirectional feedback loop exists between the Wnt/β-catenin and JAK/STAT3 cascades: STAT3 transcriptionally activates Wnt components (63,64), and Wnt signaling promotes STAT3 phosphorylation (65,66) (Fig. 2B). This crosstalk has previously been suggested to be involved in regulating the resistance of glioma cells to TMZ. Targeting this axis with the JAK1/2 inhibitor ruxolitinib downregulates Wnt-related genes and synergistically enhances TMZ-induced apoptosis in GBM cells and GSCs. This provides a potential therapeutic target within the crosstalk of this pathway (67).

*A multi-pathway drug resistance network is revealed by functional genomic screening*. The interconnected nature of TMZ resistance is also supported by genome-wide CRISPR-Cas9 screening. Knockout libraries have suggested that the loss of MMR components (such as MSH2) and sonic hedgehog signaling protect against TMZ, as evidenced by the enrichment of these knockout clones under TMZ treatment. By contrast, activation screens have revealed that the overexpression of nuclear factor erythroid 2-related factor 2 antioxidant systems and Wnt/β-catenin components (such as Fzd6 and catenin β1) directly drive resistance and are associated with worse clinical outcomes. Crucially, identifying these co-targetable nodes provides a robust translational rationale for combinatorial therapies targeting multi-pathway resistance networks (68).

## 3. Targeted therapies

*Natural compounds*. Substantial preclinical evidence demonstrates the potential of various natural compounds that can enhance chemosensitization to TMZ in glioma by targeting the Wnt signaling pathway (Fig. 3). For instance, platycodin D and mannose have been shown to effectively downregulate the canonical Wnt/β-catenin cascade, thereby inhibiting tumor cell proliferation and promoting apoptosis in TMZ-resistant models (69,70). Similarly, thymoquinone and European horse chestnut extract potentiate TMZ-induced apoptosis by directly downregulating Wnt components and stemness markers (71,72). Furthermore, resveratrol acts as a multi-target sensitizer, reversing EMT and GSC resistance by concurrently blocking the Wnt/β-catenin axis along with intertwined MAPK/AKT and STAT3 cascades (73,74).

*Small molecule inhibitors*. Despite promising preclinical efficacy, the clinical translation of these natural agents is limited by blood-brain barrier (BBB) penetrance and complex pharmacokinetics. Small-molecule targeting strategies are an important way to reverse glioma drug resistance (Fig. 3). Based on pathway gene analysis, elevated Dickkopf-related protein 3 expression is associated with worse clinical outcomes in patients with GBM. *In vitro* screening has demonstrated the activity of the BCL-2 inhibitor Navitoclax (ABT-263) against GBM cells (75). Additionally, the JAK1/2 inhibitor ruxolitinib, in combination with TMZ, increases apoptosis in GBM cells and GSCs by modulating Wnt pathway genes and Wnt-JAK/STAT3 crosstalk, although the exact molecular mechanisms require further clarification (67). The disruption of upstream Wnt regulators also shows promise. For example, the inhibitor ACT001 blocks the Midkine/c-Myc complex to effectively suppress Wnt/β-catenin signaling, showing synergistic antitumor effects with TMZ in orthotopic *in vivo* models (76). Beyond direct cytotoxicity, the Wnt inhibitor clofazimine (CFZ) sensitizes glioma cells to diverse chemotherapeutics and remodels the microenvironment by promoting pro-inflammatory microglial responses when combined with immunotherapy (77).

Regarding downstream effectors, the histone deacetylase 8 inhibitor NBM-BMX overcomes TMZ resistance in p53-wildtype GBM by repressing the β-catenin/c-Myc/SOX2 axis (78). Meanwhile, the novel inhibitor DK419 blocks β-catenin nuclear translocation to safely reverse TMZ resistance *in vivo* (79). However, balancing robust Wnt suppression with the prevention of systemic toxicity to maintain normal stem cell homeostasis remains a key challenge for clinical use.

*Combination therapy*. Combination strategies targeting Wnt-mediated resistance mechanisms offer new experimental treatment directions for glioma (Fig. 3). Combinatorial regimens help overcome Wnt-driven resistance networks. For instance, methotrexate exhibits selective toxicity against HOX transcript antisense RNA-overexpressing GBM, downregulating the miR-214/β-catenin/MGMT axis to restore TMZ sensitivity (33). Similarly, paclitaxel (PTX) sensitizes GBM to TMZ by targeting GSK-3β (80). Furthermore, dual inhibition of EGFR (lapatinib) and breakpoint cluster region-ABL/discoidin domain receptor family, member 1 (nilotinib) successfully overrides shared KRAS- and Wnt-driven stemness pathways in recurrent GBM (14). Crucially, Wnt inhibition is emerging as a potent strategy to sensitize tumors to immune checkpoint inhibitors. Combining Wnt blockers, such as the porcupine inhibitor WNT974 (81) or CFZ (82), with anti-programmed cell death-1 therapy reconfigures the immunosuppressive microenvironment. By downregulating programmed death-ligand 1, expanding dendritic cell and $CD8^+$ T cell infiltration, this synergistic approach offers a paradigm shift for breaking systemic immune evasion in GBM.

*Nano delivery*. Nanotechnology offers innovative approaches to overcome the challenges posed by the BBB and chemoresistance in glioma (Fig. 3). In strategies designed to target the endothelial cells of the BBB, the Wnt signaling pathway has emerged as a key target regulating drug penetration efficiency. Research by Xie *et al* (83) revealed that activating Wnt signaling impeded endocytic transport mediated by microcavities by downregulating MFSD2 lysolipid transporter A,


Figure 3. Comprehensive targeted therapeutic strategies to overcome TMZ resistance in glioma via the Wnt signaling network. Interventions are categorized into five modalities: i) Natural compounds for transcriptional inhibition; ii) small-molecule inhibitors blocking upstream secretion or downstream β-catenin translocation; iii) combination therapies synergizing Wnt inhibition with chemotherapy or immunotherapies (such as anti-PD-1); iv) nano delivery systems engineered for blood-brain barrier penetration; and v) cell transdifferentiation (via NeuroD1) to reprogram malignant cells into neuron-like states. These findings present how Wnt inhibition can help overcome chemoresistance. Figure created by Figdraw. TMZ, temozolomide; NeuroD1, neuronal differentiation 1; DE-FeONPs, diethyldithiocarbamate-ferrous oxide nanoparticles; PD-1, programmed cell death protein-1; ApoE, apolipoprotein E; PTX, paclitaxel; ARTPC, artesunate-phosphatidylcholine; Apt-NPs, aptamer-conjugated nanoparticles; EMNPs, exosome-mimetic nanoparticles; ANG-modified α-MEL-RES-Lips, angiopep2-modified liposomes carrying α-melittin and resveratrol.

lysophospholipid (MFSD2A) protein expression and inhibiting caveolin-1 (Cav1)-positive microcavity formation, thereby limiting drug penetration through the BBB into gliomas. Notably, inhibiting the Wnt pathway enhances nanoparticle (NP) delivery efficiency. In GBM models, NPs demonstrate improved BBB penetration and markedly elevated intratumorally accumulation levels (83). This discovery provides a novel direction for optimizing nanocarrier delivery by targeting Wnt pathway molecules (such as MFSD2A/Cav1), offering the potential to overcome transport bottlenecks in GBM therapy (83). Building on this concept (84), specific nanoplatforms, including responsive nanophores, angiopep2-modified liposomes carrying α-melittin and resveratrol (85) and exosome-mimetic nanoparticles@TMZ (86) have been engineered to directly target Wnt/β-catenin signaling and trigger non-apoptotic cell death (such as ferroptosis and

pyroptosis) in GSCs. Concurrently, targeted platforms such as apolipoprotein E-functionalized liposomes (delivering artemisinin/TMZ) (87) and aptamer-conjugated dendrimers (delivering PTX/TMZ) (88) facilitate deep tumor infiltration, downregulating stemness markers and multidrug resistance genes. However, the performance of nano delivery systems in animal models still needs to reconcile the differences in the BBB between species, and their long-term biosafety and production standardization are still translation problems which need to be solved.

*Cell transdifferentiation reprogramming*. Neuronal transdifferentiation mediated by the neural transcription factor neuronal differentiation 1 (NeuroD1) can effectively undermine the drug resistance of glioma cells (Fig. 3). Overexpression of NeuroD1 in TMZ-sensitive and drug-resistant glioma cell lines (such as T98G) effectively drives the transdifferentiation of tumor cells to neuron-like cells *in vitro*, characterized by elevated neuronal markers and inhibited malignant behaviors (89). Notably, Wnt signaling has been established as a primary modulator of this process. While NeuroD1 and β-catenin are highly expressed in normal brain tissue, they are notably downregulated in glioma; furthermore, Wnt-3a activation notably inhibits NeuroD1 expression, thereby preventing transdifferentiation. *In vivo* experiments suggest that tumors formed by NeuroD1-reprogrammed glioma cells exhibit neuronal characteristics and markedly reduced volumes (89). Thus, single-factor NeuroD1 reprogramming may transform malignant gliomas into attenuated neuron-like cells via the Wnt hub. However, its long-term safety and *in vivo* stability require further validation in high-grade glioma models before clinical translation (89).

## 4. Conclusions and perspectives

The present review highlights the aberrantly activated Wnt pathway, particularly the canonical Wnt/β-catenin axis, as an important regulator of chemoresistance in GBM. Wnt signaling does not act alone, but integrates diverse molecular dysfunctions (such as non-coding RNA regulation, protein degradation failure and epigenetic remodeling) and cross-talks with key oncogenic networks (including PI3K/Akt and JAK/STAT) to promote GSC maintenance and metabolic reprogramming (18,32,33,35,36,38,49,51-53,58). Furthermore, non-canonical signaling, such as Wnt/PCP-driven neuronal state transitions, also markedly promotes the recurrent and resistant phenotype of GBM (43). Consequently, preclinical interventions targeting this network, ranging from small molecules and natural compounds, to advanced nanocarriers and cellular reprogramming, demonstrate robust potential in re-sensitizing gliomas to standard chemotherapies and offer novel perspectives for overcoming resistance (14,33,70,72,76,77,79,85,86,89).

These findings support targeting Wnt signaling in combination therapies aimed at remodeling the immune microenvironment and disrupting DNA repair. Based on the current molecular evidence integrated in the present study, Wnt signaling serves as a potential entry point for clinical stratification and combined treatment; its synergistic intervention with DNA repair or immune microenvironment modulation provides a rational approach to overcome glioma chemoresistance.

Despite these findings, a translational gap remains. Preclinical evidence for Wnt signaling is strong, but MGMT promoter methylation remains the undisputed clinical 'gold standard' for predicting TMZ response (90,91). This implies that Wnt signaling may act as a compensatory resistance network rather than an independent prognostic replacement. Future clinical cohort studies should evaluate the interaction between Wnt hyperactivation and MGMT status in patients to bridge this gap.

Additionally, the role of the non-canonical Wnt/$Ca^{2+}$ pathway in mediating glioma chemoresistance remains an underestimated research gap. Although the importance of intracellular calcium homeostasis in regulating cellular stress and apoptosis is well recognized, the direct causal link between calcium dynamics and TMZ resistance has not been fully explored. Future studies should employ high-resolution imaging techniques to elucidate how the dynamic remodeling of calcium stores under chemotherapy stress contributes to drug resistance and explore targeted calcium signaling interventions.

Finally, overcoming the high spatiotemporal heterogeneity of GBM requires transitioning toward a comprehensive systems biology framework. To realize the clinical potential of Wnt-targeted therapies, they must be integrated with advanced multi-omics diagnostics, such as $^{23}Na$ MRI at 7 Tesla for molecular phenotyping (92), metabolomic fingerprinting (93,94) and deep-learning-based prognostic modeling (95). Validating these precision, multi-modal strategies within patient-derived organoids (14,96) will be paramount in translating experimental Wnt interventions into definitive survival benefits for patients with glioma.

## Acknowledgements

The authors are grateful to Dr Stanley Lin (Shantou University Medical College, Shantou, China) for helpful discussions and critical text editing.

## Funding

The present review was supported by the Guangdong Province Science and Technology Special Fund (grant nos. 2021-88-75 and 210713106881283), the Guangdong Natural Science Foundation (grant no. 2014A030313469) and the Guangdong Basic and Applied Basic Research Foundation (grant no. 2024A1515220016).

## Availability of data and materials

Not applicable.

## Authors' contributions

QZ designed the study, acquired and analyzed the data, prepared the figures and wrote the original manuscript. ZC and RZ participated in the conception and design of the study, contributed to literature data extraction, synthesis and interpretation, and revised the manuscript. HP contributed to the conception and design, supervised the research, and reviewed and edited the manuscript. All authors have read and approved the final manuscript. Data authentication is not applicable.

**Ethics approval and consent to participate**

Not applicable.

**Patient consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

**Use of artificial intelligence tools**

During the preparation of this work, AI tools were used to improve the readability and language of the manuscript or to generate images, and subsequently the authors revised and edited the content produced by the AI tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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