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Review

Current advances of long non-coding RNAs mediated by wnt signaling in glioma

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ABSTRACT

Glioma is the most common and aggressive brain tumor in the central nervous system (CNS), in which Wnt signaling pathway has been verified to play a pivotal role in regulating the initiation and progression. Currently, numerous studies have indicated that long non-coding RNAs (lncRNAs) have critical functions across biological processes including cell proliferation, colony formation, migration, invasion and apoptosis via Wnt signaling pathway in glioma. This review depicts canonical and non-canonical Wnt/β-catenin signaling pathway properties and relative processing mechanisms in gliomas, and summarizes the function and regulation of lncRNAs mediated by Wnt signaling pathway in the development and progression of glioma. Ultimately, we hope to seek out promising biomarkers and reliable therapeutic targets for glioma.

1. Introduction

Gliomas, deriving from neuroepithelium, are the most common primary intracranial malignant tumors, which account for 60% of brain tumors [1]. It is characterized by its excessive proliferation and relentless invasion as well as profuse infiltration into the brain parenchyma [2]. Accumulating clinical trials have demonstrated that the standard therapy for glioma is maximal safe surgical resection accompanied by adjuvant radiotherapy and chemotherapy [3,4]. In recent years, high O6-methylguanine-DNA methyltransferase (MGMT) and epithelial growth factor receptor (EGFR) have been found closely bound to chemotherapy-resistance [5,6]. However, regardless of the

Abbreviations: CNS, central nervous system; lncRNA, long non-coding RNA; MGMT, methylguanine-DNA methyltransferase; EGFR, epithelial growth factor receptor; int1, Integration 1; Wg, wingless phenotype; ORF, open reading frame; TCL6, T cell leukemia/lymphoma 6; PART1, prostate androgen-regulated transcript 1; LRG1, leucine-rich α-2-glycoprotein-1; ZEB2, zinc finger E-box binding homeobox 2; SNHG5, small nucleolar RNA host gene 5; MAGI1, Membrane-associated guanylate kinase with inverted orientation protein 1; LRP6, low-density lipoprotein receptor-related protein 6; TRIM29, tripartite motif-containing 29; TCF/LEF, T-cell factor/ lymphoid enhancer binding factor; THD, Thioridazine; FZD, frizzled family transmembrane receptor protein; GSK3β, glycogen synthase kinase 3β; Dvl1, dishevelled 1; APC, adenomatous polyposis coli; USP9X, ubiquitination substrate protein 9X; WWP1, WW domain containing E3 ubiquitin protein ligase 1; DKK1, Dikkopf-1; SFRP3, secreted FZD-related protein 3; NEDD4, neural precursor cell expressed, developmentally down-regulated 4; NEDD4L, neural precursor cell expressed, developmentally down-regulated 4-like; LGR5, leucine-rich repeat containing G protein-coupled receptor 5; PCP, planar cell polarity; JNK, Jun N-terminal kinase; RYK, receptor-like tyrosine kinase; ROR 1/2, receptor tyrosine kinase-like orphan receptor 1/2; DAAM1, dishevelled-associated activator of morphogenesis 1; ROCK 2, Rho-associated kinase 2; PLC, phospholipase C; CaN, calcineurin; CaMK II, calmodulin-dependent kinase; PKC, protein kinase C; NFAT, nuclear factor of activated T cell; MATN1-AS1, MATN1 antisense RNA 1; ERK, extracellular regulated protein kinases; MMP-9, matrix metallopeptidase 9; PVT1, plasmacytoma variant translocation 1; SNHG17, small nucleolar RNA host gene 17; MIR22HG, MIR22 host gene; HOXC13-AS, HOXC13 antisense RNA; LSINCT5, long stress-induced non-coding transcript 5; YY1, Yin Yang 1; SFRP2, secreted frizzled-related protein 2; PCDH15, protocadherin 15; EMT, epithelial-mesenchymal transition; SATB1, special AT-rich sequence binding protein 1; TMZ, temozolomide; BLACAT1, bladder cancer associated transcript 1; VASP, vasodilator-stimulated phosphoprotein; HDGF, hepatoma-derived growth factor; CEBPA, CCAAT enhancer binding protein alpha; DANCR, differentiation antagonizing non-coding RNA; AXL, anexelekto; RAB1A, ras-related protein 1A; SNHG7, small nucleolar RNA host gene 7; NEAT1, nuclear paraspeckle assembly transcript 1; EZH2, enhancer of zeste homolog 2; CDK6, cyclin-dependent kinase; MIR155HG, MIR155 host gene; CCND2-AS1, CCND2 antisense RNA 1; SOX7, sex-determining region Y-box 7; ANXA2, annexin A2; CCAT2, colon cancer-associated transcript 2; MALAT1, metastasis-associated lung adenocarcinoma transcript 1; WIF1, Wnt inhibitory factor 1; STMN1, stathmin 1; RAB5A, ras-related protein 5A; ATG4D, autophagy related 4 homolog D; SOX2, sex-determining region Y-box 2; ZHX1, zinc-fingers and homeoboxes 1; MMP2, matrix metallopeptidase 2; FBXW7, F-Box and WD repeat domain containing 7; CASC7, cancer susceptibility candidate 7; TUNAR, TCL1 upstream neural differentiation-associated RNA; MEG3, maternally expressed gene 3; WHO, World Health Organization; CASC2, cancer susceptibility candidate 2; PTEN, phosphatase and tensin homolog; PTCSC3, papillary thyroid carcinoma susceptibility candidate 3

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progress in the treatment for glioma, the median survival time of patients is still poor, which is less than 15 months [7]. Wnt signaling pathway is one of the most classic signaling pathways studied in cell biology, influencing multiple processes including embryonic development, physiology and homeostasis [8]. The Wnt gene, first found in mouse mammary, was described with the term of integration 1 (int1) in 1982, with a recognition of the mammalian equivalent of a Drosophila gene associated with a wingless phenotype (Wg) five years later [9]. Subsequently, a large amount of studies have been carried out for exploration of its roles in multiple organs or systems, including the central nervous system (CNS) [10]. In the past decades, the Wnt signaling pathway was further defined, investigated and distinguished into two major routes including the canonical and the non-canonical signaling [11]. Surprisingly, it has been certified that Wnt signaling pathway has great relevance with the progression of glioma by participating in cellular processes via activating the expression of target genes in the nucleus [12]. Long non-coding RNAs (lncRNAs) are long RNA transcripts (> 200 nucleotides) that do not encode proteins due to the lack of open reading frame (ORF) [13]. LncRNAs are virtually transcribed by RNA polymerase II and undergo 5′ end capping, RNA splicing, and polyadenylation procedures [14,15]. All lncRNAs could be classified into the following five subclasses: sense, antisense, bidirectional, intron and intergenicity according to their position in the genome [16]. Though lncRNAs were initially considered 'junk RNAs', they still exerted biological function as regulatory RNAs, serving as signals, guides, decoys, or scaffolds to regulate the expression of a wide range of target genes [17,18]. Recently, various studies have proved that lncRNAs are playing vital roles in gene regulation, cell cycle arrest, cell differentiation, immune response, tumor metabolism, and other processes of multiple solid tumors [19]. For instance, lncRNA T cell leukemia/lymphoma 6 (TCL6) developed tumor-suppressive activities directly targeting miR-106a-5p via PI3K/AKT signaling in hepatocellular carcinoma [20]. Lou et.al also reported that lncRNA prostate androgen-regulated transcript 1 (PART1) facilitated the malignant progression via miR-150-5p/leucine-rich α-2-glycoprotein-1 (LRG1) axis in colorectal cancer [21]. As in glioma, miR-205-5p/zinc finger E-box binding homeobox 2 (ZEB2) axis was regulated by lncRNA small nucleolar RNA host gene 5 (SNHG5) to promote proliferation of glioma [22]. However, the biological effects and mechanisms of these lncRNAs are far from systematic and scientific, which can't be utilized for clinical application. In this review, we try to summarize the mechanisms of canonical and non-canonical Wnt signaling pathway and overview the diverse roles of lncRNAs mediated by Wnt signaling pathway in gliomas. Hopefully, these lncRNAs may emerge as promising novel biomarkers and therapeutic targets for the treatment of gliomas.

2. Wnt signaling pathway

Wnt signaling pathway is a class of highly conserved signaling pathways during evolution, widely presented in invertebrates and vertebrates [23]. Accumulating evidence has illustrated that Wnt signaling pathway plays an important role in the early development, organ formation, tissue regeneration, and other physiological processes of animal embryos [24]. While when the core protein (Wnt) is mutated or regulated, causing abnormal activation of the signal, it may induce tumorigenesis, which also could provide therapeutic targets for various cancers, including glioma [25]. According to cell proliferation assays, silencing of membrane-associated guanylate kinase with inverted orientation protein 1 (MAGI1) in glioma cell lines enhanced cell viability via Wnt/β-catenin signaling pathway by increasing the expression level of N-cadherin, vimentin, β-catenin and cyclin D1 [26]. In angiogenesis, diallyl trisulfide inactivated Wnt/β-catenin signaling pathway targeting low-density lipoprotein receptor-related protein 6 (LRP6), tripartite motif-containing 29 (TRIM29), Pygo2 and T-cell factor/ lymphoid enhancer binding factor (TCF/LEF) transcription to inhibit angiogenesis of glioma cells [27]. More importantly, Thioridazine (THD) enhanced caspase-8-mediated apoptosis through Wnt/β-catenin signaling pathway by targeting frizzled family transmembrane receptor protein (FZD) and glycogen synthase kinase 3β (GSK-3β) and reducing β-catenin in glioma cells [28]. Therefore, it is an urgent need to investigate the Wnt signaling pathway thoroughly to understand the progression and development of glioma.

2.1. Canonical Wnt signaling pathway

The canonical Wnt signaling pathway is the β-catenin-dependent activation of Wnt signal. The main components in the canonical Wnt signaling are composed of the Wnt family secreted proteins, FZD, LRP5/6, dishevelled 1 (Dvl1), GSK-3β, adenomatous polyposis coli (APC), Axin, β-catenin and TCF/LEF family transcriptional regulators [29]. Upon binding of a Wnt ligand to its receptor FZD and co-receptors LRP 5/6, the cytoplasmic complex containing GSK-3β, Axin, APC and β-catenin undergoes inactivated phosphorylation by Dvl1 [9,30]. Subsequently, the cytoplasmic free β-catenin is translocated into the nucleus to form a transcription complex with LEF and TCF [31]. Consequently, the transcription complex upregulates the expression levels of Wnt target genes, such as c-myc and cyclin D1, to regulate numerous biological processes [32]. While when Wnt is absent, GSK-3β transforms β-catenin to degradation resulting from the deficiency of Dvl1, causing a low concentration of β-catenin in the cytoplasm [33]. Thus, the incapable combination of β-catenin, LEF and TCF negatively regulating the expression of Wnt target genes [34] (Fig.1).

Accumulating regulators have already been found in the Wnt/β-catenin signaling pathway. Ubiquitination substrate protein 9X (USP9X), a deubiquitylase, facilitated glioma proliferation and survival by stabilizing β-catenin via enhancing Wnt/β-catenin signaling pathway [35]. In addition, the combination of USP9X and WW domain containing E3 ubiquitin protein ligase 1 (WWP1), an E3 ubiquitin ligase, was also investigated to deubiquitylate Dvl2 to regulate Wnt/β-catenin signaling pathway [36]. Dikkopf-1 (DKK1), regulated by β-catenin/TCF complex, bound to LRP5/6 co-receptors and inhibited Wnt/β-catenin signaling pathway [37]. Moreover, secreted FZD-related protein 3 (SFRP3) was verified to have a synergistic reaction in the biological activities of DKK1 [38]. Novellasdemunt et.al also revealed that both neural precursor cell expressed, developmentally down-regulated 4 (NEDD4) and neural precursor cell expressed, developmentally down-regulated 4-like (NEDD4L) negatively regulated Wnt/β-catenin signaling by targeting leucine-rich repeat containing G protein-coupled receptor 5 (LGR5) receptor and Dvl2 for proteasomal and lysosomal degradation [39].

2.2. Non-canonical Wnt signaling pathway

The non-canonical Wnt signaling pathway could be divided into the Wnt/planar cell polarity (PCP) pathway involving Jun N-terminal kinase (JNK) and the Wnt/Ca^{2+} pathway.

The Wnt/PCP signaling pathway is essential for defining cellular shape, migration, and the establishment and maintenance of polarity in epithelial tissues [40]. The core of Wnt/PCP signaling pathway depends on the asymmetric distribution of key protein complexes within individual cells [41]. More importantly, dysregulation of key elements in the Wnt/PCP signaling pathway has been investigated in multiple solid tumors, which regulates cancer malignancy [42]. Once binding of a Wnt ligand, mainly Wnt 11, to its receptor FZD and co-receptors including Knypek, receptor-like tyrosine kinase (RYK) and receptor tyrosine kinase-like orphan receptor 1/2 (ROR 1/2), Rac1, induced by Dvl, activates the JNKs promoting gene transcription [9]. Meanwhile, Dvl activates the dishevelled-associated activator of morphogenesis 1 (DAAM1) to connect Rho A, which upregulates the Rho-associated kinase 2 (ROCK 2) to facilitate cytoskeletal changes [43].

The Wnt/Ca^{2+} signaling is also involved in various cellular activities by regulating calcium release from the endoplasmic reticulum to

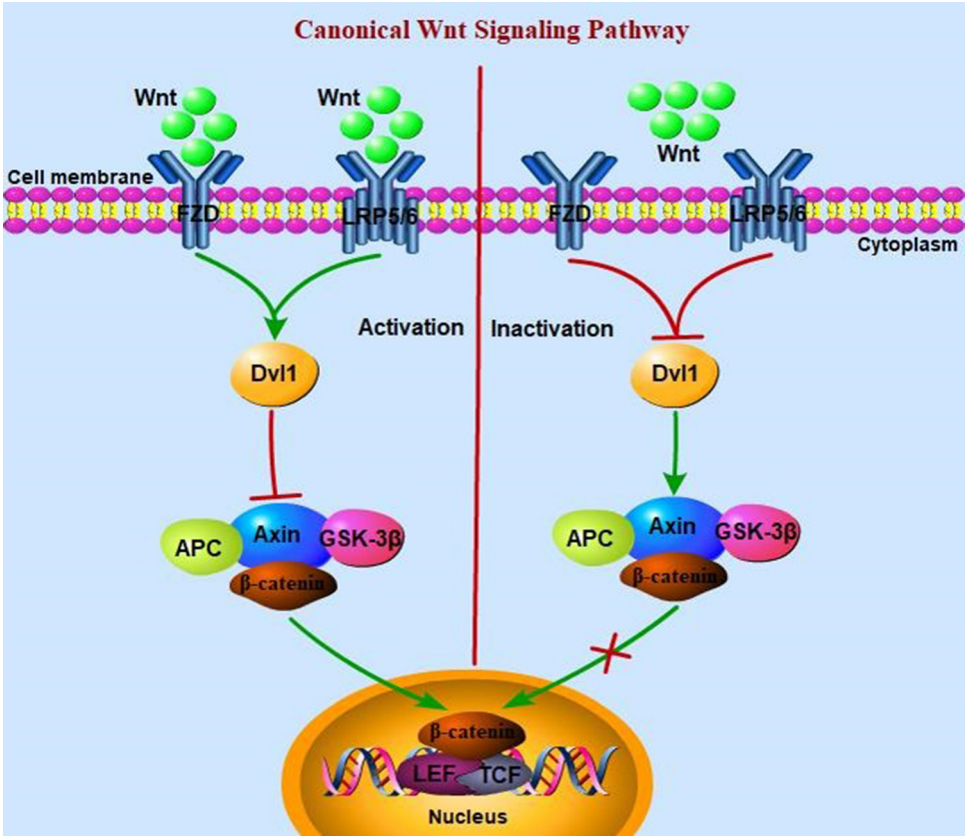

Fig. 1. Canonical Wnt signaling pathway.
Note. FZD: frizzled family transmembrane receptor proteins; LRP5/6: low-density lipoprotein receptor-related proteins 5 and 6; Dvl 1: disheveled 1; APC: adenomatous polyposis coli; GSK-3β: glycogen synthase kinase 3β; LEF: lymphoid enhancer binding factor; TCF: T-cell factor.

control intracellular calcium levels [44]. Activation of the Wnt/Ca^{2+} pathway is initiated by the combination of a Wnt ligand, mainly Wnt 5, FZD and RYK [45]. Subsequently, activation of phospholipase C (PLC) upregulates Ca^{2+} cytoplasmatic levels mediated by G-coupled proteins [46]. Thus, the elevated level of Ca^{2+} leads to the activation of calcineurin (CaN), calmodulin-dependent kinase (CaMK II) and protein kinase C (PKC), regulating the transcription of nuclear factor of activated T cell (NFAT) [47]. Interestingly, PKC could be activated by PLC [48] (Fig.2).

Above all, the canonical and the non-canonical Wnt signaling pathway have been fully elucidated in glioma. Therefore, it is imperative to overview interventions of lncRNAs via Wnt signaling pathway for glioma treatment (Tables 1 and 2).

3. Expression of LncRNAs via Wnt signaling in glioma

Currently, gathering trials have indicated that lncRNAs take participate in diverse cellular processes, including cell viability, migration, invasion, apoptosis and in vivo tumor growth in glioma [49]. For example, lncRNA MATN1 antisense RNA 1 (MATN1-AS1) reduced cell proliferation and invasion, and enhanced cellular apoptosis via downregulation of RELA, ERK1/2, Bcl-2, survivin and matrix metallopeptidase 9 (MMP-9) accompanied by increased Bax [50]. Similarly, lncRNA plasmacytoma variant translocation gene 1 (PVT1) exerted pro-tumor effects in cell proliferation, invasion and aerobic glycolysis targeting miR-140-5p [51]. Functionally, the interaction between lncRNAs and miRNAs or lncRNAs were usually acknowledged in the functional activities of lncRNAs [52–54]. More significantly, various signaling pathways including Wnt signaling, p38/MAPK signaling, Akt/GSK-3β signaling, Smad2/PKCα signaling and NF-κB signaling were involved in lncRNAs regulation [55–59]. Below, we try to summarize the lncRNAs mediated by Wnt signaling pathway in glioma, which regulate progression and malignancy of glioma.

3.1. Upregulated lncRNAs in biological activities of glioma

3.1.1. LncRNA SNHG17, MIR22HG, HOXC13-AS, LSINCT5

Compared to normal ones, the elevated expression of lncRNA small nucleolar RNA host gene 17 (SNHG17), MIR22 host gene (MIR22HG), HOXC13 antisense RNA (HOXC13-AS) and long stress-induced noncoding transcript 5 (LSINCT5) was found in glioma tissues and cells, which was also associated with poor prognoses in glioma patients [60–63]. Further in vitro and in vivo experiments illustrated that SNHG17 promoted cell proliferation and suppressed apoptosis and tumor growth [60]. Mechanistically, SNHG17, significantly upregulated by transcription factor Yin Yang 1 (YY1), targeted miR-506-3p to increase β-catenin, thus activating Wnt/β-catenin signaling pathway in glioma [60]. Han et.al also reported that MIR22HG augmented cell proliferation, invasion and in-vivo tumor growth by sponging miR-22-3p and -5p targeting secreted frizzled-related protein 2 (SFRP2) and protocadherin 15 (PCDH15) respectively via Wnt/β-catenin signaling pathway [61]. In addition, HOXC13-AS was detected to affect cellular migration, invasion and epithelial-mesenchymal transition (EMT) process via sponging miR-122-5p to indirectly regulate special AT-rich sequence binding protein 1 (SATB1) expression through Wnt/β-catenin signaling pathway. Subsequently, c-myc, a key factor of the Wnt signaling, formed a positive HOXC13-AS-miR-122-5p-SATB1-c-myc feedback loop to boost functional activities in glioma [62]. Moreover, LSINCT5 effectively enhanced cell viability, migration, invasion, and inhibited apoptosis targeting miR-451in glioma [63]. Further mechanistic investigation showed that LSINCT5 may activate PI3K/Akt, Wnt/β-catenin and NF-κB signaling pathway to exert biological effects

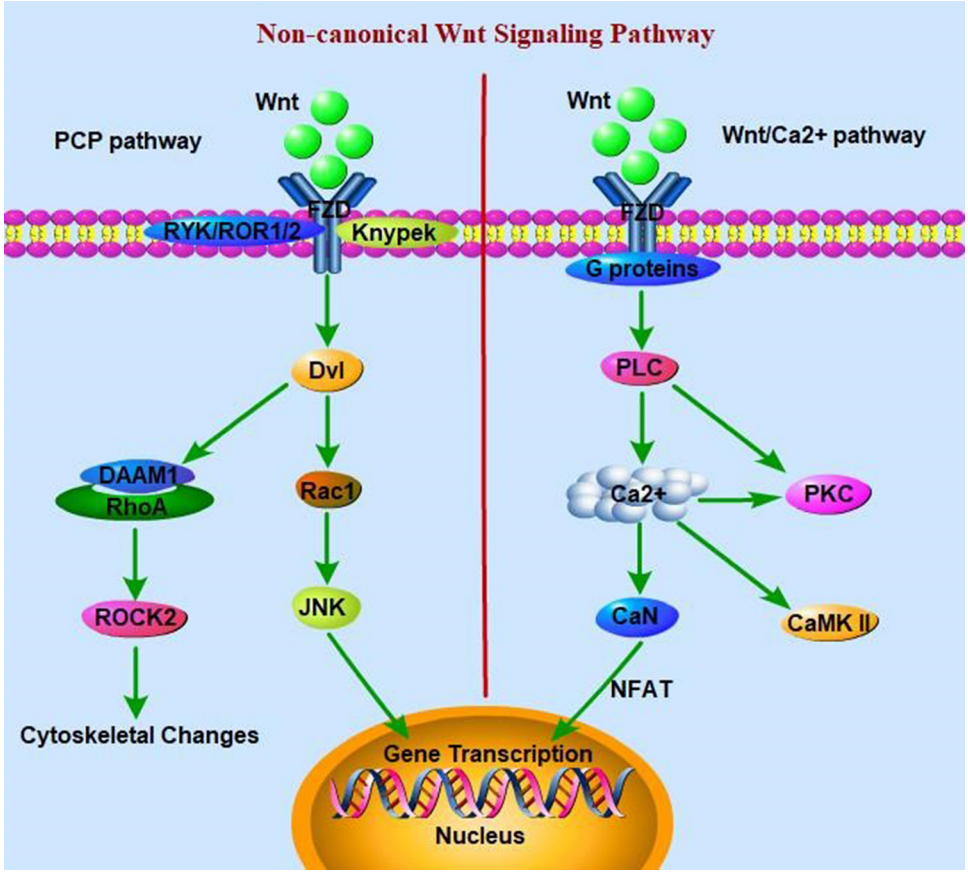

Fig. 2. Non-canonical Wnt signaling pathway. Note. PCP: the planar cell polarity signaling; FZD: frizzled family transmembrane receptor proteins; RYK: receptor-like tyrosine kinase; ROR 1/2: receptor tyrosine kinase-like orphan receptor 1/2; Dvl: disheveled; DAAM1: dishevelled-associated activator of morphogenesis 1; ROCK 2: Rho-associated kinase 2; JNK: Jun N-terminal kinase; PLC: phospholipase C; PKC: protein kinase C; CaN: calcineurin; CaMK II: calmodulin-dependent kinase; NFAT: nuclear factor of activated T cell.

[63,64].

3.1.2. LncRNA H19

It was acknowledged that the expression level of H19 in glioma tissues was distinctly higher than that in normal tissues and associated with prognoses in glioma patients [65]. Regarding chemotherapy, H19 knockdown obviously sensitized glioma cells to temozolomide (TMZ), forecasting its potential role in clinical application [66]. Gathering investigation revealed that H19 promoted cell proliferation, invasion, migration, cell cycle progression in vitro and angiogenesis and tumorigenicity in vivo [67–69]. Functionally, the pro-tumor effects resulted from the promotion of EMT process via Wnt/β-catenin signaling pathway [70]. Surprisingly, the c-myc oncogene, a Wnt signaling downstream target, had a motivation effect on H19 through allele-specific binding [71]. Moreover, H19 was also involved in the upregulation of TMZ resistance in glioma cells via activation of NF-κB signaling pathway [72]. Recently, more targets by H19 including miR-675, miR-138, miR-130a-3p, miR-152, miR-140 and miR-29a have been investigated to have assistant effects on glioma [73–80], which still needs further trials to study the correlation with Wnt signaling pathway.

3.1.3. LncRNA BLACAT1, SNHG5

The high expression level of bladder cancer associated transcript 1 (BLACAT1) was correlated with high tumor grade in glioma patients and found in glioma tissues and cell lines [81,82]. Li et.al demonstrated that BLACAT1 facilitated cell proliferation, migration, invasion and EMT process in glioma via Wnt/β-catenin signaling pathway [81]. BLACAT1 was also testified to exert pro-tumor effects by regulating vasodilator-stimulated phosphoprotein (VASP) expression via binding to miR-605-3p [82]. Besides, small nucleolar RNA host gene 5 (SNHG5) boosted cell proliferation and invasiveness as well as inhibited the apoptosis of glioma cells via Wnt/β-catenin signaling pathway [83]. MiR-205/E2F3 axis and miR-205-5p/zinc finger E-box binding homeobox 2 (ZEB2) axis were also involved in tumorigenicity of SNHG5 [22,84]. Moreover, SNHG5, induced by YY1, promoted glioma cell proliferation through p38/MAPK signaling pathway [56], which may interact with Wnt/β-catenin signaling pathway.

3.1.4. LncRNA LINC01503, AGAP2-AS1, OIP5-AS1

LINC01503, AGAP2 antisense RNA 1 (AGAP2-AS1) and OPA-interacting protein 5 antisense transcript 1 (OIP5-AS1) were significantly upregulated in glioma tissues and cells, and correlated with the lower overall survival of glioma patients [85–87]. Functionally, LINC01503 suppressed cells growth, colony formation, invasion, migration, and enhanced apoptosis by elevating TOP-FLASH activity via Wnt/β-catenin signaling [85]. AGAP2-AS1 promoted glioma cell proliferation by sponging miR-15a/b-5p to upregulate the expression of hepatoma-derived growth factor (HDGF), which was found to activate Wnt/β-catenin signaling pathway [86]. OIP5-AS1 was investigated to augment cell growth, invasion, migration, and inhibit apoptosis via Wnt-7b/β-catenin signaling pathway by downregulating miR-410 in glioma cells [87]. In addition, PIWIL3/OIP5-AS1/miR-367-3p/CCAAT enhancer binding protein alpha (CEBPA), a positive feedback loop, has been reported to regulate the biological behavior of glioma cells [88].

3.1.5. LncRNA DANCR, SNHG7, NEAT1

Currently, Li et.al confirmed that differentiation antagonizing noncoding RNA (DANCR) promoted glioma progression via Wnt/β-catenin signaling pathway [89]. Interestingly, DANCR mediated cisplatin resistance in glioma cells via activating anexelekto (AXL)/PI3K/Akt/NF-κB signaling [90]. Moreover, DANCR facilitated glioma malignancy by sponging miR-33a-5p and functioned as a competing endogenous RNA to regulate ras-related protein 1A (RAB1A) expression by sponging miR-634 in glioma [91,92]. Furthermore, it was reported that small nucleolar RNA host gene 7 (SNHG7) promoted cell proliferation,

Table 1
Upregulated lncRNAs mediated by Wnt signaling in glioma.

LncRNAs	Upstream regulators	Downstream targets	Wnt signaling	Samples	Biological Processes	References
SNHG17	Upregulated by YY1	Targeting miR-506-3p/CTNNB1 axis	Activation	33 glioma tissues, NHA, U87, U251, SHG44, A172	Proliferation, apoptosis and tumor growth.	[60]
MIR22HG	/	Sponging miR-22-3p and -5p targeting SFRP2 and PCDH15	Activation	GBM#P3, GBM#BG7, GBM#BG5, GBM#06	Tumor growth and invasion	[61]
HOXC13-AS	/	Sponging miR-122-5p to regulate SATB1	Activation	20 glioma tissues, LN229, U251, U87, U118	Migration, invasion and EMT process	[62]
LSINCT5	/	Targeting miR-451-Rac1 axis	Activation	GL15	Viability, migration, invasion and apoptosis	[63]
H19	/	Increasing Dvl2, cyclin D1, β-catenin and GSK-3β	Activation	60 glioma tissues	Proliferation, invasion, migration, and apoptosis	[65]
	/	Increasing β-catenin, c-myc and surviving	Activation	U251, M059J	Viability, apoptosis and EMT process	[70]
BLACAT1	/	Increasing β-catenin and cyclin D	Activation	35 glioma tissues, NHA, U251, T98 G, H4,A172, LN229	Viability, proliferation, migration and invasion	[81]
SNHG5	/	Negative correlation with GSK3β and positive correlation with CTNNB1	Activation	NHA, U251, U87	Proliferation, invasion and apoptosis	[83]
LINC01503	/	Increasing β-catenin, cyclin D1 and c-myc	Activation	133 glioma tissues, NHA, A172, LN229, LN18, U251, T98G	Growth, colony formation, invasion, migration and apoptosis	[85]
AGAP2-AS1	/	Upregulating HDGF by sponging miR-15a/b-5p	Activation	91 glioma tissues, NHA, U87, U251, LN229	Proliferation and apoptosis	[86]
OIP5-AS1	/	Sponging miR-410 and targeting Wnt-7b	Activation	65 glioma tissues, U87	Growth, invasion, migration, apoptosis and tumor growth	[87]
DANCR	/	Increasing c-myc and β-catenin	Activation	86 glioma tissues, U87, U251, SGC7901, BGC823	Proliferation, migration, invasion and EMT process	[89]
SNHG7	/	Downregulating miR-5095	Activation	HEB, A172, U87, T98 G, SHG44	Proliferation, migration, invasion and apoptosis	[93]
NEAT1	Upregulated by EGFR	Downregulating EZH2	Activation	N5, N9, N33	Proliferation, colony formation, invasion and apoptosis	[95]
AB073614	/	Downregulating SOX7	Activation	89 glioma tissues, NHA, U251	Proliferation, migration, invasion and tumor growth	[102]
MIR155HG	/	Increasing miR-155-5p or miR-155-3p targeting PCDH 9 or 7 respectively	Activation	10 glioma tissues, U251, U87	Proliferation, migration, invasion, and tumor growth	[103]
CCND2-AS1	/	Increasing β-catenin	Activation	NHA, U251, U87	Proliferation, colony formation and cell cycle	[104]
CCAT2	/	Increasing c-myc, MMP-7 and cyclinD1	Activation	U87-MG, U251	Proliferation, cell cycle, migration and tumor growth	[111]
MALAT1	Downregulated by WIF1	Targeting Wnt/Ca^{2+} signaling	Activation	LN229, LN319, LN18, LN428	Migration and invasion	[119]

Lnc RNAs comprising of SNHG17, MIR22HG, HOXC13-AS, LSINCT5, H19, BLACAT1, SNHG5, LINC01503, AGAP2-AS1, OIP5-AS1, DANCR, SNHG7, NEAT1, AB073614, MIR155HG, CCND2-AS1, CCAT2 and MALAT1 activate Wnt signaling pathway by upregulating self-expression in biological activities of glioma. Note. SNHG17: small nucleolar RNA host gene 17; CTNNB1: catenin β1; NHA: normal human astroglia; SFRP2: secreted frizzled related protein 2; PCDH 15: protocadherin 15; SATB1: special AT-rich binding protein; EMT: epithelial-mesenchymal transition; LSINCT5: long stress-induced non-coding transcript 5; GSK-3β: glycogen synthase kinase 3β; BLACAT1: bladder cancer associated transcript 1; SNHG5: small nucleolar RNA host gene 5; HDGF: hepatoma-derived growth factor; SNHG7: small nucleolar RNA host gene 7; NEAT1: nuclear enriched abundant transcript 1; EGFR: epidermal growth factor receptor; SOX7: SOX7: sex-determining region Y-box 7; PCDH: protocadherin; CCAT2: colon cancer-associated transcript 2; MMP-7: matrix metallopeptidase 7; MALAT1: MALAT1: Metastasis-associated lung adenocarcinoma transcript 1; WIF1: Wnt inhibitory factor-1.

Table 2
Downregulated lncRNAs mediated by Wnt signaling in glioma.

LncRNAs	Upstream regulators	Downstream targets	Wnt signaling	Samples	Biological Processes	References
CASC7	/	Decreasing β-catenin, cyclin D1 and c-myc	Suppression	80 glioma tissues, M059 J, A172, U251, U87MG, U118	Proliferation and apoptosis	[127]
Linc00320	Downregulated by HMGB1	Binding to β-catenin and separating TCF4	Suppression	18 glioma tissues, U251, LN229, NHE	Colony formation and tumor growth	[128]
TUNAR	/	Sponging miR-200a to inhibit Rac1	Suppression	NHA, SHG44, U251, GL15, U87	Viability, migration, invasion and apoptosis	[129]
MEG3	/	Decreasing β-catenin	Suppression	54 glioma tissues, NHA, U251, U87	Viability, colony formation, cell cycle and apoptosis	[131]
CASC2	/	Decreasing β-catenin, cyclin D1 and c-myc	Suppression	47 glioma tissues, NHA, U251, U87	Proliferation, migration and invasion	[140]
PTCSC3	/	Downregulating LRP6 targeting β-catenin, c-myc and cyclin D1	Suppression	U87, U251, SHG44, SHG139	Proliferation, migration, invasion, apoptosis and EMT process	[143]

Lnc RNAs comprising of CASC7, Linc00320, TUNAR, MEG3, CASC2 and PTCSC3 inactivate Wnt signaling pathway by downregulating self-expression in biological activities of glioma. Note. CASC7: cancer susceptibility candidate 7; HMGB1: High mobility group box 1; TCF4: T-cell factor 4; TUNAR: TCL1 upstream neural differentiation-associated RNA; MEG3: maternally expressed gene 3; CASC2: cancer susceptibility candidate 2; PTCSC3: papillary thyroid carcinoma susceptibility candidate 3; LRP6: low-density lipoprotein receptor-related protein 6.

migration and invasion through the inhibition of miR-5095 and concomitant activation of Wnt/β-catenin signaling pathway in glioma [93]. Besides, aberrant expression of nuclear paraspeckle assembly transcript 1 (NEAT1) was associated with tumor grade and clinical outcomes in glioma patients [94]. Mechanistically, NEAT1 could be induced by EGFR and targeted enhancer of zeste homolog 2 (EZH2)/β-catenin axis to act as a critical effector of tumorigenesis and progression via Wnt/β-catenin signaling pathway [95]. Other downstream targets by NEAT1 including miR-449b-5p/c-Met axis, miR-92b, miR let-7e, miR-107/cyclin-dependent kinase (CDK6) axis, miR-132 and miR-107 were found participation in the progression and development of glioma [96–101], of which the connection with Wnt signaling pathway needs additional studies.

3.1.6. LncRNA AB073614, MIR155HG, CCND2-AS1

High expression of AB073614, MIR155 host gene (MIR155HG) and CCND2 antisense RNA 1 (CCND2-AS1) was considered a prognostic biomarker and associated with glioma grade, mesenchymal transition and poor prognosis [102–104]. Further investigation illustrated that AB073614 promoted cell progression and EMT process targeting sex-determining region Y-box 7 (SOX7) via Wnt/β-catenin signaling pathway [105,106]. Wang et.al also found that AB073614 regulated proliferation and metastasis of colorectal cancer cells via PI3K/Akt signaling pathway, which needs further research in glioma [107]. MIR155HG could promote cell proliferation, migration, invasion and orthotopic glioma growth by upregulating miR-155 − 5p and miR-155 − 3p via Wnt/β-catenin signaling pathway [108]. Furthermore, miR155HG targeted miR-185/annexin A2 (ANXA2) axis contributed to cell growth and progression in glioma [109]. In addition, CCND2-AS1 promoted glioma cell proliferation through Wnt/β-catenin signaling pathway [104], which was also found in breast cancer [110].

3.1.7. LncRNA CCAT2, MALAT1

It was recognized that colon cancer-associated transcript 2 (CCAT2) inhibited proliferation, cell cycle progression, migration and invasion of glioma cells through inhibiting Wnt/β-catenin signaling pathway [111]. Moreover, CCAT2 regulated EMT-associated gene expression [112]. Interestingly, CCAT2 was found in the exosomes released by glioma cells to enhance angiogenesis and inhibit endothelial cell apoptosis [113]. Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) was linked with the expression of stemness markers in vitro and malignant status and poor prognosis in glioma patients [114,115]. In chemotherapy, MALAT1 decreased the sensitivity of glioma cells to TMZ via suppressing miR-203 or miR-101 [116–118]. Further mechanistic investigation showed that MALAT1, downregulated by Wnt inhibitory factor 1 (WIF1), promoted migration and inhibited apoptosis through Wnt/Ca^{2+} signaling pathway [119,120]. Accumulating trials demonstrated that MALAT1 exerted biological activities through upregulating stathmin 1 (STMN1), ras-related protein 5A (RAB5A) and autophagy related 4 homolog D (ATG4D) or suppressing Rap1B by sponging miR-101, targeting miR-129/sex-determining region Y-box 2 (SOX2) axis or miR-199a/zinc-fingers and homeoboxes 1 (ZHX1) Axis [121–124]. Instead, downregulation of matrix metallopeptidase 2 (MMP2) with inactivation of ERK/MAPK signaling pathway or suppressing miR-155 expression with activation of F-Box and WD repeat domain containing 7 (FBXW7) may act as suppressors in the function of MALAT1 [125,126].

3.2. Downregulated lncRNAs in biological activities of glioma

3.2.1. LncRNA CASC7, Linc00320, TUNAR

Cancer susceptibility candidate 7 (CASC7), Linc00320 and TCL1 upstream neural differentiation-associated RNA (TUNAR) were downregulated in glioma tissues and predicted good prognosis for patients with gliomas [127–129]. Mechanistic investigation showed that CASC7 suppressed cell proliferation and induced apoptosis via Wnt/β-catenin signaling pathway in glioma cells [127]. Moreover, Linc00320 inhibited glioma cell proliferation by restraining Wnt/β-catenin signaling pathway through segregating β-catenin and TCF4 [128]. Further investigation revealed that TUNAR overexpression significantly inhibited glioma malignancy by decreasing cell viability, migration, invasion, and promoting cell apoptosis through sponging miR-200a and inhibiting Rac1, thus inactivating the Wnt/β-catenin and NF-κB signaling pathways [129].

3.2.2. LncRNA MEG3

The expression level of materally expressed gene 3 (MEG3) was significantly downregulated in glioma tissues and cell lines, and negatively correlated with World Health Organization (WHO) grade in glioma patients [130]. Further in vitro experiments demonstrated that the low expression of MEG3 remarkably facilitated the proliferation while suppressing cell cycle arrest, apoptosis and autophagy in glioma cells through Wnt/β-catenin signaling pathway [130,131]. It was also verified that MEG3 was associated with p53 activation and inactivated PI3K/Akt/mTOR signaling pathway [132–134]. Thus, decreased MEG3-induced autophagy improved the chemosensitivity of glioma cells to cisplatin [135]. More promising targets including miR-19a, miR-93 and miR-96-5p were also detected in biological activities of MEG3 [136–138].

3.2.3. LncRNA CASC2, PTCSC3

In several glioma tissues and cell lines, the expression of cancer

susceptibility candidate 2 (CASC2) was downregulated, which was also correlated with advanced clinic pathologic features and shorter survival time [139]. The overexpression of CASC2 remarkably suppressed glioma cell proliferation, migration, and invasion via suppressing Wnt/β-catenin signaling pathway or via negative regulation of miR-21 [140,141]. Interestingly, CASC2 played a pivotal role in facilitating TMZ response resulting from upregulation of phosphatase and tensin homolog (PTEN) through direct inhibiting miR-181a or reduction of TMZ-induced autophagy via mTOR upregulation [139,142]. Besides, papillary thyroid carcinoma susceptibility candidate 3 (PTCSC3) was significantly downregulated in glioma cell lines and inhibited the proliferation and migration of glioma cells via Wnt/β-catenin signaling pathway [143]. Notably, Xia et.al also found that LRP6, as a receptor of the Wnt/β-catenin signaling pathway, was a direct target of PTCSC3 [143].

In summary, these findings have suggested that lncRNAs play important roles in the initiation and progression of glioma, which may emerge as promising novel biomarkers and therapeutic targets for glioma.

4. Discussion

Despite the advances in the diagnosis and treatment of glioma, it still remains the most malignant disease in neurosurgery with worst prognosis. Due to the hysteresis of pathological results of biopsy specimens clinically, novel biomarkers would play essential roles in individualized diagnosis and treatment of glioma patients. For example, miRNA-210 and miR-574-3p, extracted from serum exosomes, served as potential biomarkers for their roles in pathological grades and overall survival of glioma patients [144,145]. Qian et.al also revealed similar biological effects of pleckstrin homology and RhoGEF domain containing G5 (PLEKHG5) and ADP-ribosylation factor-like 3 (ARL3) in glioma [146,147]. In our review, oncogenic lncRNA SNHG17, MIR22HG, HOXC13-AS, LSINCT5, H19, BLACAT1, SNHG5, LINC01503, AGAP2-AS1, OIP5-AS1, DANCR, SNHG7, NEAT1, AB073614, MIR155HG, CCND2-AS1, CCAT2 and MALAT1 are correlated with high tumor grade in glioma patients, whereas lncRNA CASC7, Linc00320, TUNAR, MEG3, CASC2 and PTCSC3 exert anti-tumor effects in proliferation, colony formation, migration, invasion, apoptosis and cell cycle on glioma cell lines. In addition, lncRNA HOXC13-AS, H19, DANCR and PTCSC3 were detected to play a pivotal part in EMT process. More importantly, H19, DANCR, MALAT1, MEG3 and CASC2 have been verified to facillitate sensitivity of glioma to TMZ or other chemotherapy drugs. Mechanistically, lncRNA H19, BLACAT1, LINC01503, DANCR, CCND2-AS1, CCAT2, CASC7, MEG3 and CASC2 induced changes in β-catenin, cyclin D1, c-myc and MMP-7, which were definite downstream targets of Wnt signaling pathway. Moreover, lncRNA SNHG17, MIR22HG, HOXC13-AS, LSINCT5, AGAP2-AS1, OIP5-AS1, SNHG7, MIR155HG and TUNAR were found interactions with miRNAs to regulate Wnt signaling pathway. Interestingly, lncRNA LSINCT5 and TUNAR had a same target of Rac1, which needs further investigation for their interrelationship. More mechanistic investigation showed that lncRNA MALAT1, downregulated by WIF1, was involved in Wnt/Ca^{2+} signaling pathway. Taken together, these lncRNAs have shown their clinical significance, which forecasts their potential application for glioma treatment.

Further investigation of these lncRNAs with treatment outcomes would facilitate the development of novel tools for treatment individualization. Interestingly, lncRNAs themselves could serve as therapeutic molecules. A study by Tsagakis et.al demonstrated that lncRNAs with tunable sequence elements targeted mRNAs, thus modulating their translation specifically [148]. It was also reported that this highly customizable approach participated in disrupting physiological protein levels, which could be adapted for any disease [149]. Moreover, peptide nucleic acid (PNA), a kind of artificially synthesized nucleic acid analog, could recognize DNA and RNA specifically obeying the Watson-Crick hydrogen bonding scheme and invade into duplex homopurine sequences of DNA, forming a stable PNA-DNA-PNA triplex [150]. Velagapudi et.al also reported that targeting an offending RNA molecule with small molecule drugs or using anti-sense oligos to specifically interfere with RNA function [151]. All these results have confirmed the potential clinical application of lncRNAs and provided their possible involvement in the gene therapy of glioma. Nevertheless, there are still several limitations to break through with our manuscript, which are also the directions of our progress. Firstly, the biological effects of lncRNAs in glioma mentioned above are still far from satisfactory, suggesting a great demand for further in vitro and in vivo studies. Secondly, the definite interaction between lncRNAs and Wnt signaling is still blurred, which provides a direction to explore. Last but not the least, due to the rapid development of high-throughput RNA-seq technology, more lncRNAs associated with tumor progression and clinical outcome should be detected.

In conclusion, lncRNAs mediated by Wnt signaling pathway have a tight connection with cellular proliferation, migration, invasion, apoptosis in vitro and tumorigenesis and progression in vivo via Wnt signaling pathway. All these lncRNAs were also of great clinical significance, emerging as reliable biomarkers and promising therapeutic targets for glioma, which still needs further exploration.

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Declaration of Competing Interest

The authors declare no conflict of interest.

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