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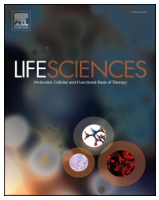

Wnt signaling in the tumor microenvironment: A driver of brain tumor dynamics

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ABSTRACT

The Wnt signaling pathway is important for cell growth and development in the central nervous system and its associated vasculature. Thus, it is an interesting factor for establishing anti-brain cancer therapy. However, simply inhibiting the Wnt signaling pathway in patients with brain tumors is not an effective anti-cancer therapy. Due to their complex microenvironment, which comprises various cell types and signaling molecules, brain tumors pose significant challenges. It is important to understand the interplay between tumor cells and the microenvironment for developing effective therapeutic strategies for both benign and malignant brain tumors. Thus, this research focused on the role of the tumor microenvironment (TME) in brain tumor progression, particularly the involvement of Wnt-dependent signaling pathways. The brain parenchyma comprises neurons, glia, endothelial cells, and other extracellular matrix elements that can contribute to the TME. The TME components can secrete Wnt ligands or associated molecules, resulting in the aberrant activation of the Wnt signaling pathway, followed by tumor progression and therapeutic resistance. Therefore, it is essential to understand the intricate crosstalk between the Wnt signaling pathway and the TME in developing targeted therapies. This review aimed to elucidate the complexities of the brain TME and its interactions with the Wnt signaling pathways to improve treatment outcomes and our understanding of brain tumor biology.

1. Introduction

The TME refers to the surroundings of a tumor, including normal cells, vessels, lymph nodes, nerves, and metabolites. Furthermore, the mechanical microenvironment comprises various components such as intracellular elements, including vimentin and actin; extracellular elements, including collagen and fibrin; intercellular elements, including integrin, and stromal cells. These environments can either promote the transformation of cells into cancer cells or restrain tumor growth [1,2]. Due to rapid tumor growth, tumor tissues have lower oxygen concentrations (hypoxia) than normal tissues. Hypoxia induces the outgrowth of cancer cells [3] and stimulates excessive angiogenesis by upregulating the expression of vascular endothelial growth factor [4]. Hypoxia affects various mechanisms, particularly immune response, lactate and reactive oxygen species metabolism, and acidity, in cancer cells and the TME. Further, hypoxia is associated with an increased mutation of somatic variation, alternation of oncogenes, and tumor suppressors such as *TP53*, *PTEN*, and *MYC* [5,6]. Tumor cells prefer aerobic glycolysis to produce energy, and they have an elevated lactate metabolism where the extracellular matrix (ECM) help regulating tumor cell glycolysis [7] and integrin-dependent hypoxia-inducible factor 1 signal pathways [8]. Moreover, ECM stiffness can accelerate cancer cell progression and metastasis [9]. In summary, the TMEs synergistically interact with each other, thereby contributing to tumorigenesis (Fig. 1).

Wnt signaling has been persistently investigated since the discovery of the *Wnt* gene that induces wing development in *Drosophila melanogaster* in 1976 [10]. The *Wnt* gene is highly conserved across animal species, from fruit flies to humans. It was named Wnt based on the

Abbreviations: APC, Adenomatous polyposis coli; BBB, Blood–brain barrier; BDNF, Brain-derived neurotrophic factor; CNS, Central nervous system; CSF, Cerebrospinal fluid; ECM, Extracellular matrix; FZD, Frizzled receptor; IDH, Isocitrate dehydrogenase; KO, Knockout; OPC, Oligodendrocyte progenitor cell; TAA, Tumor-associated astrocyte; TAM, Tumor-associated macrophage; TME, Tumor microenvironment; TREM2, Triggering receptor expressed on myeloid cells 2; WIF 1, Wnt inhibitory factor 1.

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combination of the names *wingless* in Drosophila and *int* in mouse [11]. Wnt is among several signals that regulate developmental processes including Notch, Hedgehog, transforming growth factor β, bone morphogenetic protein, and hippo. However, Wnt is unique as it can provide direction for tissue growth and polarity [12–14]. Wnt signals regulate cell proliferation and allocation. Thus, it has been a focus of studies on embryonic development, stemness, and tissue regeneration [15].

The Wnt signaling pathway also has a significant impact on tumorigenesis, particularly in cancers that originate from epithelial cells. Further, it contributes to the initiation, progression, and metastasis of various types of cancer such as gastrointestinal cancer and melanoma [16]. Thus, there are diverse categories of antitumor agents targeting Wnt-mediated signaling including the Wnt ligand/receptor inhibitor, β-catenin complex destructor, and Wnt/β-catenin signaling inhibitor of cancer stem cell [17,18]. Moreover, emerging evidence shows that the Wnt signaling pathway from the TME, which is traditionally recognized for its involvement in primary tumor development, plays an important role in both primary tumor growth and metastatic spread. For example, the infiltration of immune cells induced Wnt signaling, which then enhanced the development of human pancreatic cancer. The inhibition of Wnt signaling by the clinical inhibitor porcupine in immune cells can suppress cancer growth [19]. According to several studies, the downstream signaling of Wnt in the TME components enhanced the progression of colorectal, lung, oral, and cervical cancer. Thus, targeting the Wnt signaling in TME may offer novel insights into the therapeutic strategies for cancer treatment and management.

To the best of our knowledge, the significance of Wnt signaling in the TME of brain tumors has not been comprehensively evaluated thus far. Brain tumors are often resistant to therapy due to the presence of the blood–brain barrier (BBB). Patients with brain tumors, even if benign, are at increased risk of seizure or coma due to tumor location. Thus, targeting the TME of brain tumors is important to prevent invasive surgery or aggressive anti-cancer therapy. Wnt signaling typically enhances neural stem cell differentiation and survival during neurogenesis. Meanwhile, the excessive activation of Wnt signaling induces the progression of brain tumors. Aberrant Wnt signaling within the brain TME, including peritumoral cells and ECM, can be strongly associated with tumor development and progression. A few studies have shown that targeting Wnt signaling in peritumoral cells or structures is highly

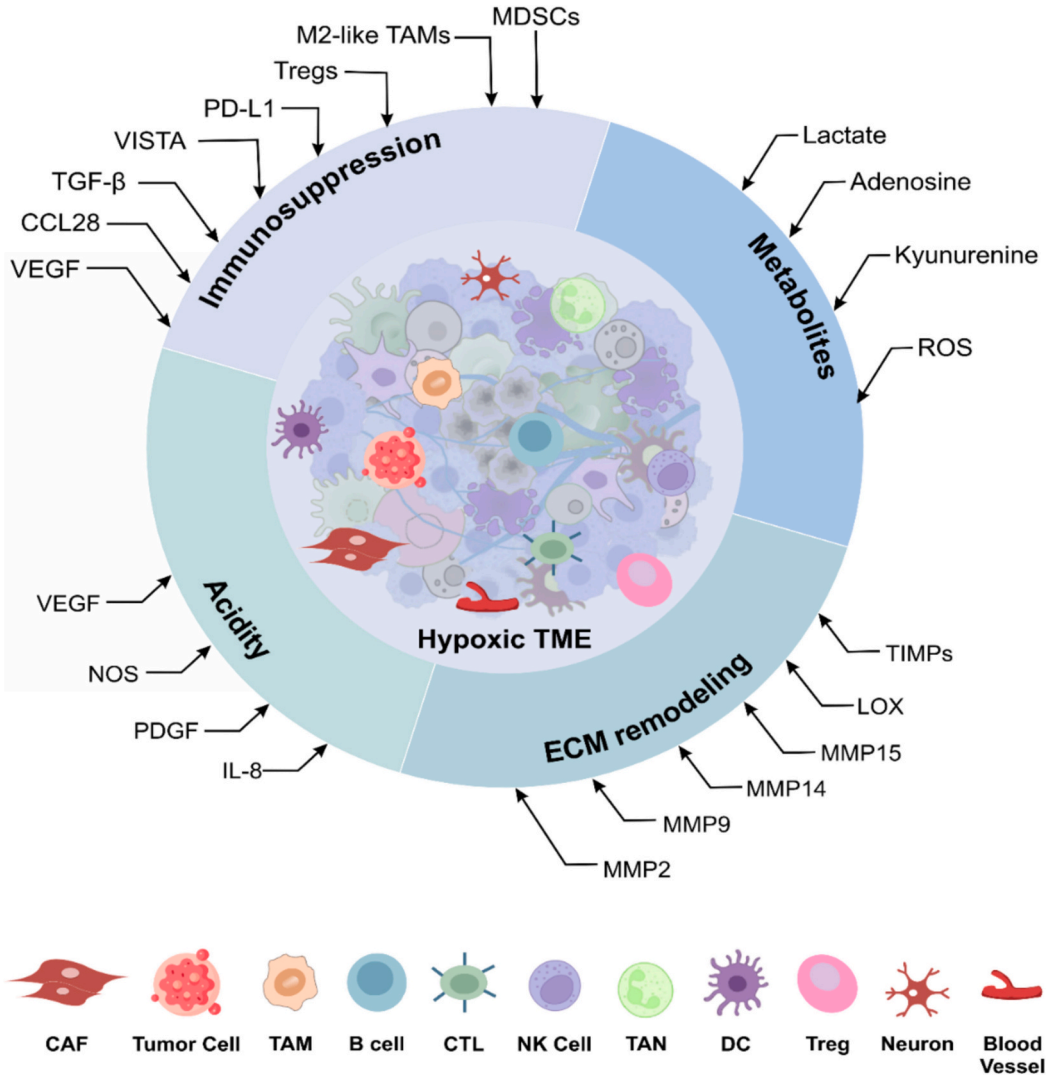

Fig. 1. General schematic figure of tumor microenvironment. Lower oxygen concentration (hypoxia), immune cells, acidity, ECM, and metabolites are present in TME. They interact with each other and determine the fate of tumor cells, such as metastasis and invasion. CAF: Cancer-associated fibroblast; CCL28: C—C motif chemokine ligand 28; CTL: Cytotoxic T cell; DC: Dendritic cell; LOX: Lysyl oxidase; MDSC: Myeloid-derived suppressor cell; MMP: Matrix metalloproteinase; NK cell: Natural killer cell; NOS: Nitric oxide synthase; PDGF: Platelet-derived growth factor; TAN: Tumor-associated neutrophil; TIMP: Tissue inhibitor of metallopeptidase; Treg: Regulatory T cell; VEGF: Vascular endothelial growth factor; VISTA: V-domain immunoglobulin of T cell activation.

associated with an increased risk of malignancy and transformation of brain tumors. Meanwhile, reducing immunosuppressive TME by regulating Wnt signaling can effectively inhibit tumor growth. Therefore, understanding the multifaceted roles of Wnt signaling in tumor initiation, progression, and metastasis within the TME may offer novel insights into inhibiting brain tumors and developing effective therapies based on the tumor-suppressive effects of Wnt-related signaling. This review aimed to evaluate the role of Wnt signaling in the brain microenvironment and its related mechanisms in brain tumors.

2. Brain TME and Wnt: a focus on the TME

2.1. Types of brain tumor

Brain tumor, also known as intracranial tumor, is characterized by abnormal growth of cells in the brain (including the nerves, blood vessels, and glands). This type of tumor can be either benign or malignant as it can grow in other types of tissues. However, it is usually challenging to resect. Hence, both benign and malignant tumors can cause major symptoms such as headaches, seizures, personality changes, loss of responsiveness to stimuli, and vomiting. The examination (biopsy), diagnosis, and treatment of brain tumors are difficult to execute due to their localization. Thus, the early detection or prevention of brain tumors is important for maintaining a healthy life. Further, to treat tumors that are challenging to resect, it is important to understand how to suppress brain tumor proliferation by regulating the therapeutic target gene.

More than 150 different brain tumors have been documented according to the 2021 5th edition of the World Health Organization classification of central nervous system (CNS) tumors (WHO, 2021). Among the benign brain tumors, meningioma is the most common brain tumor originating from the meninges and schwannoma, commonly occurring in the vestibulocochlear nerve. A pituitary adenoma is the most common benign brain tumor after meningioma and schwannoma, which can cause various hormonal imbalances. Again, despite their benign characteristics, they can still have harmful health effects as they are challenging to remove.

Gliomas are the most prevalent type of adult brain tumor, accounting for 78 % of malignant brain tumors [20]. Regardless of grade and prognosis, gliomas are highly infiltrative and resistant to therapy; thus, they are incurable [21]. Based on cell origin, glioma is subdivided into astrocytoma, ependymoma, oligodendroglioma, and glioblastoma. Among them, astrocytoma is the most common glioma that develops from astrocytes and is frequently found in the cerebrum. The classification of diffuse gliomas is significantly based on isocitrate dehydrogenase (IDH) enzyme mutation. IDH mutations and metabolic reprogramming of the Krebs cycle are prevalent in glioma [22]. Thus, it is important to identify a novel molecular targeting strategy for IDH-mutant glioma by boosting energy balance, targeting DNA repair enzymes, or altering the tumor immunological microenvironment.

2.2. Brain TME

The highly dynamic brain TME includes the surrounding peritumoral region and brain-resident cells, which help induce the growth and infiltration of brain tumors. Thus, the brain TME contains several different non-cancerous cell types, including neurons, glia, endothelial cells, pericytes, fibroblasts, and immune cells (Fig. 2). In addition, the blood vessels, signaling molecules such as exosomes and ECM components form a complex network around the brain tumor. Surgical processes or therapy can transform the TME, which then allows the invasion of brain tumor cells. Thus, strategies that regulate alterations in TME are emerging as a good anti-cancer therapy. The following sub-sections present explanations about the major components of brain TME.

2.2.1. Neuron

Brain parenchyma comprises four major types of cells that make up the functional tissue of the brain. Neurons, also referred to as nerve cells, are the most important cell type of the brain as they are responsible for transmitting information throughout the brain and CNS. Most neurons

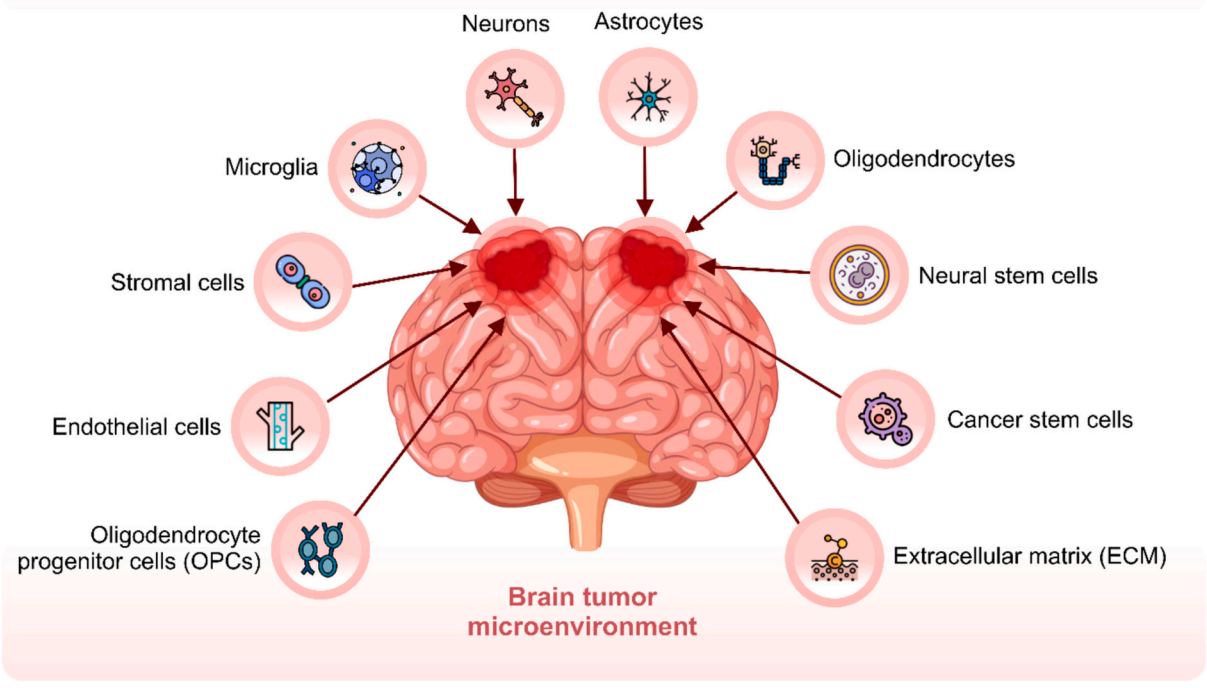

Fig. 2. Components of the brain TME. The diverse cellular constituents of the brain TME includes the surrounding peritumoral region and brain-resident cells, regulating the growth and infiltration of brain tumors. Neurons, glia (astrocytes, microglia, oligodendrocytes), pericytes, precursor cells such as OPCs and cancer/neural stem cells, stromal cells, endothelial cells, and even ECM can interact within the brain TME, creating a complex network that influences tumor growth, invasion, and response to therapy.

in the CNS are post-mitotic if they are differentiated from progenitors, which then are hard to proliferate [23]. Further, neurons are highly polarized cells with extensively long axons and dendrites. Therefore, to maintain their homeostasis, neurons require the cell organelles/proteins to be sorted into the appropriate localization [24,25].

Neurons can affect glioma proliferation in the TME if the neurons become peritumoral cells in glioma. The neurons interact with brain cancer cells via the innervation and transfer of their proliferative paracrine mitogen secretion or electrical signals [26,27]. Tumors enhance neurogenesis and then recruit nerves to themselves that then release oncogenic factors such as brain-derived neurotrophic factor (BDNF), neuroligin, glial cell line-derived neurotrophic factor, and nerve growth factor [28–30]. These factors from reprogrammed neural tissues regulate axonogenesis, angiogenesis, and immune response, which then promote vasculature formation and growth around cancer cells [31,32]. Further, changes in neurotransmitter levels and neural activity around the tumor can also significantly contribute to cell proliferation and resistance to apoptosis [33]. For example, the number of glutamatergic neurons in glioma synapses is increased by calcium signaling, which then leads to glioblastoma invasion [34]. At the relatively late stage, neurons are involved in the formation of tumor-related pain. With the increasing effects of inflammatory cytokines and sensitizing sensory nerves around the cancer cells, innervated neurons cause evident cancer pain [35,36]. Thus, potential anti-neurogenic using neuroendocrine factor inhibitors, receptor antagonists, or denervation therapy is emerging as an anti-cancer therapy by regulating TME [37].

2.2.2. Glia

Glial cells, also referred to as neuroglia or glia, provide metabolic support and protection for neurons with coordinating function with multiple brain glia [38,39]. Astrocytes, microglia, and oligodendrocytes are the three representative types of glial cells in the brain.

2.2.2.1. Astrocyte. The star-shaped astrocytes are the most abundant type of glial cell. Astrocytes release gliotransmitters (such as ATP, glutamate, and D-serine), neurotrophic factors (fibroblast growth factor and BDNF), ions to regulate synaptic plasticity, inflammatory/anti-inflammatory cytokines, and provide metabolic/structural support to neurons [40].

Tumor-associated astrocytes (TAAs) are typically reactive astrocytes that change the immune system around the brain tumor. A1, which is one type of reactive astrocyte, exacerbates the neuroinflammatory response and directly transfers the neurotoxic molecules via the brain tumor-forming gap junction to the neurons. Meanwhile, A2-like astrocytes support tissue repair by releasing BDNF or STAT3 factors [39,41]. TAA presents different characteristics based on age or sex according to a transcriptomic analysis of human brain tissues [42]. However, if brain cancer occurs, astrocytes usually undergo astrocytosis that promotes numerous signaling pathways that are involved in the invasion and migration of brain cancer such as glioblastoma and glioma by regulating glutamine–glutamate metabolism, ECM remodeling, synaptic function dysregulation, and immunosuppressive microenvironment [43–45]. Thus, depletion of reactive TAA can be a promising therapy against brain cancer [46].

2.2.2.2. Microglia. Unlike other glial cells derived from the neuroectoderm, microglia originate from the mesoderm acting as major immune cells regulating brain immune system. Microglia extend their processes that surveil their environment, monitoring the signs of infection or injury. Thus, they play an important role in clearing debris and phagocyting dysfunctional cells or proteins, thereby regulating inflammation and responding to injury and diseases.

Microglia are the key cells acting as a TME component. Microglia are classified into two phenotypes, which are as follows: a pro-inflammatory M1 phenotype and an anti-inflammatory M2 phenotype [47]. Based on the phenotypes, microglia can be either a neurotoxic or neuroprotective cell, which commonly contributes to tumor growth or regression. Inflammatory cytokines from M1 type is usually known to inhibit tumor growth by suppressing angiogenesis whereas molecules from M2 type enhance tumor growth by promoting angiogenesis and immunosuppression. Numerous surface molecules and cytokines released from the microglia regulate the expression of T or B lymphocytes, dendritic cells, and brain macrophages which can dysregulate the brain immune system and enhance tumor growth under an immunosuppressive environment [48]. In addition to this well-known function, the exosomes and microRNAs from the microglia also support glioma proliferation and migration that induce brain tumor cells to release angiogenic or proliferative factors [49–51]. As a TME component, microglia also interact with astrocytes by STAT3/NF-κB, which induces reactive astrocytosis and enhances the anti-inflammatory state of the brain [43]. Under the immunosuppressive environment in glioblastoma, microglia can cause reactive astrocytes to release cytokines [43]. However, if the glioma size increases, this pathway is suppressed and STAT3-dependent A2-like astrocyte shift is then reduced, resulting in inflammation around the brain tumor.

2.2.2.3. Oligodendrocyte. Oligodendrocytes primarily function to insulate CNS axons, thereby facilitating saltatory signal transmission. Nevertheless, they also fulfill the metabolic requirements of neurons regulating metabolites such as lactate and secreting growth factors [38].

Recently, oligodendrocytes have gained attention as a major component of the brain TME because the infiltration of oligodendrocytes or oligodendrocyte progenitor cells (OPCs) is observed around the brain glioblastoma [52]. To date, oligodendrocytes have shown several roles contributing to brain tumor growth, but little is known about their specific roles. Glioblastoma releases several microRNAs or oligodendrocyte transcription factors around the tumor border, which increases the differentiation of OPCs into oligodendrocytes, resulting in enhanced stemness of glioblastoma and the tumor growth [53,54]. Oligodendrocytes are frequently associated with cell cycle proteins, neuroligin proteins, myelin plasticity, or growth factors that enhance the heterogeneity of glioblastoma [55–58]. Oligodendrocytes or astrocytes differentiated from OPCs can also promote neovascularization in glioma and induce BBB dysfunction by dysregulating platelet-derived growth factor [59]. Taken together, oligodendrocyte or OPC infiltration around the brain tumor generally induces stemness and death-resistance of brain tumor [60].

2.2.3. Others

In addition to neurons and glia, the rest of the brain tissue is structural or connective tissue (referred to as stroma) that includes immune cells, endothelial cells, pericytes, ependymal cells, and neural/cancer stem cells. Endothelial cells of the blood vessels in the CNS constitute the BBB where pericytes, which are cells that wrap around the endothelial cells lining the capillaries and venules, are found. The interaction between endothelial cells and pericytes is important to sustain the BBB integrity by secreting ECM components or cell adhesion molecules that suppress the random passage of molecules [61]. Ependymal cells, also classified as glial cells according to several research, line the ventricles of the brain and spinal cord to produce cerebrospinal fluid (CSF), which can protect and nourish the CNS. Ependymal cilia ensure CSF flow/circulation and homeostasis to provide specific nutrients to the brain cells, transfer metabolites, sustain acid-base balance in the CNS, and regulate neuroblast migration [62]. The neural stem cell niche defines a zone for producing new neurons or glia in postnatal and adult brains. Its niche is restricted to a few specific zones in the brain, such as the dentate gyrus of the hippocampus, which responds to stimuli and supports regeneration. However, unlike in other tissues, neurogenesis or gliogenesis does not rigorously occur. If damaged, the CNS is thereby challenging to repair [63].

Brain TME is a complex system that comprises various cellular and molecular types in addition to the neurons and glia. The immune microenvironment, including macrophages or T cells, can induce both tumor-promoting and tumor-suppressive functions. Macrophages comprise a relatively large percentage of the brain tumor mass, and they are attracted by chemokines from the brain tumor, such as prostaglandin and IL-10. Further, the interaction between macrophages and T cells is important for brain cancer progression by enhancing the immunosuppressed environment in the CNS [64]. Neural stem cells and other stem/progenitor cells are strongly attracted by tumor cells, and accumulation around the tumor border was observed. In addition, endothelial cells and their supporting/surrounding pericytes are the important components of the brain TME that enhance neovascularization and angiogenesis, thereby forming vascular niches, which are essential for tumor growth and nutrient supply [65,66]. Neural stem cells and OPCs release several neurotrophic or growth factors that can contribute to tumor growth and enhance interactions with surrounding cells. Mesenchymal and cancer stem cells participate in the promotion of tumor progression by bridging tumor cells with other stromal cells and the maintenance of self-renewal in the TME [67]. The origin of cancer stem cells in brain has not been definitively identified; transformation of neural stem cell into cancer stem cell or dedifferentiation of glial or neural progenitor cells derived from cancer stem cells were usually observed. They have stem or progenitor cell characteristics, contributing to tumor recurrence and heterogeneity [68]. Cancer stem cells also have a niche, which maintains the ability to self-renew and produce more differentiated progenitors. Cancer stem cells release various molecules such as exosomes to maintain hypoxic and acidic environment, enhance ECM stiffness, and change the characteristics of other cells in TME. Finally, ECM components, including collagen, fibronectin, hyaluronan, and associated-releasing factors from various cells such as fibroblasts, are the important key components of the brain TME, which remodels ECM around the brain tumor and tumor growth [69]. ECM can convey signals such as cytokines, chemokines, neurohormones, and exosomes released from various cells to the primary brain tumor and enhance its growth. Specifically, exosomes or extracellular vesicle can carry various ligand proteins and small RNAs such as miRNAs from all brain TME cell components, contributing to chemo/radioresistance and immune evasion of cancer cells [70].

2.3. Wnt signaling from brain TME

Before discussing the influence of Wnt signaling pathways emerging from each component of the brain TME on brain tumor progression in Subsection 2.3.2, Subsection 2.3.1 provides a brief description of the Wnt signaling pathway.

2.3.1. Wnt signaling

2.3.1.1. Wnt subtypes. Currently, there are several known *Wnt* genes in mammals. These include the *Wnt1*, *Wnt2*, *Wnt2b*, *Wnt3*, *Wnt3a*, *Wnt4*, *Wnt5a*, *Wnt5b*, *Wnt6*, *Wnt7a*, *Wnt7b*, *Wnt8a*, *Wnt8b*, *Wnt9a*, *Wnt9b*, *Wnt10a*, *Wnt10b*, *Wnt11*, and *Wnt16* genes. Previous studies have conducted gene knockout (KO) experiments to investigate the function of different Wnt subtypes. Results showed that deleting the *Wnt3a* gene resulted in somite and tailbud defects that were mediated by Lef-1 [71–74]. In addition, the loss of the *Wnt3a* gene led to a neural crest defect, characterized by a reduction in dorsolateral neural precursors in the neural tube when combined with *Wnt-1* KO [75]. The *Wnt5a* gene regulates the longitudinal skeletal outgrowth coordinated with the *Wnt5b* gene [76], posterior growth of the female reproductive tract [77], and intestinal elongation [78]. Based on these findings, the Wnt subtypes affect the phenotypical and functional changes either individually or in combination with other subtypes.

2.3.1.2. Wnt biosynthesis. The different types of Wnt possess distinct intrinsic properties for their functions. However, the mechanisms of Wnt signaling are similar. Cystein-rich Wnt proteins are synthesized and modified by porcupine, a palmitoyl transferase in the endoplasmic reticulum [79,80]. After binding with lipid, Wnt combines with the transmembrane protein Wntless/Evi in the Golgi apparatus. Then, Wnt is transported to the plasma membrane and released outside of the cells [81]. Lipids restrain the Wnt protein near neighboring cells by binding to the Frizzled receptor (FZD) and initiate the downstream signal via two different mechanisms [82].

2.3.1.3. Canonical Wnt pathway. The two types of Wnt signal pathways are as follows: canonical and noncanonical (Fig. 3). These pathways are distinguished by the involvement of cytoplasmic β-catenin. The canonical pathway is initiated if Wnt binds to the extracellular N-terminal cysteine-rich domain of FZD and LRP5/6 [83]. The hydrophobic pocket in the cysteine-rich domain of FZD has a nanomolar range of binding affinity with Wnt [81]. After Wnt binding, the C-terminal of FZD binds to Dishevelled, and LRP binds with Axin. These bindings induce the relocalization of the destruction complex (Axin, β-catenin, Adenomatous polyposis coli [APC], CK1α/β, and GSK3α/β) to the cell membrane, which is saturated by the phosphorylation forms of β-catenin, leading to the accumulation of synthesized β-catenin in the cytoplasm. Then, β-catenin translocates to the nucleus, and β-catenin/TCF activates the target gene expression related to cell proliferation [84].

2.3.1.4. Noncanonical Wnt pathway. The different types of noncanonical Wnt pathways are categorized for clarity and simplicity. Two noncanonical pathways are the planar cell polarity pathway and the Wnt/calcium pathway. In Wnt/planar cell polarity pathway, both Wnt5a and Wnt11 bind to FZD [85]. This binding activates Dishevelled and effector complexes and then small GTPases such as RHOA and RAC1, which regulate actin cytoskeleton and cell adhesion [86,87]. Moreover, Wnt5a-bound FZD regulates the intracellular calcium level via phospholipase C, diacylglycerol/inositol, cyclic GMP, and protein kinase G. This Wnt-cyclic GMP/calcium signaling regulates cell adhesion and tissue separation during gastrulation [88,89]. Other noncanonical Wnt pathways mediated by FZD (Wnt8-RAP1, Wnt1/7a-PKA, Wnt-GSK3, Wnt-aPKC, and Wnt-mTOR) control the expression of target genes, actin cytoskeleton, and microtubule [90–92]. In addition, the interaction of Wnt5a with the receptor tyrosine kinase-like orphan receptor 2 pathway and the interaction of Wnt with the receptor related to tyrosine kinase induces signal transduction [93].

2.3.2. Wnt-dependent signaling from the brain TME

Wnt usually increases the differentiation potential of neural stem cells and their survival during neurogenesis and proliferation. However, excessive Wnt-dependent signaling strongly cross-communicates among cancer cells and TME, thereby contributing to brain tumor development. Indeed, Wnt deregulation is strongly associated with brain tumor progression [94]. Within the brain TME, Wnt ligands, receptors, and downstream effectors are expressed by both peritumoral cells and ECM. Moreover, the aberrant activation of these molecules in the brain TME can lead to tumor growth, invasion, and therapeutic resistance. Thus, understanding the essential molecules in Wnt-dependent signaling in the brain TME is important for developing novel therapeutic strategies that can effectively target these signaling pathways and improve the treatment outcomes of patients with brain tumors.

Several studies have shown that the expression of Wnt, including Wnt1/2/3a/5a, is increased in neural progenitor cells or glia that support neurogenesis or neurite growth [95,96]. Hence, neurons can release Wnt ligands to adjacent tumor cells and promote tumor growth and invasion [97]. Indeed, neuronal differentiation, which can also be enhanced by Wnt, resulted in the activation of Wnt5a-dependent invasiveness in glioma [98,99]. Further, the inhibition of Wnt3 in cerebellar

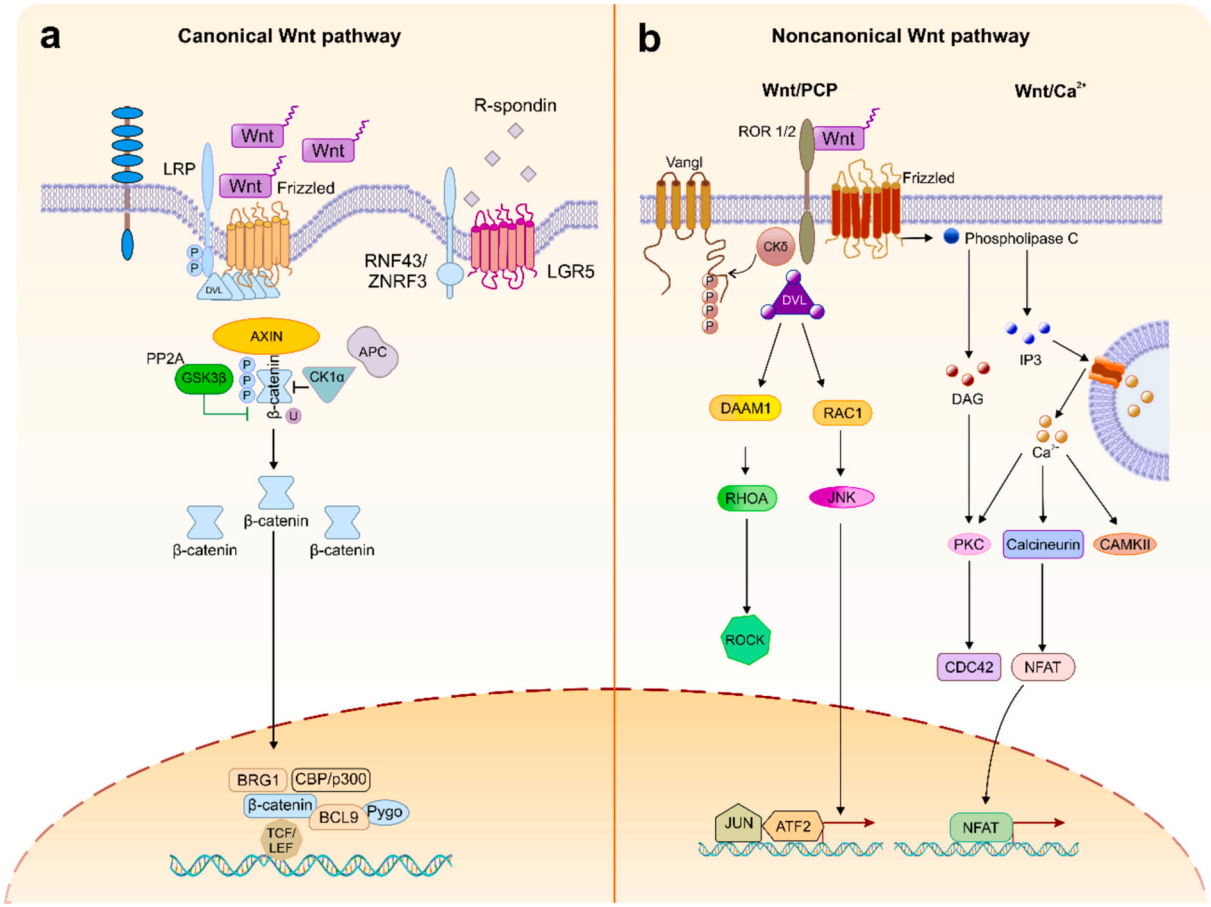

Fig. 3. Canonical Wnt pathway and noncanonical Wnt pathway. a. Canonical Wnt pathway (β-catenin-dependent). When the Wnt ligand binds to the FZD and LRP co-receptor, it induces the translocation of Axin and the destruction complex (consisting of Axin, APC, PP2A, GSK3β, and CK1α) to the plasma membrane, leading to the inactivation of the destruction complex. This allows β-catenin accumulation and translocation to the nucleus, which induces gene transcription. b. Noncanonical Wnt pathway (β-catenin-independent). Left: Wnt/planar cell polarity pathway (PCP) starts with Wnt binding to the FZD and receptor tyrosine kinase-like orphan receptor complex. This interaction activates Dishevelled, which then binds to the small GTPases RHOA. The small GTPases RHOA and RAC1 trigger ROCK and JNK, regulating cytoskeleton rearrangement and the transcriptional response of ATF2. Right: Wnt/Ca^{2+} pathway is initiated by trimeric G-protein-mediated phospholipase C. Phospholipase C leads to intracellular calcium influx and calcium-dependent transcriptional responses.

granule neuron progenitors induced by the noncanonical Wnt signaling pathway reduces the proliferation of medulloblastoma tumor growth in a mouse model [100]. In contrast, the activation of Wnt-related signals in rigorously proliferating glioblastoma cells vampirizes Wnt from neurons, which then induces neuronal loss [101]. According to this study, the depletion of Wnt in neurons around glioblastoma cells enhances glioblastoma progression by triggering JNK/MMP signaling. In these cases, Wnt from neurons in the TME can present with tumor-suppressive properties. In conclusion, the research so far has revealed that neurons and glioma/glioblastoma closely interact by regulating the Wnt-related signaling pathways. As a component of TME, neuronal growth and differentiation commonly enhance brain tumor growth. However, their effects on neurons in proliferating cancer cells can be controversial.

The Wnt factors released from astrocytes are highly associated with neuronal activation. However, the aberrant activation of Wnt-signaling in astrocytes can also lead to tumor growth [102]. For example, the canonical Wnt/β-catenin-pathway has been upregulated in astrocytoma, which confirms the importance of β-catenin in tumor growth [103,104]. As a component of TME, astrocyte transformation induced by dead-hesion/adhesion cycles increased the risk of malignant gliomagenesis. The involvement of PI3K/Akt and Wnt/β-catenin was observed in this astrocyte transformation. Hence, targeting Wnt/β-catenin can restore astrocyte function and reduce tumorigenesis progression [105]. Further, increased Wnt and β-catenin signaling leads to the activation of reactive astrocytes, which cause the proliferation of adjacent astrocytoma [106]. An aberrant increase in PLAGL2 in astrocytes led to the upregulation of Wnt signaling components including Wnt6, which then contribute to cancer stem cell stemness maintenance and gliomagenesis by canonical Wnt signaling [107]. Thus, reducing Wnt/β-catenin signaling is important in suppressing the number of astrocytes and subsequently compromising brain tumor growth. According to previous research, downregulating Wnt/β-catenin signaling can inhibit early astrogliogenesis from neural stem cells, which then results in the disruption of proliferation in neurogenesis [108]. Overall, thus far, the normalization of the related signal transduction of Wnt in astrocytes can be helpful in inhibiting the growth of primary brain tumors.

Microglia are the most evaluated TME constituent cells in relation to Wnt signaling pathway-based brain cancer development due to their immune-regulatory function. Wnt signaling from the microglia can be a good molecule for tumor growth. Both M1- and M2-type microglia secrete Wnt ligands which then participate in neural stem cell growth and differentiation [109]. Further, transcriptomic data revealed that the Wnt signaling pathway is strongly associated with tumor-associated macrophage (TAM) or microglia activation [110]. Wnt-induced signaling protein from glioma stem cells increases tumor-supportive M2 TAMs, which then enhance glioblastoma growth [111]. Because M1-like TAMs enhance anti-tumor immunity by producing cytokines such as TNF-α or IFN-γ, polarization of M2 type to M1 type TAM will be effective to induce tumor suppression and inhibit the brain tumor

metastasis [112]. Several studies have revealed that the Wnt pathways derived from the microglia induce neural regeneration. Nevertheless, most studies have revealed the essential role of Wnt in the microglia in cancer progression [113]. For example, patients with glioblastoma commonly present with the overexpression of β-catenin protein in the microglia [114]. Interestingly, Matias et al. revealed that Wnt3a from the glioblastoma-conditioned media enhance the recruitment of microglia and microglial activation as M2-like phenotype. Further, these microglia in turn increase the invasiveness of glioblastoma [115]. In this study, blocking the canonical Wnt/β-catenin signaling attenuated microglial polarization into the immunosuppressive subtype and activated the immune system, improving the prognosis of patients [116]. In addition, the Wnt5a protein levels were upregulated in malignant gliomas due to the increased expression of microglia/monocytes around the tumor [117]. Similarly, an increased expression of Wnt3a and Wnt5a from the microenvironment of astrocytes and microglia were observed around glioma cells according to a gene analysis [118]. These studies have revealed that the activation of microglia can exacerbate tumor progression by releasing Wnt ligands. The application of DKK-2 (a secreted Wnt antagonist) to the microglia reduced the invasiveness of brain tumors [119]. In addition, the expression of several proteins that enhance Wnt signaling is increased in the microglia. For example, the expression of triggering receptor expressed on myeloid cells 2 (TREM2) is upregulated in the microglia which then activates Wnt/β-catenin signaling in both microglia and tumor [120]. TREM2 inhibition then triggers the antitumor cell activity of myeloid cells in mouse glioblastoma models by increasing the expression of programmed cell death in tumor cells [121]. Overall, the microglia and primary brain tumor interact with each other to drive microglia to an immunosuppressive state and brain tumor growth by communicating with each other with Wnt signaling-associated molecules. Therefore, microglia further contribute to the stemness of brain cancer stem cells.

Oligodendrocytes or OPCs can also release Wnt ligands to support brain tumor growth, even though only a few research has evaluated the role of Wnt-associated signaling in these cells. According to previous research, the Wnt inhibitory factor 1 (WIF 1) of oligodendrocytes is the most promising candidate for reducing astrocytoma growth. Thus, non-neoplastic oligodendrocytes, which strongly express WIF 1, contribute to the inhibition of tumor cells by paracrine signaling [122]. In OPCs, Wnt signaling is dependent on the marker of OPCs. Wnt7a/b derived from $Olig2^{+}$ OPC is increased, which then induces the invasion and vascularization of glioma. The inhibition of Wnt7-dependent signaling then inhibits glioma growth and improves the response to temozolomide therapy [123,124]. In summary, Wnt release from oligodendrocytes/OPCs can also induce brain tumor progression.

In the endothelial cells of BBB, Wnt signaling in endothelial cells is strongly associated with brain tumor growth. Thus, Wnt7a is a therapeutic target in Wnt-driven tumors [125]. Around the glioma, high expression of CD161 in T cells and microglia, which has strong correlation with Wnt-signaling pathway, help infiltration of other immune cells around the tumor to help inhibition of glioma cell growth. It can be inferred from this result that immune cells with CD161 expression fight against tumor growth induced by Wnt-mediated pathways from brain TME [126].

In neural stem cells, cancer stem cells, or mesenchymal stem cells, Wnt signaling can enhance self-renewal and differentiation potential, which then strongly triggers tumor progression where WIF 1 then induces senescence of these cells and impedes tumor growth [127,128]. In addition, SOX 10, which inhibits Wnt/β-catenin pathway, is highly observed in M1 microglia, neurons, and neural stem cells around glioma. These cells with high SOX10 levels play a significant role in immune cell chemotaxis, leading to infiltration of various immune cells that can reduce the overall survival of glioma cells [129]. Regarding cancer stem cells, downregulation in period circadian clock 2 expression in glioma stem cells, which targets Wnt signaling, was observed. Therefore, inducing Wnt/β-catenin signaling in glioma stem cells can increase the risk of malignant glioma compared with that in non-stem glioma cells [130]. Furthermore, cancer stem cells increase secretion of synaptic protein neuroligin3 by Wnt/β-catenin pathway, resulting in transformation of neighboring cells to cancer stem cells and subsequent glioblastoma progression [131]. Epigenetic regulation of the canonical pathway by miRNA can directly/indirectly increase the cancer stem cell self-renewal, triggering glioma progression [132]. These results suggest that the canonical pathway of Wnt in cancer stem cells significantly induces glioma cell proliferation [133]. According to previous research, mesenchymal stromal cells around the neuroblastoma have an activated Wnt pathway, closely related to tumor cell stemness and epithelial-mesenchymal transition, which then result in tumor metastasis [134]. The transformation of mesenchymal stem cell in glioblastoma can also increase the chemoresistance where ablation of β-catenin resulted in overcome tumor resistance to temozolomide chemotherapy [124].

In cases of ECM components, extracellular heparanase from ECM increases intracellular Wnt3a signaling in human medulloblastoma, which then alters the localization and expression of β-catenin [135]. This study showed that patients with brain tumors are present with higher levels of heparanase than those with control brain lesions. Exosomes transferred via ECM can significantly impact brain TME via various mechanisms. For example, astrocyte-derived extracellular vesicles induce glioma stem cell proliferation [136]. Wnt5-containing extracellular vesicles from glioblastoma is also involved in glioma stem cell survival and progression [137]. Glioma stem cells release Wnt-induced signaling protein 1 by exosomes, which then helps maintain M2 TAM by canonical pathway [138]. M2 type TAM will then contribute to immunosuppressive TME for brain tumor progression [139]. Additionally, the exosomal miR-301a derived from glioblastoma represses the expression of tumor suppressor gene TCEAL7, which then activates the canonical pathway of Wnt pathway [140]. Therefore, it is important to identify the mechanism associated with increased ECM components in Wnt-driven brain tumors [141].

Understanding the intricate crosstalk between Wnt signaling from the TME and brain tumor is important for developing targeted therapies that can exploit the tumor-suppressive effects. Nevertheless, further research should be conducted to elucidate the specific roles of Wnt signaling within the brain TME to inhibit brain tumors effectively.

3. Conclusion

Increasing evidence has shown that Wnt signaling plays a key role in the pathogenesis of malignant brain tumors including glioma. In particular, it contributes to the growth of tumors and stem cells, tumor invasion, and angiogenesis. This review focused on the diverse roles of Wnt within the brain TME in brain tumor progression. Brain tumors represent a formidable challenge in oncology, with limited treatment options and poor prognosis in patients. Neurons, glial cells, immune cells, stem cells, and ECM components create a complex network within the TME, resulting in tumor growth and therapy resistance to conventional radio- and chemotherapy. Notably, aberrant canonical and non-canonical Wnt signaling pathways in the TME can be an important factor in promoting brain tumor progression (Fig. 4). Thus, the pharmaceutical industry has been developing potent inhibitors for Wnt and associated molecules such as SEN461 (targeting Axin), WNT974 (porcupine inhibitor), and PKF115-584 (targeting β-catenin) for the future therapy of glioblastoma [142–144]. In addition, the Wnt-subtype medulloblastoma that was locally treated with active Wnt inhibitors such as WIF 1 and DKK1 had the best prognosis [145]. These Wnt inhibitors, which are evaluated in ongoing clinical trials, can be used in combination with irradiation or chemotherapy against brain tumors (Table 1). Moreover, previous studies have identified Wnt-associated molecules that can be potential prognostic biomarkers of glioblastoma. Thus, understanding the specific roles of Wnt signaling in different cell types within the brain TME is essential for developing targeted therapeutic strategies.

Elucidating the mechanisms of Wnt signaling in tumor progression

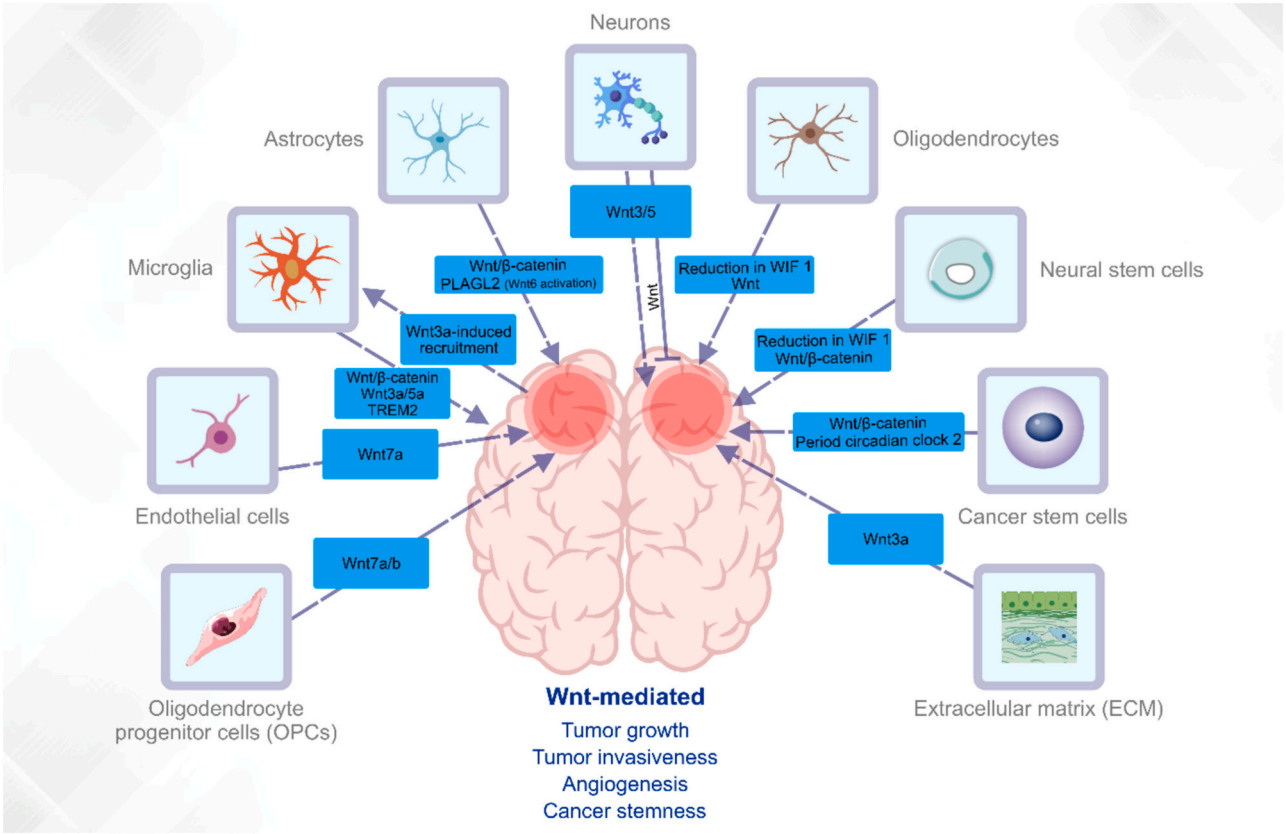

Fig. 4. Wnt-mediated pathways in the brain TME. Various Wnt subtypes produced by different cell types within the brain TME result in tumor progression. Central to this network is the Wnt-mediated regulation of tumor growth, invasiveness, angiogenesis, and stemness, highlighting the intricate communication between different cell types within the brain TME.

Table 1
Pharmacological inhibitors targeting Wnt signaling in brain tumors.

Drug name	Target	Mechanisms of action	Target tumor
SEN461	Axin	Stabilizes Axin by preventing proteasomal degradation	Glioblastoma
WNT974	Porcupine	Inhibits porcupine activity required for Wnt ligand secretion	Glioma
PKF115-584	β-catenin	Blocks β-catenin-TCF interaction	Glioblastoma
WIF 1	Wnt ligand	Inhibits Wnt ligand activity	Medulloblastoma
DKK1	LRP5/6	Blocks Wnt signaling at receptor level	Medulloblastoma

and TME can help develop more sophisticated anti-cancer drugs. Future research should focus on elucidating the precise mechanisms underlying Wnt-mediated interactions within the brain TME. By identifying key signaling molecules and cellular pathways, novel therapeutic targets can be identified to improve the treatment outcomes of patients with brain tumors. Ultimately, elucidating the complexities of the TME and Wnt signaling can improve our understanding of brain tumor biology. Moreover, it can lead to the development of more effective therapeutic interventions to improve overall survival in patients with brain tumors.

CRediT authorship contribution statement

Han Na Suh: Writing – original draft, Conceptualization. **Gee Euhn Choi:** Writing – original draft, Conceptualization.

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Declaration of competing interest

None.

Data availability

No data was used for the research described in the article.

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