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REVIEW ARTICLE

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The role of Shh signalling pathway in central nervous system development and related diseases

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Sonic hedgehog (Shh) plays important roles in developmental of vertebrate animal central nervous system (CNS), and Gli is its downstream signal molecule. Shh signalling is essential for pattern formation, cell-fate specification, axon guidance, proliferation, survival and differentiation of neurons in CNS development. The abnormal signalling pathway of Shh leads to the occurrence of many nervous system diseases. The mechanism of Shh signalling is complex and remains incompletely understood. Nevertheless, studies have revealed that Shh signalling pathway is classified into canonical and non-canonical pathways. Here we review the role of the Shh signalling pathway and its impact in CNS development and related diseases. Specifically, we discuss the role of Shh in the spinal cord and brain development, cell differentiation and proliferation in CNS and related diseases such as brain tumour, Parkinson's diseases, epilepsy, autism, depression and traumatic brain injury. We also highlight future directions of research that could help to clarify the mechanisms and consequences of Shh signalling in the process of CNS development and related diseases.

Significance of the study

This review summarized the role of Shh signalling pathway in CNS development and related diseases such as brain tumour, Parkinson's diseases, epilepsy, autism, depression and traumatic brain injury. It also presented the author's opinions on the future research direction of Shh signalling pathway.

KEYWORDS

brain, central nervous system, signalling pathway, Sonic hedgehog, spinal cord

1 | INTRODUCTION

Sonic hedgehog (Shh) is a secretory protein, which is one of three mammalian orthologs of the Hedgehog (Hh) family of secreted proteins that were identified in the famous Drosophila.[1] The expression products of the Hh gene family are a series of secretory proteins that can act on adjacent or distant cells and regulate the expression level of related genes. In vertebrates, there are three homologous genes of Hh, namely, dessert hedgehog (Dhh), Indian hedgehog (Ihh) and Sonic hedgehog (Shh). Among the three types of Hh genes, the function of the Shh gene has been studied the most.[2] The Shh pathway is involved in the development of many tissues and organs, such as eyes, limbs, CNS, skin, hair, teeth, cochlea and lung, and plays an indispensable role in the determination of tissue polarity.[3,4] It has been shown that Shh plays an important role in the establishment of the ventral spinal cord model, the induction of basal plate and motor neuron formation, and has many functions in early embryonic development. For example, the formation of neural tube patterns, the establishment of the anterior-posterior axis and the dorsal-ventral axis, and the formation of somites and limbs.[5,6] Abnormal regulation of the Shh signalling pathway in the brain may lead to a variety of neurological diseases, such as autism, depression, dementia, stroke, Parkinson's disease,

Huntington's disease, motor disorders, epilepsy, demyelinating disease, neuropathy and brain tumours.[7] Therefore, the Shh signalling pathway is a promising target for the treatment of nervous system diseases. The further study of this signalling pathway will provide significant guidance and scientific value in understanding the pathogenesis and clinical diagnosis of nervous system disease, and in the development of new treatments.

Shh signalling is essential for patterning and cell-fate specification, particularly in the CNS. During the development of the vertebrate CNS, Shh plays important roles as a morphogenic factor in ventral patterning, proliferation, differentiation and survival of neural precursor cells along the neuraxis, including the telencephalon.[8-11] Shh signalling plays different roles depending on its concentration, temporal and spatial variation.[12] Shh signalling in the development of CNS had been elucidated by the study of Shh knock out (KO) mouse embryos. Early defects are observed in the establishment or maintenance of midline structures, such as the notochord and the floorplate, and later defects include absence of distal limb structures, cyclopia, absence of ventral cell types within the neural tube and absence of the spinal column and most of the ribs.[5] In the human, Shh mutations have been shown to result in serious influence on both the forebrain and the face, such as holoprosencephaly.[13] Abnormal expression of the Shh gene was observed in the floor plate of embryos with craniorachischisis (CRS) and spina bifida (SB).[14] On the other hand, recent studies have revealed that Shh may be involved in the development of the other tissues and organs, including the polydactyly syndrome, congenital heart disease, desmoplastic medulloblastoma and Gorlin syndrome in the setting of Down syndrome.[15-17] In the present review, the roles of Shh on the spinal cord and brain development are discussed, including the effect of Shh on the neural precursor cell proliferation and differentiation and related diseases.

2 | SHH SIGNALLING PATHWAY

In mammals, Shh secreting cells first synthesize 45 kDa large Shh precursor proteins, including the amino terminus and the carboxy terminus, which are further proteolytic processing into two peptide fragments. One fragments is the carboxy terminus of the precursor protein, size 27 kDa, and the specific function is unknown. The other fragments is the amino terminus of the precursor protein, size 19 kDa, is a morphogen protein as we known Shh (Figure 1).[18,19]

Shh signalling pathway is classified into canonical and non-canonical pathways. The canonical Shh signalling pathway comprises three main components: the Shh ligand binding to the receptor Patched (Ptch), a twelve-pass membrane protein; Ptch interacts with and inhibits smoothened (SMO), a seven-pass membrane protein; and finally a cytoplasmic complex that regulates the Gli family of transcriptional effectors (Figure 1). There is activation role and inhibition role feedback at the transcriptional level as the Gli1 and Ptch1 genes are direct transcriptional targets of activation of the pathway.[20] In the presence of Shh ligand, Shh binds Ptch, its interactions with SMO are altered that lead to SMO is no longer inhibited. This leads to Gli protein entering into the nucleus and acting as a transcriptional activator for the downstream gene expression. In the absence of Shh ligand, the Ptch is free to interact with Shh and inhibit SMO. This leads to Gli protein no longer entering the nucleus and acting as a transcriptional activator for the downstream gene expression (Figure 1). The processing and nuclear import of Gli is regulated through a complex of Gli with the cytoplasmic members of the Shh signalling pathway, fused (Fu) and suppressor of fused (SuFu).[21] SuFu regulates Gli factors processing and nuclear localization.[22-24] Most of Gli is available for cleavage in a process which is dependent on its phosphorylation by the Protein kinase-A (PKA). PKA oppose activation of the Shh pathway by regulating the stability of intermediate signalling transcription factors of Shh pathway[24,25] Activated nuclear Gli interacts with the CREB Binding Protein (CBP) to further activate the transcription of Shh target genes expression (Figure 1).

In addition to the canonical Shh signalling pathway, there are also non-canonical pathways related to Shh signalling. Non-canonical Shh signalling refers to either: activation of signalling from Ptch1/SMO but independent of Gli transcription factors; or activation of Gli transcription factors independent of Shh ligand or Ptch1/SMO.[26] Many studies show that Shh is involved in cellular activity through non-canonical Shh signalling pathway. Such as, Shh as an axon guidance signal in vertebrates. Shh stimulates the activity of Src family kinase (SFK) members in a SMO dependent manner. Moreover, SFK activity is required for Shh-mediated guidance of commissural axons, but not for induction of Gli transcriptional activity.[27] Additionally, the Gli proteins have been shown to be negatively regulated by PKA (Figure 1).[28] In contrast non-canonical, canonical Shh signalling is mediated via SMO activation, which induces activation of the Gli transcription factors. Transcription of Gli target genes as a consequence of SMO activation such as proliferation (Cyclin-D1, MYC), apoptosis (Bcl-2), angiogenesis (ANG1/2), epithelial-to-mesenchymal transition (SNAIL), and stem cell self-renewal (NANOG, SOX2), then transduce the major cellular effects of canonical Shh signalling.[29-33] In a word, the regulation mechanism of Shh on the cells some of them through canonical Shh signalling, some of them through non-canonical signalling pathways.

In vitro and in vivo experiments further proved the regulatory mechanism of key molecules of the Shh signalling pathway. Binding of the secretory protein Shh with the membrane protein Patched 1 (Ptch1) relieved its inhibition of the transmembrane protein SMO. The transmembrane protein SMO, encoded by the proto-oncogene, is homologous to the G-protein coupled receptor and activates the intracellular transcription factor Gli. In vertebrates, Gli has three members, Gli1, Gli2 and Gli3. Although their structure and function differ,[34] they all contain highly conserved DNA binding and C-terminal activation regions, but only Gli2 and Gli3 have N-terminal inhibition regions, and only Gli1 is not hydrolysed by proteases. Studies have shown that Gli1 highly activates transcription whereas Gli3 is a transcription inhibitor.[35] Gli2 has dual functions of transcription activation and inhibition but mainly exists as an activator, whose transcriptional activation function is stronger than Gli3, but weaker than Gli1. As both Gli2 and Gli3 contain N-terminal inhibition

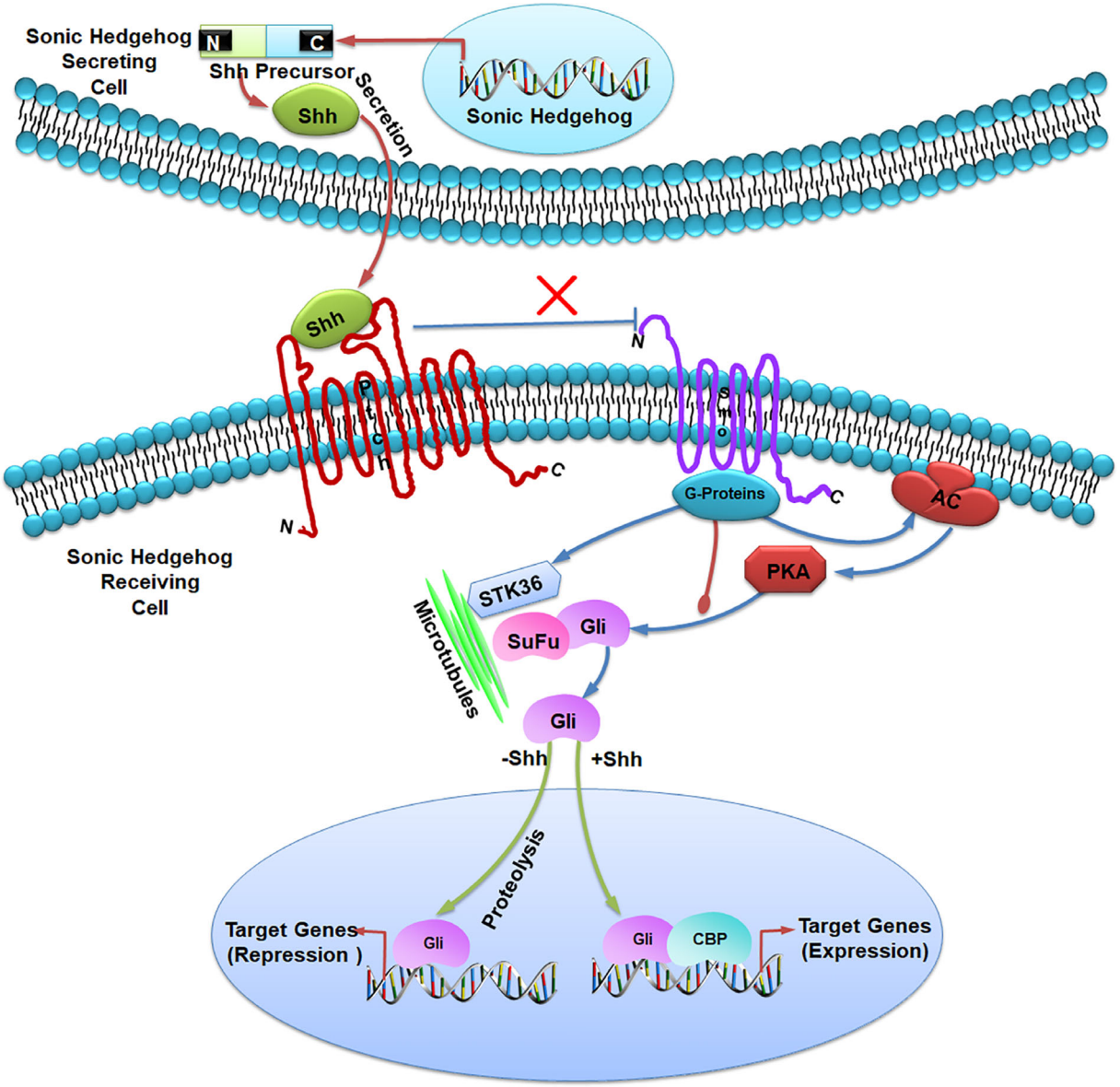

FIGURE 1 Shh signalling pathway. Without Sonic hedgehog (Shh), Patched (Ptch1) inhibits the activity of Smoothened (SMO). Ptch1 inhibits SMO, thereby inhibiting the downstream signalling transduction. The Gli proteins are phosphorylated by protein kinase A (PKA), leading to their cleavage by the proteolysis and the formation of carboxyl-terminus-truncated repressor Glis, which move to the nucleus and repress the Gli-dependent transcription of target genes. Under the expression of Sonic hedgehog (Shh+), Shh binding to the Ptch1, thus releasing SMO activity and the Su (Fu) (Suppressor of fused), Fu (Fused), PKA, the Gli proteins and other possible components, acts to produce labile Gli activators. These are imported into the nucleus and transactivate target genes

regions, only after the N-terminal protease is removed or phosphorylated will they be considered transcriptional activators.[36,37] Therefore, Gli1 is the only direct activator of the three transcription factors, and its activation regulation occurs at the transcription level. As Gli2 and Gli3 are only potential activators of transcription, the expression level of Gli1 mRNA is a reliable indicator of the activity of the Shh signalling pathway which in turn directly affects the fate of Gli proteins.

At present, it has been shown that the nuclear factors involved in Shh signal transduction mainly include transcription factors Ci/Gli, Fu, SuFu, protein Costal-2 (Cos2), and protein kinase A (PKA), among which Ci/Gli and Fu play a positive role, while Cos2 and PKA play a inhibition role. In the absence of ligands, Gli forms a large protein complex with Cos2, Fu and SuFu, and binds simultaneously to both SMO and microtubule. The Gli protein is cleaved by protease and transported to the nucleus by a C-terminal fragment to perform transcriptional repressor functions. In the presence of ligands, Ptch binds to the ligands, and the G-protein coupled receptor kinase 2 (GRK2) phosphorylation of the C-terminus relieves the inhibition of SMO, releasing Gli from the large complex. Only through maintaining the full-length Gli protein transfer to the nucleus can the transcription of downstream target genes be initiated.[36-39]

Gli1 has been shown to be a direct activator of transcription, containing five zinc finger domains, of which the fourth and fifth are able to bind to specific DNA sequences.[40] Studies in human tissues have shown that Gli1 binds to a specific 9 nucleotide DNA sequence (5′-GACCACCCA-3′), to regulate gene transcription.[41] This sequence is the same in mice. The latest research shows that there are six binding regions of Gli in the first intron of Gli1, and Both Gli1 and Gli2 can bind all six regions to activate the expression of the proto-oncogene.[42] However, in the development of the CNS, whether Gli1 is able to regulate the proliferation, differentiation, and axon formation of neural precursor cells by combining with specific DNA sequences is rarely studied.

3 | EFFECT OF SHH SIGNAL PATHWAY ON CNS

3.1 | Role of Shh in spinal cord development

One of fundamental goals in developmental neuroscience is to understand how distinct classes of neurons in the vertebrate CNS are generated.[43] The spinal cord represents a well-characterized region of the CNS, where our understanding of the mechanisms that regulate neuronal subtype identity are most advanced. Distinct neuronal subtypes including motor neurons (MNs) and four groups of interneurons (V0-V3) are formed along the dorsal-ventral axis in the ventral tube in response to graded Shh signalling. To understand the mechanisms underlying this process, a greater knowledge of the molecular control of the acquisition of neuronal identity is required.

Shh is expressed in the floor plate and notochord in the vertebrate neural tube and exhibits a gradient distribution along the dorsal-ventral axis of the neural tube during embryonic development.[44] The gain-and loss-of-function experiments have showed that Shh is both necessary and sufficient to induce ventral-neural-cell types.[8,45] Shh deficiency affects not only the formation of spinal cord structures, but also brain development.[5] In our previous studies, in vivo electroporation was employed to achieve the ectopic expression of Shh in the developing chicken spinal cord.[46] Compared with the control group, the abnormal morphology and structure of the spinal cord were observed in Shh ectopic expression group. From the in situ hybridization results of tissue section, it can be seen that the spinal cord at one side of the ectopic expression of Shh appears bent in comparison with normal controls, it may be due to the Shh expression promote the proliferation of cells. In past study have showed that Shh ectopic expression in dorsal of spinal cord could inhibited the expression of Pax family. In ventral of spinal cord, Shh overexpression could affect the motor neuron positioning of MNR2 positive motor neurons.[46] In fact, Shh regulates the expression of numerous proteins in the spinal cord. Such as Nkx2.2, Olig2, Nkx6.1, Nkx6.2, Dbx1, Dbx2, Irx3, Pax6 and Pax7 from ventral to dorsal is regulated by graded Shh signalling.[44] Thus, as a morphogenetic protein, Shh is involved in the development of ventral spinal cord, which determines the expression of ventral spinal cord related proteins, and is a key factor in the formation of normal ventral structures.

Studies have shown that Shh and netrin-1 jointly regulate the projection of spinal cord commissural fibres.[47] Shh regulates the projection of spinal cord commissural fibres both directly and indirectly through the Wnt signalling pathway.[48] Shh expression in the spinal cord regulates the abnormal expression of multiple molecules during development and play a decisive role in the formation of its normal structure. For example, Shh and cadherin 7 have a mutual regulation mechanism during the early development of the spinal cord of chickens.[49,50]

The expression of Shh in the spinal cord showed a gradient distribution from the ventral to the dorsal side. The expression of different gradients is necessary for the formation of correct spinal cord structures and the formation of correct neurons in different regions, which further shows that Shh is a concentration-dependent regulatory molecule. in vitro experiments have additionally confirmed this point. in vitro culture of chicken embryo neural tissue with a 2-3 time increase in Shh concentration, or increased exposure to Shh leads to the transformation of dorsal cells to ventral cells. Exposure of neural plates cultured in vitro to different Shh protein concentrations leads to different types of cells.[51,52] In the spinal cord, oligodendrocyte precursors originate from the ventral ependymal area, which is consistent with the area of motor neurons.[44,53] Additionally, many experiments have shown that Shh is necessary for the production of oligodendrocyte precursors. Whether through chemical inhibitors or Shh blocking antibodies, the loss of Shh function inhibits oligodendrocyte differentiation,[54-56] while the addition or knockout of SMO by additional Shh protein leads to the production of ectopic oligodendrocytes.[57] Both cells of the spinal cord and spinal floor can secrete Shh, so the question is, do the Shh signals from these two sources play the same role in the formation of the spinal dorsal-ventral axis? Studies have shown that Shh is first secreted by the spinal cord, and originates from the mesoderm. Before the closure of the neural tube, the spinal cord is directly connected to the ventral midline of the neural plate, but shortly after the closure, basal cells begin to secrete Shh protein. Later, the spinal cord gradually separates from the ventral spinal cord, making the basal cells the only source of Shh, which is required for the formation of most neurons and glial cells.[58] Although Shh is produced in both the notochord and the basal plate, it is connected with it in early neurogenesis. Basal plate cells only begin producing Shh after the transcription factors of marker molecules are induced, indicating that ventral pattern formation depends mainly on Shh released from the notochord, responsible for providing spatial signals for precursor cells, with Shh produced by the basal plate playing a smaller role.[59,60] Owing to the complexity of the structure of the different regions of the spinal cord, the mechanism of Shh in the proliferation of neural precursor cells, the formation of neurons and the formation of spinal cord commissural fibres remains to be further studied.

3.2 | Role of Shh in brain development

In brain development, the formation of normal morphology and structure requires the expression of many factors at the precise locations

and at precise times. Shh belongs those factors. Within the brain, Shh is first expressed ventrally at early embryonic development stages, including the development of ventral hindbrain, midbrain and forebrain.[61,62] The Shh through Gli pathway induces different classes of neurons in the ventral brain and regulates the size of the ventral midbrain.[10,63,64] In addition to, Shh signalling controls the development of the cerebellum at multiple levels. In vivo, inhibition of Shh signalling with a monoclonal antibody results in the Purkinje layer is disorganized in the brains of chicks.[65] This also indicates that Shh is necessary for Purkinje neurons. There have showed that Shh is produced by chick and mouse Purkinje neurons and also transiently by early mouse external germinal layer cells.[65] It has been previously reported that normal growth of the tectum was repressed by ectopically expressed Shh unilaterally in the brain vesicles including whole midbrain of E1.5 chick embryos in ovo.[66]

In our previous studies, in vivo electroporation was employed to overexpress Shh in the developing chicken tectum.[67] Compared with the control group, the abnormal morphology and structure of the tectum were observed in Shh overexpression group. In the control group, the optic tectum of the expression GFP and contralateral side were symmetrical, but in the experimental group, the optic tectum of the expression GFP was significantly larger than the contralateral side. From fluorescence immunohistochemistry results, it can be seen that no Shh expression was observed in the GFP control group and Shh overexpressed in the experimental group. In the GFP control group, GFP positive cells were distributed in the six layers of the optic tectum. In the Shh overexpression group, GFP positive cells were aggregated in the stratum griseum central (SGC) layer. From the results we speculate that Shh overexpression may inhibit the neurons migration during optic tectum development, there may be Shh changes the cell fate of neural precursor cells, and the cells after Shh overexpression all differentiate into SGC layer cells. A previous study has showed that Shh plays a critical role in early forebrain and CNS development.[68] Shh can control pattern of brain development and the size, shape and orientation of the cell populations.[10] The function of Shh in the brain is similar to that in the spinal cord. Shh is first expressed ventrally at early embryonic development stages, including the development of ventral hindbrain, midbrain and forebrain, which determines the normal formation of its ventral structure. The expression of Shh spatiotemporal patterns changes could lead to the formation of abnormal brain structures.

3.3 | The Shh signalling pathway in cell differentiation and proliferation in the CNS

Shh is a secreted protein that acts as a morphogen in normal development of vertebrate animal CNS, such as neural tube and brain.[5,62] Shh signalling is essential for patterning and cell-fate specification, it has been shown to regulate cell cycle kinetics of radial glial cells and intermediate progenitor cells, thereby maintaining the proliferation, survival and differentiation of neurons in the neocortex.[12] In previous studies, we have revealed that the ectopic expression of Shh in the spinal cord of dorsal area lead to changes in the pattern of spinal cord development such as the distortion and neuroepithelial cell layer at the roof plate increased. This study demonstrated that Shh ectopic expression induction of ventral identity due to the high levels of Shh signalling.[11] One study showed that Shh represses cell proliferation and enhances neural differentiation in the chicken midbrain at E1.5 ectopic expression of Shh in the brain vesicles including whole midbrain.[66] It has been reported that Shh is required for differentiation of midbrain dopaminergic neurons in rat and chick.[54,63,69] According to the results of existing research, we can conclude that Shh can promote the differentiation of vertebrate animal midbrain neural precursor cells, but inhibit the proliferation of neural progenitor cells.

3.4 | Shh signalling pathway and CNS diseases

The disorder of the Shh signal transduction in the brain would lead to the occurrence of various nervous system diseases, such as brain tumours,[70] Parkinson's disease,[71] epilepsy,[72] autism,[73] depression[74] and traumatic brain injury[75] (overall symptoms of the Shh-related CNS diseases are summarized in Table 1).

3.4.1 | Shh signalling pathway and brain tumorigenesis

The activation of Shh signalling pathway has been found in different types of solid and non-solid cancers, including medulloblastoma, glioma, and neuroblastoma.[76]

Medulloblastoma (MB) is a highly aggressive malignant tumour in brain. It is one of the most common malignant tumours in childhood.[77] Studies have shown that MB is caused by the abnormal expression of Shh in clinical cases. Research on the molecular mechanism and clinical characteristics of MB divides it into four subtypes: Wnt-MB, Shh-MB, group 3 MB and group 4 MB.[70] The subtype Shh-MB is caused by an abnormal Shh signal pathway, accounting for more than 30% of human patients with MB.[78] In the mouse model, heterozygous Ptch1 ($Ptch1^{+/-}$) and $SMO^{+/+}$ mice all express MD similar to humans, indicating that the mutation of key molecules of the Shh signalling pathway is closely related to the development of MB tumours.[79,80]

Glioma, also known as glioblastoma is the most common primary central nervous system tumour, accounting for 50% of all primary intracranial tumours.[81] Hedgehog Gli1 pathway affects the growth of glioma and the population of Gli positive neural stem cells are thought to be the origin of glioma stem cells.[81] Endogenous Shh promotes the growth of oligodendroglioma and astrocytoma.[82] SMO is reported to promote glioma cells proliferation, migration and invasion while inhibit cells apoptosis.[83-85] In consistent, the application of SMO specific blocker inhibits the growth of glioma cells.[83-85] The study of neuroblastoma (NB) shows that persistent activation of the Shh pathway can promote the development of NB. Blockage of the Shh signalling pathway by cyclopamine induces apoptosis and G1 arrest of NB cell lines. These results indicate that the Shh pathway affects the

TABLE 1 Shh signalling pathway and CNS diseases

Disease name	Symptoms	Major causal genes (Shh-related)	References
Brain tumour			
Medulloblastoma (MB)	In children, early symptoms are not obvious, the first symptoms are headache, vomiting, gait instability, late would ataxia, vision loss	Ptch1, Smo	Tamayo-Orrego and Charron[70]; Katoh and Katoh[76]
Glioma	Also known as glioblastoma is the most common primary central nervous system tumour	SMO	Zhang et al[81]; Xiong et al[83]; Dahmane et al[84]; Bar et al[85]
Parkinson's diseases (PD)	Static tremor, bradycardia and reduction, increased muscle tension, postural instability	Shh	Lee et al[71]
Epilepsy	Transient brain dysfunction and chronic obstruction	Shh, SMO, Gli2	Feng et al[72]; Hildebrand et al[92]
Autism	Inability to create normal, biological determination and emotional contact with others	Ptch1	Halepoto et al[73]; Chaste et al[96]
Depression	Low mood, lack of energy, sadness, insomnia, and inability to enjoy life	Gli1/2/3, Nkx2.2,	Tayyab et al[74]; Cui [102]; Tayyab[105]
Traumatic brain injury (TBI)	Brain damage caused by external forces	Shh	Capizzi et al[75]; Maas et al[106]; Wu et al[108]

end-point for NB cell lines through regulating apoptosis and cell cycle arrest.[86] The study of olfactory neuroblastoma (ONB) shows that Shh signalling pathway is crucial for the growth of ONB. The blockage of Shh signalling inhibits the proliferation of ONB cells and induced ONB cell cycle arrest and apoptosis.[87]

3.4.2 | Shh signalling pathway and Parkinson's diseases

Due to the complexity of the brain structure, the pathogenesis study is still a subject that neurobiologists have been working on. However, most of the final pathological changes caused by these nervous system diseases have been clarified. For example, the most important pathological change in Parkinson's disease is the degeneration and death of dopaminergic neurons in the nigrostriatal region of the midbrain, leading to a significant reduction of dopamine (DA) content in the nigrostriatal pathway thus resulting in the disease. It reported that Shh could inhibit the death of midbrain dopaminergic neuron induced by the neurotoxin N-methyl-4-phenylpyridinium (MPP^+).[88] After Shh-N was given to the brain of Parkinson's disease rats, the motor function of rats was improved and the number of tyrosine hydroxylase immunoreactive neurons in striatum increased, indicating that Shh has a certain therapeutic prospect for Parkinson's disease.[89] Dopamine transporter-Smo knockout mice are hyperactive in young adults and have altered responses to methamphetamine, this indicating the role of Shh pathway in DA.[90] It is reported that the expression of Shh protein is significantly increased in substantia nigra of PD model animals. The activation of Shh signalling pathway can protect dopaminergic neurons and reduce the damage.[91] In astrocyte oxidative stress model treated with H_2O_2, exogenous Shh can reduce the oxidative stress of astrocytes by regulating PI-3K/Akt/Bcl-2 signalling pathway and reduce the rate of apoptosis induced by H_2O_2.[92] These results indicate that Shh signalling pathway can protect dopaminergic neurons, and the activation of Shh signalling pathway can effectively treat PD.

3.4.3 | Shh signalling pathway and epilepsy

Epilepsy is caused by the sudden abnormal discharge of neurons in the brain, resulting in transient brain dysfunction and chronic obstruction. However, the reason for these morphological changes or electrophysiological abnormalities is the abnormal expression of genes. Shh is one of these genes, thus it is essential to further study the potential roles of both activation and inhibition regulatory factors of the Shh pathway in nervous system diseases. It is reported that Shh inhibits the activity of glutamate transporter a in neurons, greatly enhances the level of extracellular glutamate, and affects the development of epilepsy.[72] Studies have demonstrated that the mutations of multiple molecules in the genome of gelastic epilepsy patients are associated with important molecules in the Shh signalling pathway, including the ligand itself (Shh), the receptor SMO, and several downstream members in Shh pathway (CREBBP and Gli2).[93] Studies in human and rat brain tissue find the upregulation of Sonic hedgehog in temporal lobe epileptic (TLE) foci of human and experimental rats. These results suggest that Shh may play an important role in the development of TLE.[94] Hemiconvulsion-hemiplegia-epilepsy (HHE) syndrome is a rare syndrome characterized by childhood onset partial motor convulsions, hemiplegia, and epilepsy in sequence.[95] Previous studies have shown that HHE syndrome is associated with 1q44 microdeletion. Chromosome 1q44 microdeletion results in the deletion of two crucial genes,

HNRNPU and FAM36A. HNRNPU gene regulation the expression of *Shh* gene.[95]

3.4.4 | Shh signalling pathway and autism

Autism is an innate inability to create normal, biological determination and emotional contact with others. The primary of the social deficit is widely recognized, and lack of social reciprocity is a central part of the diagnosis.[96] The incidence of autism is closely related to heredity and environment, especially its high heritability. Therefore, most studies focus on autism and gene mutation. Previous genetic studies demonstrated the link between transcription factor engrailed2 (EN2) and Autism Spectrum Disorder (ASD). According to the post mortem cerebellum study, the upregulation of EN2 may contribute to the increase of Shh expression in cerebellum.[97] In addition, the results in human cell lines are consistent with those in gene knock-out mice, which indicate that EN2 and Shh were co-regulated.[97] Furthermore, the relationship between the occurrence of autism and Shh is explained. In the study of children with autism spectrum disorder (ASD), the serum levels of Ihh and Shh are significant higher in autistic subjects than those in control subjects. These findings support the correlation between Shh, IHH and BDNF in autistic children.[73,98] Studies have proved that ciliopathies have autistic traits. In ciliopathies mouse, Shh signalling pathway is abnormal, which also indirectly explains the role of Shh in autistic.[99] The researchers found that $Ptch1^{+/-}$ females mice interacts more with both new and old family members in the partner preference task compared to the same sex wild type controls.[100] It is known that PTCH1 is the membrane receptor of Shh, which indicates that the blocking of Shh signalling pathway can increase the interaction between experimental animals and avoid the occurrence of ASD. Previous studies have shown that impaired 7-dehydrocholesterol reduction (DHCR7) function is associated with ASD.[101] The expression reduction of DHCR7 leads to the impairment of SMO activation, and SMO is the key molecule in Shh signalling pathway, which fully indicates that Shh signalling pathway is related with ASD.

3.4.5 | Shh signalling pathway and depression

Depression is a widespread chronic medical illness affecting thoughts, mood, and physical health. It is characterized by low mood, lack of energy, sadness, insomnia and inability to enjoy life.[102] Studies have shown that electroacupuncture (EA) treatment is effective for post-stroke depression (PSD). The mechanism of EA to treat PSD is to suppress inflammation and oxidative stress through activation of the Shh-signalling pathway.[103] Studies have shown that naringenin via Sonic hedgehog-Gli1 cell signalling pathway has antidepressant and neuroprotective effects.[104] It has been proved that chronic unpredictable mild stress induced depression results decided expression of brain derived neurotrophic factor (BDNF), Wnt/β-Catenin, Shh and its downstream transcription factors Gli1/2/3 and Nkx2.2 in the hippocampus.[105] The antidepressant mechanism of nicotine is to increase the expression of these signalling molecules.

3.4.6 | Shh signalling pathway and traumatic brain injury

Traumatic brain injury (TBI) is the brain damage caused by external forces, which has become one of the important diseases affecting human life and health, and brings serious burden to the society.[106] TBI is one of the risk factors of Alzheimer's disease (AD).[107] It is known that Shh has the ability to maintain neural stem cells and promote oligodendrogenesis.[108] The repair of TBI requires the differentiation of neural stem cells and the formation of functional nerve cells. Shh also has the function of promoting cell differentiation, which may provide an effective way for the treatment of TBI. It is reported that the repair of TBI is achieved by activating Shh signalling pathway in TBI model and the up-regulation of Shh reduces cerebellar oedema and neural apoptosis, and promotes neurological recovery.[108]

4 | CONCLUSIONS AND FUTURE DIRECTION

The Shh signalling pathway is classified into canonical and non-canonical pathways. Shh is a morphogen in the normal development of the CNS of vertebrate animals, such as the neural tube and brain. Shh signalling is involved in regulating pattern formation, cell-fate specification, and maintenance of the proliferation, survival and differentiation of neurons in the CNS. The abnormal signal pathway of Shh leads to the occurrence of many nervous system diseases. Despite considerable research done on Shh in the past two decades, there are still many unresolved questions. It is likely that new tools and reagents would provide new insights and perhaps the increasing power of genomic, transcriptomic and proteomic techniques could address how Ptch regulates SMO activity as well as the role of Shh in the process of CNS development.

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CONFLICT OF INTEREST

The authors declare that they have no known conflicts of interest associated with this publication.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article, as no new data were created or analyzed in this study. This study does not need ethical approval.

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