Adv Exp Med Biol - Cell Biology and Translational Medicine
https://doi.org/10.1007/5584_2024_830

Wnt/β-catenin Signaling in Central Nervous System Regeneration

Dilek Nazli, Ugur Bora, and Gunes Ozhan

Abstract

The Wnt/β-catenin signaling pathway plays a pivotal role in the development, maintenance, and repair of the central nervous system (CNS). This chapter explores the diverse functions of Wnt/β-catenin signaling, from its critical involvement in embryonic CNS development to its reparative and plasticity-inducing roles in response to CNS injury. We discuss how Wnt/β-catenin signaling influences various CNS cell types—astrocytes, microglia, neurons, and oligodendrocytes—each contributing to repair and plasticity after injury. The chapter also addresses the pathway's involvement in CNS disorders such as Alzheimer's and Parkinson's diseases, psychiatric disorders, and traumatic brain injury (TBI), highlighting potential Wnt-based therapeutic approaches. Lastly, zebrafish are presented as a promising model organism for studying CNS regeneration and neurodegenerative diseases, offering insights into future research and therapeutic development.

Keywords

Alzheimer's disease · Astrocytes · Autism spectrum disorder · CNS injury · Microglia · Neurodevelopment · Neurons · Neuroregeneration · Oligodendrocytes · Parkinson's disease · Plasticity · Repair · Schizophrenia · Traumatic brain injury · Zebrafish

Abbreviations

Aβ	Amyloid-beta
AD	Alzheimer's disease
ANP	Atrial natriuretic peptide
APC	Adenomatous polyposis coli
APP	Amyloid precursor protein
ASD	Autism spectrum disorder
BACE	β-amyloid precursor protein cleaving enzyme 1
BBB	Blood-brain barrier
BDNF	Brain-derived neurotrophic factor
CK1	Casein kinase 1
CNS	Central nervous system
DISC	Disrupted-in-schizophrenia-1
Dkk1	Dickkopf1

Authors Dilek Nazli and Ugur Bora have equally contributed to this work

D. Nazli and G. Ozhan (✉)
Izmir Biomedicine and Genome Center (IBG), Dokuz Eylul University Health Campus, Izmir, Türkiye

Department of Molecular Biology and Genetics, Izmir Institute of Technology, Izmir, Türkiye
e-mail: gunes.ozhan@ibg.edu.tr; gunesozhan@iyte.edu.tr

U. Bora
Izmir Biomedicine and Genome Center (IBG), Dokuz Eylul University Health Campus, Izmir, Türkiye

Izmir International Biomedicine and Genome Institute (IBG-Izmir), Dokuz Eylul University, Izmir, Türkiye

Dvl	Dishevelled
Fzd	Frizzled
GDNF	Glial cell-derived neurotrophic factor
GFAP	Glial fibrillary acidic protein
GSK-3β	Glycogen synthase kinase-3β
Lrp5/6	Lipoprotein receptor-related protein 5/6
MS	Multiple sclerosis
NSPCs	Neural stem/progenitor cells
OL	Oligodendrocyte
OLP	Oligodendrocyte progenitor
OPC	Oligodendrocyte progenitor cell
PD	Parkinson's disease
RG	Radial glial
SCI	Spinal cord injury
SGZ	Subgranular zone
SOL	Solifenacin
TBI	Traumatic brain injury
Tcf/Lef	T-cell factor/lymphoid enhancer factor
TREM2	Triggering receptor expressed on myeloid cells 2
VPA	Valproic acid
Wif1	Wnt inhibitory factor 1
6-OHDA	6-Hydroxydopamine

1 Introduction

The CNS is a highly complex and dynamic system, responsible for regulating numerous physiological processes and cognitive functions. One of the key signaling pathways that govern CNS development, maintenance, and response to injury is the Wnt/β-catenin pathway. Wnt/β-catenin signaling pathway is key to regulation of fundamental cellular processes, including embryonic development, stem cell maintenance, tissue homeostasis, and regeneration (Nusse 2008; Ozhan and Weidinger 2014; Ozhan and Weidinger 2015; Steinhart and Angers 2018; Van Camp et al. 2014). During CNS development, Wnt/β-catenin signaling plays a crucial role in the proper formation of neural tissues, guiding the patterning and growth of the brain and spinal cord.

As research has progressed, it has become evident that Wnt/β-catenin signaling also plays significant roles in the adult CNS, particularly in response to injury and in the context of neurodegenerative diseases. The pathway's ability to promote cellular plasticity and repair mechanisms makes it a promising target for therapeutic interventions aimed at enhancing CNS regeneration and mitigating the effects of disorders such as Alzheimer's and Parkinson's diseases. Dysregulations in Wnt/β-catenin signaling have been linked to the pathogenesis of various conditions, including congenital disorders, cancer, and neurodegenerative diseases (Li et al. 2020a, b; Azbazdar et al. 2021; Karabicici et al. 2021).

In this chapter, we will first explore the foundational role of Wnt/β-catenin signaling in CNS development, followed by an examination of its involvement in various CNS cell types during injury-induced repair and plasticity. We will then discuss the pathway's implications in CNS disorders and potential Wnt-based therapeutic strategies. Finally, we will highlight the use of zebrafish as a model organism for studying CNS regeneration and neurodegenerative diseases, emphasizing its importance in advancing our understanding and treatment of CNS injuries and disorders.

2 Wnt/β-Catenin Signaling Pathway

The discovery of the Wnt gene family dates back to 1959, originating from investigations into the oncogenic mechanisms associated with the mouse mammary tumor virus, which led to the discovery of the founding member, Int-1 (Callahan and Smith 2000). Five years later, the identification of the *'wingless'* gene in *Drosophila* revealed its homologous relationship with Int-1 (Clevers 2006). Subsequently, in 1992, Nusse and Varmus formally named this gene the 'Wnt gene' (Nusse and Varmus 1992).

Wnt signaling is divided into two main types. The first is the canonical pathway, which is dependent on β-catenin (Hayat et al. 2022). The

second is the non-canonical pathway, which operates independently of β-catenin. Wnt proteins are classified based on their downstream signaling effects. Canonical Wnt signaling involves ligands such as Wnt1, 2, 3, 8a, 8b, 10a, and 10b, while the non-canonical pathway involves Wnt ligands like Wnt4, 5a, 5b, 6, 7a, 7b, and 11 (Qin et al. 2024). In this chapter, we will focus on the canonical (β-catenin-dependent) pathway.

In the canonical pathway, Wnt ligands bind to a receptor complex formed by frizzled (Fzd) receptor and lipoprotein receptor-related protein 5/6 (Lrp5/6), leading to the recruitment of the scaffold protein Dishevelled (Dvl) (Azbazdar et al. 2021). This recruitment inactivates the destruction complex composed of the scaffold protein Axin, the tumor suppressor adenomatous polyposis coli (APC), casein kinase 1 (CK1), and glycogen synthase kinase-3β (GSK-3β). Inactivation of this complex prevents the phosphorylation and proteasomal degradation of β-catenin. As a result, β-catenin accumulates in the cytoplasm and eventually translocates into the nucleus, where it binds to the T-cell factor/lymphoid enhancer factor (Tcf/Lef) family of transcription factors, stimulating the transcription of Wnt target genes (Nusse and Clevers 2017). In the absence of Wnt ligands, β-catenin is phosphorylated by CK1 and GSK-3β, leading to its ubiquitination and degradation, preventing its nuclear translocation and subsequent transcriptional activation.

3 Development of the Central Nervous System and Wnt/β-Catenin Signaling

The CNS is a complex structure composed of neurons, astrocytes, oligodendrocytes, microglia, and ependymal cells. CNS development follows interconnected stages: (1) initiation of the brain cell formation (proliferation/differentiation), (2) relocation to appropriate positions (migration), (3) growth of axons and dendrites essential for intercellular connections (neurogenesis), (4) establishment of synaptic connections for communication (synaptogenesis), and (5) refinement of these connections (maturation and pruning). These processes are tightly regulated by a series of signaling pathways and intercellular communication, orchestrated in a spatiotemporal manner (Catala 2019; Stiles and Jernigan 2010). Among these pathways, the Wnt/β-catenin signaling pathway plays a pivotal role in regulating every phase of CNS development. Its influence is evident from the earliest stages of neurodevelopment and patterning to later processes, such as corticogenesis, axon growth and guidance, synaptic formation and function, eye morphogenesis, and adult neurogenesis (Arredondo et al. 2020; Bielen and Houart 2014; Brafman and Willert 2017; Dickins and Salinas 2013; Fortress and Frick 2016; Fujimura 2016; Inestrosa and Varela-Nallar 2015; Ji et al. 2019; Rosso and Inestrosa 2013; Salinas 2012; Stanganello et al. 2019).

Neurons and glia derive from a limited population of multipotent stem cells, the so-called neural stem/progenitor cells (NSPCs), which undergo proliferation and subsequent differentiation to establish specific cellular lineages. Defects in NSPC proliferation or differentiation may lead to abnormal cell numbers, CNS malformations, and neurodevelopmental disorders (Ernst 2016; Homem et al. 2015). Activation of the Wnt pathway promotes the expansion of the NSPC pool by stimulating their cell cycle progression and inhibiting premature neuroglial differentiation during development. Moreover, Wnt/β-catenin signaling regulates the specification of distinct cellular subtypes by controlling the expression of lineage-specific transcription factors. For instance, N-myc mediates Wnt signaling activation, promoting the commitment to neuronal fate and proliferation of neural precursor cells both in vitro and in vivo (Kuwahara et al. 2010). Activation of Wnt signaling and its downstream target N-myc increases the production of basal progenitors in the neocortex, while deletion of *N-myc* reduces basal progenitors and neocortical neurons, highlighting its importance in neuron production during neocortical development.

Another study explored the role of Wnt/β-catenin signaling in vertebrate neural development, focusing on the dopaminergic system in zebrafish. The study revealed the expression of Wnt ligands, receptors, and antagonists near

developing dopaminergic neurons (Westphal et al. 2022). Although Wnt/β-catenin activity is absent in these neurons, it is present in adjacent cells. Manipulations of Wnt/β-catenin signaling affect dopaminergic neuron development, with Wnt signaling positively correlating with neuron number. These findings suggest that Wnt/β-catenin signaling promotes dopaminergic development by influencing proliferative progenitors in the hypothalamus, particularly regulating the size of DC5 and DC6 dopaminergic neuron groups.

A study investigated the effects of conditionally activating Wnt signaling in human glial fibrillary acidic protein (hGFAP)-positive neural precursors during postnatal cerebral and cerebellar cortex development in mice. The researchers observed an enlarged ventricular zone and reduced cortical development due to continuous proliferation and a failure in cell cycle exit during prenatal stages (Pöschl et al. 2013). Aberrant activation of β-catenin led to abnormal proliferation of granule neurons and disrupted Bergmann glia development, which impaired normal granule cell migration and cortical layering. Pöschl and colleagues highlighted the divergent roles of Wnt signaling in the CNS development, showing how its effects are both cell-specific and time-dependent.

Wnt/β-catenin signaling has also been shown to play a significant role in oligodendrocyte development and myelin formation in the CNS. While the importance of this pathway was previously recognized, its precise role in oligodendrocyte specification and differentiation has been debated. One study demonstrated that β-catenin activation in neural progenitor cells inhibits the generation of oligodendrocyte progenitors (OLPs), but once OLPs are formed, β-catenin is required for their differentiation (Dai et al. 2014). Disruption of β-catenin signaling delayed oligodendrocyte maturation, indicating that the Wnt/β-catenin pathway regulates oligodendrocyte development in a stage-dependent manner.

Overall, the Wnt/β-catenin signaling pathway plays a central role in CNS development by orchestrating neural proliferation, differentiation, and connectivity. A deeper understanding of the intricacies of Wnt/β-catenin signaling could enhance knowledge of neurodevelopmental disorders and contribute to the development of novel therapeutic strategies.

4 Wnt/β-Catenin Signaling in Post-injury CNS Cells: Mechanisms of Repair and Plasticity

4.1 Astrocytes

Astrocytes, the most abundant glial cell population in the CNS, were traditionally thought to primarily provide structural support to neural tissue (Siracusa et al. 2019). However, recent studies have revealed their involvement in a wide array of functions beyond this role (Boghdadi et al. 2020). Notably, astrocytes respond to injury or disease by undergoing reactive gliosis, a process characterized by cellular hypertrophy, increased proliferation, and upregulation of GFAP expression (Karve et al. 2016). During reactive gliosis, astrocytes create a physical barrier to limit CNS damage while secreting cytokines that regulate inflammation and support tissue repair (Liddelow and Barres 2017).

Astrocytes also play a key role in neuronal restoration after CNS injury. Through the activation of β-catenin signaling, astrocytes facilitate neurorestoration by regulating genes that enhance cell survival and reduce oxidative stress. For instance, following CNS damage, astrocytes release Wnt1-like ligands that activate β-catenin signaling, which is essential for promoting neuronal recovery (L'Episcopo et al. 2011a, b). A study involving ischemic stroke demonstrated that the intranasal application of Wnt-3a significantly reduced infarct volume, enhanced neurogenesis, and improved sensorimotor functions in mice, highlighting the role of Wnt/β-catenin signaling in post-injury brain repair (Wei et al. 2018). This process, often associated with reactive gliosis, includes the expression of neurotrophic factors such as brain-derived neurotrophic factor (BDNF) and glial cell-derived neurotrophic factor (GDNF), which promote neuronal survival and regeneration (Chiareli et al. 2021).

Moreover, Wnt/β-catenin signaling has been shown to be essential for the polarization of reactive astrocytes following spinal cord injury (SCI), further supporting its importance in CNS repair (Sonn et al. 2020). Astrocytes can promote neuroprotection by stimulating the Wnt1-Fzd-1 receptor and β-catenin signaling pathway, particularly in the context of protecting dopaminergic neurons (L'Episcopo et al. 2011a, b). However, astrocytes can also contribute to negative outcomes by producing Wnt inhibitors, which may exacerbate inflammation and CNS injury (Fig. 1). For example, excessive reactive gliosis accompanied by high levels of reactive oxygen species and reactive nitrogen species has been linked to the inhibition of Wnt/β-catenin signaling in the subventricular region of Parkinsonian mice brain, reducing neurogenesis and impairing NSPC function (L'Episcopo et al. 2012). The activation of GSK-3β facilitates this inhibition, leading to β-catenin degradation and diminished neurogenic potential. These findings suggest that abnormal reactive gliosis, in conjunction with dysregulation of the Wnt/β-catenin signaling

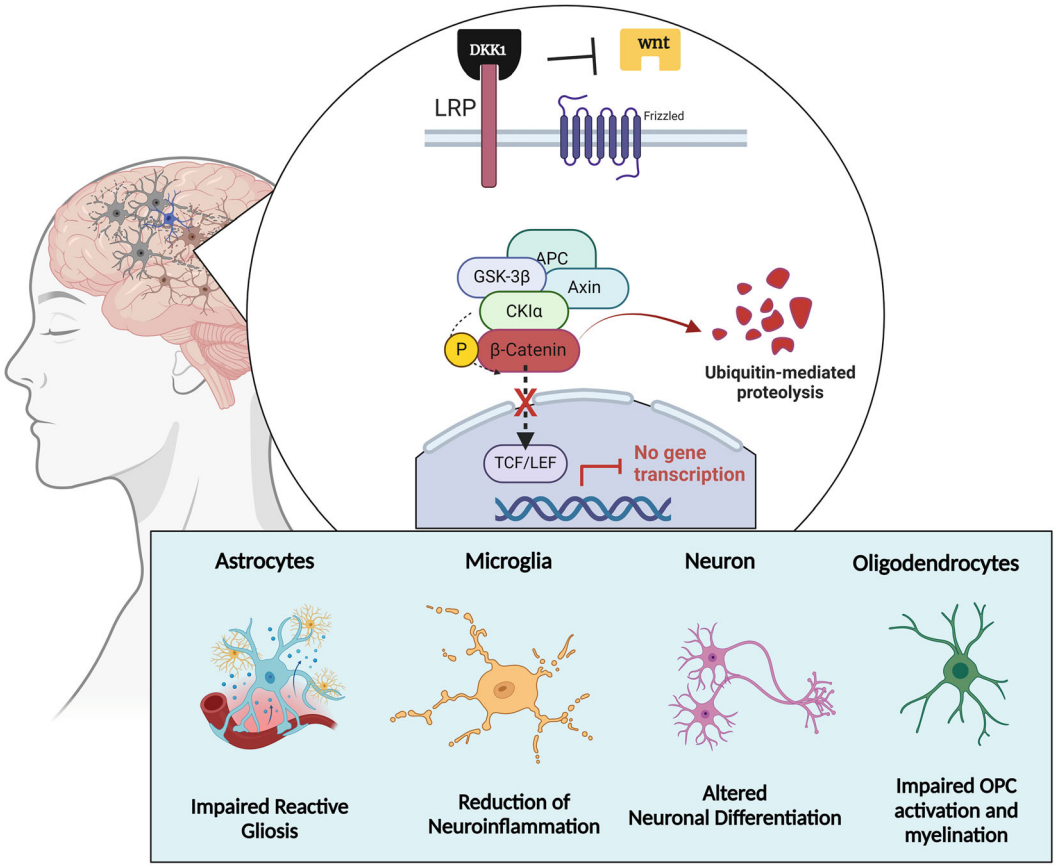

Fig. 1 Effects of Wnt/β-catenin signaling inhibition on various brain cell types. DKK1 inhibits Wnt signaling by blocking its interaction with the Frizzled receptor and LRP, leading to the phosphorylation and subsequent ubiquitin-mediated proteolysis of β-catenin by the destruction complex (GSK-3β, APC, CK1α, and Axin). This prevents gene transcription through TCF/LEF and results in several downstream effects, including impaired reactive gliosis in astrocytes, reduced neuroinflammation in microglia, altered neuronal differentiation, and compromised OPC activation and myelination in oligodendrocytes. These alterations suggest a critical role of Wnt signaling in maintaining brain cell function

pathway, may be a primary cause of decreased neurogenesis in aging (L'Episcopo et al. 2013; Marchetti and Pluchino 2013).

In summary, astrocytes are key players in linking the canonical Wnt signaling pathway to CNS repair and maintenance. Although their role in CNS development, function, and homeostasis is evident, the precise mechanisms by which they influence neuronal functions remain incompletely understood. Further research is needed to fully unravel the interaction between astrocytes, the Wnt signaling pathway, and CNS health.

4.2 Microglia

Microglia, the specialized immune cells of the CNS, play a crucial role in modulating inflammation and stimulating nerve regeneration. Recent research has highlighted the significant role of the Wnt signaling pathway in regulating microglial functions. Microglial cells detect Wnt signaling through receptors on their surface, and the activation of these receptors by Wnt ligands initiates intracellular processes that dictate their responses. Notably, activating the Wnt signaling pathway in microglia has been directly linked to reduced neuroinflammation and enhanced tissue repair (Knotek et al. 2020) (Fig. 1).

A recent study demonstrated that Wnt-3a treatment following SCI mitigated neuronal inflammation via the β-catenin signaling pathway, fostering tissue repair and promoting the recovery of motor function (Gao et al. 2024). Another investigation revealed that Wnt1 plays a protective role against infection-induced microglial polarization and brain injury by activating the LKB1-AMPK pathway (Gao et al. 2022). This activation suppresses inflammation-mediated microglial activation, promotes the conversion of microglia to an M2-type phenotype, and alleviates inflammation-related neonatal brain injuries.

Microglia express various immunological receptors, enabling them to perform both protective and detrimental roles in neuronal survival. One such receptor, triggering receptor expressed on myeloid cells 2 (TREM2), is crucial for microglial function and can activate the canonical Wnt pathway by preventing β-catenin degradation (Mo et al. 2022). Genetic mutations in TREM2 can disrupt Wnt/β-catenin signaling, potentially leading to microglial overactivation and neurodegeneration.

In the context of neurogenesis, microglia selectively engulf specific synapses by detecting distinct chemokine signals. For example, the interaction between the CR3 receptor and CX3CL1 (fractalkine) on neurons stimulates microglial activation for phagocytosis (Cardona et al. 2006). However, inhibiting the Wnt/β-catenin pathway significantly reduces fractalkine expression, resulting in synapse degeneration, thereby establishing a direct connection between Wnt signaling and synaptic modifications involving microglia (Paolicelli et al. 2011).

While microglia are essential for CNS repair, their actions can also have adverse effects. In conditions such as ischemic stroke or SCI, the increased presence of the C1q complement amplifies microglial phagocytic activity, leading to the engulfment of healthy synapses (Mercurio et al. 2022). This excessive phagocytosis can cause neuronal damage and eventual cell death. Dying neurons can activate apoptotic signaling pathways mediated by p53, which in turn stimulate the expression of Dickkopf1 (Dkk1), an inhibitor of the Wnt/β-catenin signaling pathway (Xiao et al. 2022). Additionally, the release of harmful substances from dying synapses can further escalate microglial chemokine release, promoting an inflammatory response and exacerbating synaptic damage.

Overall, while microglia are integral to CNS repair processes, their activation and functions must be tightly regulated to prevent adverse outcomes in neurodegenerative conditions. Further exploration of the Wnt signaling pathway's influence on microglial activity could provide valuable insights into therapeutic strategies for CNS injuries and disorders.

4.3 Neurons

New neurons are consistently produced in two key areas of the adult brain: the subventricular

zone near the lateral ventricles, and the subgranular zone (SGZ) within the hippocampal dentate gyrus. In the SGZ, radial NSPCs generate granule cells, which are essential for hippocampal plasticity. These newly formed neurons migrate along the rostral migratory stream to differentiate (Varela-Nallar and Inestrosa 2013). The Wnt family of secreted glycoproteins plays a crucial role in regulating various processes in both developing and mature brains, including neurogenesis and neuronal maintenance and regeneration (Marchetti and Pluchino 2013).

Wnt ligands are closely associated with neural progenitor proliferation and differentiation, though their effects in injured tissue environments are less well understood. Astrocytes that secrete Wnt3 have been linked to neurogenesis, with Wnt signals activating the Wnt/β-catenin pathway in neural progenitor cells, promoting neuronal differentiation (Varela-Nallar and Inestrosa 2013) (Fig. 1). In TBI models, intranasal administration of Wnt3a has been shown to increase levels of β-catenin, GDNF, and vascular endothelial growth factor (VEGF), enhancing neurogenesis and neuroprotection by reducing autophagic and apoptotic responses while promoting neurovascular repair (Zhang et al. 2018). Similarly, in ischemic stroke models, lentivirus-mediated Wnt3a expression in neural progenitor cells increased the proliferation of immature neurons in the striatum and subventricular zone, improving functional recovery and neuronal survival (Shruster et al. 2012).

The role of the canonical Wnt pathway has been explored in various disease and damage models. In SCI, Rong et al. studied harpagide, a traditional Chinese herbal medicine, and found it enhanced β-catenin, c-myc, and cyclin D1 expression in spinal cord neurons, increased motor neuron numbers, and improved functional recovery, while inhibiting glial scar formation (Rong et al. 2019). Similarly, Gao et al. demonstrated that simvastatin improved recovery in a rat SCI model by activating the Wnt/β-catenin pathway, increasing β-catenin levels and Wnt target genes *LEF1* and *TCF1*, effects that were reversed by β-catenin suppression (Gao et al. 2016). Additionally, Xiang et al. reported that resveratrol also enhanced recovery after SCI through activation of Wnt/β-catenin signaling (Xiang et al. 2021). In adult zebrafish, Wnt/β-catenin signaling is elevated following SCI, and overexpression of Dkk1b, which inhibits this signaling pathway, hinders functional recovery (Strand et al. 2016).

The optic nerve crush injury serves as a common experimental model for studying axonal damage and the signaling pathways involved in CNS axonal regeneration. In a retinal ganglion cell (RGC) axon crush injury model using transgenic Wnt reporter mice, intravitreal injections of Wnt3a led to significant axonal regrowth beyond the lesion site (Patel et al. 2017). Wnt3a stimulation activated Wnt signaling and increased activation of the transcription factor Stat3, promoting axonal regeneration and RGC survival. However, conditional Stat3 knock-out mice exhibited reduced Wnt3a-mediated axonal regeneration and RGC survival. Müller glia, which can dedifferentiate and generate retinal cells in adult mammals, also respond positively to Wnt3a treatment, promoting their proliferation in models of photoreceptor damage (Osakada et al. 2007). Injury triggers nuclear accumulation of β-catenin, upregulating cyclin D1, and increasing Wnt/β-catenin activity. Activating Wnt signaling by inhibiting glycogen synthase kinase-3β enhances retinal regeneration, while its attenuation impedes the regeneration process.

Overall, these findings suggest that the Wnt pathway is crucial in CNS damage and regeneration, representing a promising avenue for promoting CNS repair through the modulation of the canonical Wnt pathway across various vertebrate models.

4.4 Oligodendrocytes

Oligodendrocytes (OLs) are essential for myelination in the CNS, facilitating rapid action potential conduction and supporting homeostasis. They differentiate from oligodendrocyte progenitor cells (OPCs), which are widely distributed in the adult brain and serve as a reservoir for OL replacement and remyelination. Recent research has highlighted the roles of OLs, OPCs, and myelin structure in CNS injuries and neurodegenerative diseases (Ettle et al. 2016).

The Wnt/β-catenin signaling pathway plays a crucial role in CNS regeneration, though its effects on OL regeneration and remyelination after CNS injury remain controversial (Xie et al. 2014). For instance, Wang et al. explored how OPCs maintain blood-brain barrier (BBB) integrity during ischemic stroke in mice (Wang et al. 2022). Their study found that OPC transplantation reduced edema and infarct volume, enhancing neurological recovery by activating the Wnt/β-catenin pathway in endothelial cells. This activation was essential for decreasing BBB leakage through the upregulation of specific proteins. Conversely, inhibiting β-catenin negated these positive outcomes, while application of Wnt7a increased β-catenin and claudin-5 expression in endothelial cells after oxygen-glucose deprivation (Fig. 1). In another study, the conditional loss of Wnt7a/b in OPCs led to decreased white matter vascularity due to reduced angiogenesis and endothelial cell proliferation following hypoxic injury (Chavali et al. 2020). This diminished vascular density correlated with impaired OL maturation and hypomyelination.

In demyelinating diseases like multiple sclerosis (MS), both demyelination and OL injury occur. While OPCs are present in affected areas, they often fail to mature into OLs. Dysregulation of canonical Wnt signaling can disrupt repair mechanisms; for instance, Tcf4 expression in OL lineage cells was found in demyelinating lesions, indicating that the Wnt/β-catenin pathway negatively regulates OL fate (Fancy et al. 2009). Additionally, *Foxg1* knockout in a cuprizone-induced demyelination model was shown to hinder OPC proliferation but promote their differentiation into mature OLs by regulating Wnt/β-catenin signaling (Dong et al. 2021). This effect was linked to increased GSK-3β levels in OPCs, which could be reversed by inhibiting GSK-3β. Similarly, solifenacin (SOL) was found to enhance OPC differentiation and promote remyelination by modulating Wnt/β-catenin signaling (Xu et al. 2024). SOL treatment decreases GSK-3β and total β-catenin while increasing phospho–βcatenin, indicating its role in remyelination.

The complexities of Wnt/β-catenin signaling in CNS regeneration remain poorly understood. While its role in promoting OL differentiation and myelination is recognized, the mechanisms involved in injury-induced regeneration warrant further study. Notably, knocking out β-catenin-dependent signaling in OPCs was shown to reduce their proliferation, decrease microglial infiltration, and increase astrocyte hypertrophy in a spinal cord injury model, suggesting that Wnt signaling is crucial for OPC activation and glial scar formation (Rodriguez et al. 2014).

In conclusion, CNS injury presents significant challenges to neuronal repair and recovery, with OLs and myelin maintenance being vital for effective regenerative responses. Targeting Wnt/β-catenin signaling holds potential as a therapeutic strategy to enhance regeneration and improve outcomes following CNS injuries.

5 Wnt/β-Catenin Pathway in CNS Disorders: Pathogenesis and Therapeutic Potential

5.1 Alzheimer's Disease

Alzheimer's disease (AD) is a progressive neurodegenerative condition characterized by memory loss, cognitive and behavioral impairments, and diminished decision-making ability. Although the pathophysiology of AD is not fully understood, key features include the accumulation of amyloid plaques, formation of neurofibrillary tangles, and neuronal loss in brain tissue (Knopman et al. 2021). While there is no cure, various medications and therapies can help manage symptoms and slow disease progression.

Dysregulated Wnt/β-catenin signaling, mediated by amyloid-beta (Aβ) and Dkk1, disrupts synaptic integrity and contributes to cognitive decline in AD (Karabicici et al. 2021). Elevated levels of Dkk1 have been observed in the brains of AD patients and mouse models (Caricasole et al. 2004; Ren et al. 2019; Rosi et al. 2010). In a transgenic mouse model with inducible Dkk1 expression, Dkk1 caused synapse and memory loss, while reducing long-term potentiation in the striatum and hippocampus, without affecting cell viability (Galli et al. 2014). Similarly, postnatal deletion of the Wnt

and Dkk1 receptor Lrp6 from forebrain neurons in a mouse AD model triggered amyloid precursor protein (APP) amyloidogenesis, leading to synaptic loss and exacerbating AD pathology (Liu et al. 2014). Neutralizing Dkk1 with antibodies or drugs has been shown to completely counteract Aβ's effects on synapses (Purro et al. 2012; Sellers et al. 2018). In addition, anti-sense oligonucleotides targeting *DKK1* reduced apoptosis in neurons with Aβ accumulation and protected against tau hyperphosphorylation. A molecule known as IIIC3, which binds to Lrp6 and prevents Dkk1 from binding, has been shown to reactivate the Wnt/β-catenin signaling pathway (Li et al. 2012).

Components of the Wnt pathway, including β-catenin, Tcf4, Gsk3β, and Dvl1, are linked to Aβ production from APP (Mudher et al. 2001; Palomer et al. 2019; Parr et al. 2015; Tapia-Rojas and Inestrosa 2018). Inhibition of Wnt signaling can enhance Gsk3β activity, leading to Tau hyperphosphorylation (Salcedo-Tello et al. 2014; Scali et al. 2006). Genes associated with increased AD risk, such as APOE4, TREM2, and Clusterin, also disrupt Wnt/β-catenin signaling (Caruso et al. 2019; Killick et al. 2014; Zheng et al. 2017). Moreover, patient brains exhibit increased Gsk3β activity, Lrp6 polymorphisms, reduced Wnt signaling, and lower cytoplasmic β-catenin levels (Alarcón et al. 2013; De Ferrari et al. 2007; Kawamura et al. 2001; Pei et al. 1999; Zheng et al. 2017). Mass spectrometry further confirms diminished canonical Wnt signaling in brain samples from AD patients (Bai et al. 2020; Elliott et al. 2018; Xu et al. 2019).

Given the significant suppression of the Wnt/β-catenin pathway in the brains of Alzheimer's patients, reactivating this signaling pathway has emerged as a crucial area for research and potential treatment (Jia et al. 2019). Reactivating Wnt signaling by inhibiting Dkk1 and Gsk3β or enhancing Wnt ligand levels has been shown to mitigate Aβ-induced synaptic damage in cell and mouse AD models (De Ferrari et al. 2003; Alvarez et al. 2004; Quintanilla et al. 2005; Chacón et al. 2008; Cerpa et al. 2010; Vargas et al. 2015; Licht-Murava et al. 2016; Marzo et al. 2016; Ross et al. 2018). GSK3β inhibitors, in particular, represent a promising therapeutic approach for AD due to their role in modulating Wnt/β-catenin signaling and their relevance in AD pathology (Joshi and Reddy 2024). Dual and multitarget inhibition of GSK-3β offers broad-spectrum activity across various stages and pathologies of AD, potentially influencing both tau and neuroinflammation pathways.

In the context of mouse AD models, GSK-3β inhibitors have been reported to improve cognitive abilities. For example, compounds such as NP12, AR-A014418, and Indirubin have demonstrated efficacy in reducing memory deficits, tau phosphorylation and amyloid accumulation in transgenic mouse models (Ding et al. 2010; Ly et al. 2013; Serenó et al. 2009) (Fig. 2). Additionally, L803-mts has shown improvements in learning capabilities in 5XFAD mice (Avrahami et al. 2013). Despite these promising preclinical results, clinical findings in AD patients have been somewhat disappointing (Godyń et al. 2016; Llorens-Martín et al. 2014). While therapeutic approaches targeting GSK-3β have shown potential in correcting cognitive impairments in mouse models, it is important to recognize that these treatments may not fully resolve the condition and could potentially harm healthy cells due to GSK-3β's role in cell survival.

Amyloid plaques, a key feature of AD, disrupt neuron communication and contribute to neuronal death. These plaques form due to the aberrant cleavage of APP by the β-amyloid precursor protein cleaving enzyme 1 (BACE1) (Vassar et al. 2009). Parr and colleagues demonstrated that following Wnt3a stimulation, TCF4 binds to the same region on the *BACE1* promoter, acting as a transcriptional repressor of the *BACE1* gene (Parr et al. 2015). This study showed that increased Wnt3a activation led to inhibition of BACE1 expression and a reduction in Aβ levels, suggesting that Wnt/β-catenin stimulation can suppress *BACE1* transcription through TCF4 binding.

APOE4, a genetic risk factor for AD, inhibits the Wnt co-receptor Lrp6, leading to decreased expression of this receptor and increased amyloid plaque production by APP, which is associated with AD development (Liu et al. 2014). Prajapat and colleagues found that the compounds LAS

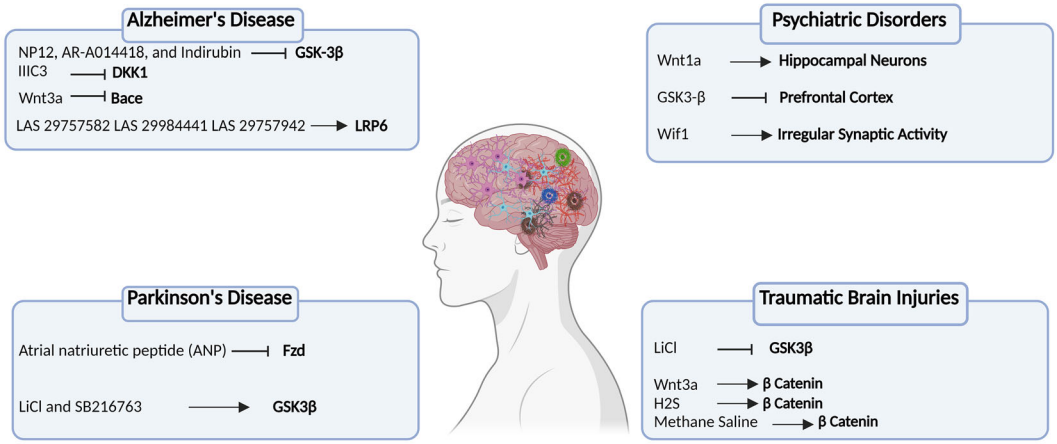

Fig. 2 Therapeutic targeting of Wnt/β-catenin signaling in Alzheimer's disease, Parkinson's disease, psychiatric disorders, and traumatic brain injuries. Various compounds and molecular targets modulate the inhibition or activation of components within the Wnt/β-catenin signaling pathway, offering potential therapeutic strategies for neurodegenerative diseases, psychiatric disorders, and traumatic brain injuries

29757582, LAS 29984441, and LAS 29757942 block the interaction between Lrp6 and Dkk1 proteins, thereby increasing Lrp6 expression and potentially reducing the risk of AD (Prajapat et al. 2023). Additionally, compounds such as curcumin and statins have been proposed as potential activators of the Wnt/β-catenin signaling pathway for AD treatment. Curcumin is suggested to increase Wnt proteins and agonists while reducing Dkk1 expression, potentially offering benefits in AD management (Farkhondeh et al. 2019; Sakr et al. 2023; Vargas et al. 2015). Despite its limited bioavailability, curcumin may still enhance neurogenesis and mitigate cognitive impairments. Statins, primarily used to reduce cholesterol production, have also been recommended for AD protection due to their ability to activate the Wnt/β-catenin signaling pathway (Jia et al. 2019).

In summary, targeting the canonical Wnt pathway presents a promising therapeutic approach for AD. While currently FDA-approved acetylcholinesterase inhibitors such as tacrine, donepezil, rivastigmine, and galantamine provide symptomatic relief, they do not offer a definitive solution. Modulating the canonical Wnt pathway could potentially halt disease progression, enhance neuronal survival, and promote neurogenesis. Therefore, further research and development in this area are crucial for advancing AD treatment.

5.2 Parkinson's Disease

Parkinson's disease (PD) is a prevalent neurodegenerative condition characterized by the degeneration of dopaminergic neurons in the substantia nigra region of the brain (Poewe et al. 2017). This degeneration leads to the accumulation of α-synuclein and the formation of Lewy bodies. The decrease in dopamine (DA), the primary neurotransmitter regulating motor activities, results in uncontrolled motor functions including tremors, muscle rigidity, impaired balance, and reduced mobility. Currently, there is no definitive cure for PD; however, symptomatic relief can be achieved through dopamine replacement therapies (Jankovic and Tan 2020).

The Wnt signaling pathway has emerged as a promising therapeutic target for PD due to its significant role in the CNS. Research into activating neuroprotection and neurogenesis through the Wnt pathway is ongoing. Wnt1 and its agonists, which act directly on the β-catenin pathway, have demonstrated neuroprotective effects against neuron-specific toxins such as 6-hydroxydopamine

(6-OHDA) and MPTP, which induce parkinsonism (L'Episcopo et al. 2011a, b; Wei et al. 2013). Improvement in motor symptoms has been observed in animal models treated with Wnt1 and its agonists. Additionally, studies have explored the reprogramming of pluripotent stem cells into dopaminergic neurons or progenitors in vitro using these Wnt agonists (Serafino and Cozzolino 2023).

Research has also highlighted the role of the atrial natriuretic peptide (ANP) in PD. ANP activates Wnt signaling through modulation of the Fzd-mediated pathway and has shown therapeutic potential (Serafino et al. 2020) (Fig. 2). While ANP inhibits Wnt signaling in colorectal cancer—where Wnt is continuously active—it acts as a Wnt agonist in PD models. This dual role underscores the complexity of Wnt signaling modulation in different disease contexts. Further investigations by Zhang et al. demonstrated neuroprotective effects against rotenone-induced neurotoxicity in PD model cells (PC12) through Wnt signaling modulation via a GSK3β inhibitor (Zhang et al. 2016). They used LiCl and SB216763 as GSK3β inhibitors, which stabilized β-catenin and induced Nurr1, a transcription factor essential for the maintenance of dopaminergic neurons, thereby achieving neuroprotection (Fig. 2). Additionally, certain pharmacological agents, including specific statins and nicotinic receptor modulators, have been found to activate the Wnt/β-catenin signaling pathway, promoting neuron survival and preservation (Marchetti 2018; Zhao et al. 2015; Zhou et al. 2016). These findings, combined with ongoing research, highlight the Wnt signaling pathway as an attractive therapeutic target for neuronal rescue and protective effects for PD.

5.3 Traumatic Brain Injury

Traumatic brain injury (TBI) occurs when the brain sustains damage due to rapid movement within the skull, either from direct impact with an object or exposure to a non-impact force, such as a blast wave. The primary injury caused by these external forces can lead to brain tissue damage, hemorrhage, and axonal cutting, initiating a cascade of neurometabolic and neurochemical events, including oxidative stress, inflammation, and disruption of the BBB (Ng and Lee 2019). These processes not only alter the trajectory of recovery but can also persist for months post-trauma. Secondary injury in TBI is primarily driven by neuroinflammation, characterized by the release of cytokines and oxidative stress following the activation of microglia and astrocytes. Suppressing this activation has emerged as a crucial target improving TBI outcomes. Recent studies highlight the significant regulatory role of the canonical Wnt signaling pathway, which has been shown to offer cerebrovascular and neuroprotective benefits.

Abnormal activation of GSK-3β has been implicated in exacerbating neuroinflammation, contributing to neurodegeneration and chronic inflammation in various TBI studies (Dash et al. 2011; Farr et al. 2019; Lv et al. 2014; Shaik et al. 2023). The beneficial effects of GSK-3β inhibitors in TBI have been demonstrated; for instance, one study showed that increased GSK-3β activity days after TBI was inhibited by lithium chloride, leading to enhanced Wnt/β-catenin signaling (Leeds et al. 2014) (Fig. 2). This treatment was associated with reduced neuronal death and improved cognitive function. In rodent models of TBI, researchers observed rapid but transient increase in LRP6 phosphorylation, accompanied by a slight decrease in β-catenin phosphorylation (Dash et al. 2011). By the third day post-injury, levels of phospho-GSK-3β had significantly elevated, prompting the administration of lithium to counteract this increase. These findings suggest that selective GSK-3 inhibition might partially restore cognitive function, while lithium treatment could provide neuroprotection and substantial cognitive improvement.

Further supporting the potential of Wnt signaling in TBI recovery, studies have shown that activating this pathway may enhance regeneration in neural tissues. For instance, in a Wnt reporter mouse model, increased Wnt signaling in Müller cells after laser-induced TBI led to their proliferation and dedifferentiation, suggesting that Wnt activation may promote neural regeneration (Liu et al. 2013). In another study, neural stem cells

overexpressing Wnt3a were transplanted into rats with optic nerve crush injuries, resulting in the activation of the Wnt signaling pathway, which triggered proliferation and differentiation (Yang et al. 2014) (Fig. 2). Additionally, treatment with hydrogen sulfide in TBI-modeled mice was proposed as a potential therapeutic strategy, as it activated the Wnt signaling pathway, inhibited ferroptosis, and reduced neuronal loss (Chen et al. 2023).

Other studies have explored additional therapeutic approaches targeting the Wnt pathway. For example, methane saline has demonstrated promising therapeutic potential in TBI by activating the Wnt signaling pathway, leading to anti-inflammatory, anti-apoptotic, and antioxidative effects (Li et al. 2020a, b). Another study highlighted the neuroprotective effects of licoricidin in mice with TBI, suggesting its efficacy through the modulation of oxidative stress and apoptosis via the FoxO3/Wnt/β-catenin pathway (Liu et al. 2020).

TBI can lead to serious lifelong consequences. While traditional treatments generally focus on managing symptoms, targeting the Wnt signaling pathway offers a promising strategy for potentially achieving more complete recovery. However, despite the significant potential of these approaches, further clinical studies are necessary to establish their efficacy and safety.

5.4 Psychiatric Disorders

The Wnt/β-catenin signaling pathway plays a significant role in the pathophysiology of several psychiatric disorders, including schizophrenia and autism spectrum disorder (ASD). Schizophrenia, a profound neurodevelopmental condition, is characterized by disrupted cognitive functions, interpersonal conduct, and affective responses, arising from a complex interplay of genetic predispositions and environmental influences. Post-mortem histopathological evaluations have revealed reduced neuron size within the hippocampal subfields of individuals with schizophrenia (Hussaini et al. 2014).

Precise regulation of Wnt1 is crucial for healthy brain development and homeostasis. Post-mortem studies indicate an accumulation of Wnt1 in hippocampal neurons of schizophrenia patients, suggesting that alterations in the Wnt pathway may contribute to impaired neuroplasticity associated with the disorder (Miyaoka et al. 1999). Additionally, analyses of post-mortem tissue from patients have shown decreased GSK-3β levels in the prefrontal cortex, while levels of β-catenin and Dvl-2 remained unchanged (Beasley et al. 2001). This finding suggests that dysregulation of Wnt/β-catenin pathway in specific neuronal populations may contribute to the etiology of schizophrenia. The disorder has also been associated with abnormal Wnt-related gene expression, particularly increased levels of FZD7 and NFATc3, alongside lower plasma levels of soluble dickkopf 1 and sclerostin (Hoseth et al. 2018). A study using patient-derived human induced pluripotent stem cells revealed increased β-catenin levels and elevated Wnt activity, underscoring the involvement of Wnt/β-catenin signaling in schizophrenia (Topol et al. 2015). More recently, RNA-seq analysis of neural progenitor cells derived from patients and controls identified differentially expressed genes, with a significant overrepresentation of cadherin and Wnt-related genes, particularly those involved in Wnt5a-related signaling (Evgrafov et al. 2020).

The disrupted-in-schizophrenia-1 (DISC1) protein, which regulates the fate of OPCs, has been implicated in schizophrenia. A significant variant, DISC1-Δ3, characterized by the absence of exon 3, has been identified in individuals with schizophrenia. This variant is associated with excessive branching of OPCs, stemming from aberrant OPC activity driven by hyperactivation of the Wnt/β-catenin pathway (Yu et al. 2022). Although this hyperactivation does not affect myelination, it leads to the upregulation of Wnt inhibitory factor 1 (Wif1), resulting in irregular synaptic formation and neuronal activity. Importantly, this phenotype can be rescued with Wif1 inhibition (Fig. 2). Together, these findings suggest a potential role for the Wnt pathway in the pathophysiology of schizophrenia and suggest

that therapeutic strategies targeting this pathway might be beneficial.

ASD is a multifactorial disorder associated with neurodevelopmental impairment, characterized by deficits in social interaction and communication, alongside patterns of repetitive behavior and narrow interests. The biological etiology of ASD is complex, involving various genetic factors and both prenatal and postnatal environmental influences (Kumar et al. 2019; Kwan et al. 2016). Prenatal exposure to valproic acid (VPA) is a well-established method for inducing autism-like behavior in rodents. High-resolution mass spectrometry-based quantitative proteomic analysis has revealed that differentially expressed proteins in VPA-exposed models significantly overlap with ASD risk genes (Park et al. 2023). This study identified a significant enrichment in the Wnt/β-catenin pathway, driven by the upregulation of Rnf146. Overexpression of Rnf146 impaired social behavior in adult mice and increased excitatory synaptic transmission in prefrontal cortex neurons. Moreover, dysregulated genetic networks involving the PI3K-AKT, RAS-ERK, and Wnt/β-catenin signaling pathways have been identified in leukocyte transcriptomic data from toddlers aged 1–4 years with ASD (Gazestani et al. 2019). There is a notable correlation between the severity of network dysregulation and the extent of socialization deficits observed in these toddlers. These findings highlight the intricate molecular mechanisms underlying ASD, suggesting that dysregulation in Wnt/β-catenin signaling may contribute to the neurodevelopmental impairments and social deficits characteristic of the disorder.

6 Zebrafish as a Model Organism for CNS Regeneration and Neurodegenerative Disease Research

Zebrafish (*Danio rerio*) have emerged as a vital model organism for studying central nervous system (CNS) regeneration and neurodegenerative diseases due to their remarkable ability to regenerate lost tissue functions in critical organs, including the brain and spinal cord (Beffagna 2019; Fleisch et al. 2011; Gemberling et al. 2013). Given the increasing prevalence of neurodegenerative diseases and brain injuries, zebrafish offer an invaluable platform for targeted therapeutic research. A key advantage of using zebrafish is their optical transparency throughout development, which enables high-resolution, live, in vivo imaging of the entire CNS, surpassing conventional methods in clarity and detail. This transparency facilitates the observation of transgene expression levels, particularly when using the UAS/Gal4 system, and allows for the assessment of neuronal health following induced mutations (Kawakami et al. 2016).

Zebrafish have successfully modeled various human brain pathologies, including neurological, developmental, psychotic, and neurodegenerative diseases. They are widely employed in behavioral tests and drug development for CNS disorders, contributing to a deeper understanding of evolutionarily conserved CNS mechanisms (Azbazdar et al. 2023; Kalueff et al. 2014). A significant factor in their regenerative capability is the use of radial glial (RG) cells in neurogenesis, which possess stem cell potential. Unlike mammals, where RG cells are replaced by astrocytes during embryogenesis, these cells remain active throughout the zebrafish CNS, including the retina and cerebellum. In zebrafish, the neurogenic functions of RG cells are regulated by the Wnt/β-catenin signaling pathway, a mechanism also observed in mammalian astrocytes (Demirci et al. 2020). This pathway facilitates the production of GFAP, TGF-β, FGF, GLT-1, and AQP4, mirroring the functions of mammalian astrocytes (Alunni and Bally-Cuif 2016; Lyons and Talbot 2014).

The zebrafish CNS contains continuously active neurogenic regions, and many genes associated with human neurodegenerative diseases have homologs in zebrafish, underscoring their significance as a model organism. While similar neurogenic traits exist in mammals, they are far less abundant (Chapouton et al. 2007; Diotel et al. 2015). Following CNS injury, zebrafish activate various mechanisms that promote neurogenesis and the activation of neuronal progenitors. Notably, zebrafish can resolve glial scars and inflammation, promoting the prolonged survival

of neurons—an ability largely absent in mammals (Demirci et al. 2020; Di Giaimo et al. 2018; Kroehne et al. 2011). Remarkably, zebrafish can restore damaged neurons and motor neuron activity within 4–8 weeks after SCI (Becker et al. 2004; Reimer et al. 2008). One study observed the activation of a restoration mechanism within just 30 min after a single motor neuron was damaged in larval zebrafish (Morsch et al. 2015).

Zebrafish also offer distinct advantages for stem cell therapeutic research in SCI models. Unlike traditional models, which often require immunosuppressive approaches to prevent immune rejection, zebrafish do not face this issue. The zebrafish model allows for direct screening of transplanted cells, providing insights into underlying mechanisms that are difficult to achieve with other models (Tayanloo-Beik et al. 2021).

In the context of neurodegenerative diseases such as Alzheimer's and Parkinson's, which cause severe brain damage and impaired neurogenesis in humans and mammals, zebrafish exhibit a notable ability to renew neurons during neurodegeneration (Wirths 2017). For instance, in an AD model created through Aβ1–42 peptide microinjections, zebrafish have been observed to regenerate neurons by activating the IL-4/STAT6 pathway, which triggers the proliferation of NSPCs (Bhattarai et al. 2016; Saleem and Kannan 2018). This NSPC plasticity is unique to zebrafish, as mammals do not respond to AD in this manner. In zebrafish AD models, the NGFRA/NFkB pathway is activated, facilitating RG proliferation and differentiation (Bhattarai et al. 2020). Zebrafish are also employed to study mechanisms underlying neurodevelopmental disorders and epilepsy (Kobylarek et al. 2019; Zabegalov et al. 2019). For instance, a study on epileptic zebrafish revealed disrupted glutamate turnover in RG cells, resulting in excessive extracellular glutamate levels during seizures (Diaz Verdugo et al. 2019).

Overall, zebrafish provide a powerful and versatile model for studying CNS regeneration, neurodegenerative diseases, and other neurological disorders. Their unique regenerative capabilities, coupled with their genetic and physiological similarities to humans, make them an indispensable tool in the quest for novel therapeutic approaches.

7 Conclusion

The Wnt/β-catenin signaling pathway is integral to both the development and repair of the CNS. Its influence across various CNS cell types highlights its versatility and importance in maintaining neural function and integrity. As discussed, this pathway is not only crucial during early CNS development but also plays a significant role in the adult CNS, particularly in response to injury and neurodegeneration.

Understanding the complexities of Wnt/β-catenin signaling in the CNS opens new avenues for therapeutic intervention, particularly for neurodegenerative diseases and brain injuries. By harnessing the pathway's potential to promote repair and plasticity, we can develop novel strategies to enhance CNS regeneration and improve outcomes for individuals with CNS disorders. The use of model organisms, such as zebrafish, will be essential in these efforts, providing valuable insights into the mechanisms of CNS repair and the development of effective therapies.

Author Contributions DN and UB drafted the manuscript. GO edited and finalized the manuscript. All authors read and approved the final version.

Conflict of Interest The authors declare that they have no conflict of interest.

Funding This work was supported by the Scientific and Technological Research Council of Türkiye (TÜBITAK, grant numbers 215Z365 and 121Z900) and the Health Institutes of Türkiye (TÜSEB, grant numbers 24352 and 31808). The GO Lab is funded by the EMBO Installation Grant (IG 3024). DN and UB received TÜBITAK 2211 Doctoral Scholarship, while UB was additionally supported by the Council of Higher Education (YÖK) 100/2000 Ph.D. Scholarship Program.

References

Alarcón MA, Medina MA, Hu Q, Avila ME, Bustos BI, Pérez-Palma E, Peralta A, Salazar P, Ugarte GD, Reyes AE, Martin GM, Opazo C, Moon RT, De Ferrari GV (2013) A novel functional low-density lipoprotein receptor-related protein 6 gene alternative splice variant is associated with Alzheimer's disease. Neurobiol Aging 34(6):1709.e1709–1709.e1718

Alunni A, Bally-Cuif L (2016) A comparative view of regenerative neurogenesis in vertebrates. Development 143(5):741–753

Alvarez AR, Godoy JA, Mullendorff K, Olivares GH, Bronfman M, Inestrosa NC (2004) Wnt-3a overcomes beta-amyloid toxicity in rat hippocampal neurons. Exp Cell Res 297(1):186–196

Arredondo SB, Valenzuela-Bezanilla D, Mardones MD, Varela-Nallar L (2020) Role of Wnt signaling in adult hippocampal neurogenesis in health and disease. Front Cell Dev Biol 8:860

Avrahami L, Farfara D, Shaham-Kol M, Vassar R, Frenkel D, Eldar-Finkelman H (2013) Inhibition of glycogen synthase kinase-3 ameliorates β-amyloid pathology and restores lysosomal acidification and mammalian target of rapamycin activity in the Alzheimer disease mouse model: in vivo and in vitro studies. J Biol Chem 288(2):1295–1306

Azbazdar Y, Karabicici M, Erdal E, Ozhan G (2021) Regulation of Wnt signaling pathways at the plasma membrane and their misregulation in cancer. Front Cell Dev Biol 9:631623

Azbazdar Y, Poyraz YK, Ozalp O, Nazli D, Ipekgil D, Cucun G, Ozhan G (2023) High-fat diet feeding triggers a regenerative response in the adult zebrafish brain. Mol Neurobiol 60(5):2486–2506

Bai B, Wang X, Li Y, Chen P-C, Yu K, Dey KK, Yarbro JM, Han X, Lutz BM, Rao S, Jiao Y, Sifford JM, Han J, Wang M, Tan H, Shaw TI, Cho J-H, Zhou S, Wang H, Niu M, Mancieri A, Messler KA, Sun X, Wu Z, Pagala V, High AA, Bi W, Zhang H, Chi H, Haroutunian V, Zhang B, Beach TG, Yu G, Peng J (2020) Deep multilayer brain proteomics identifies molecular networks in Alzheimer's disease progression. Neuron 105(6):975–991.e977

Beasley C, Cotter D, Khan N, Pollard C, Sheppard P, Varndell I, Lovestone S, Anderton B, Everall I (2001) Glycogen synthase kinase-3beta immunoreactivity is reduced in the prefrontal cortex in schizophrenia. Neurosci Lett 302(2–3):117–120

Becker CG, Lieberoth BC, Morellini F, Feldner J, Becker T, Schachner M (2004) L1.1 is involved in spinal cord regeneration in adult zebrafish. J Neurosci 24(36):7837–7842

Beffagna G (2019) Zebrafish as a smart model to understand regeneration after heart injury: how fish could help humans. Front Cardiovasc Med 6:107

Bhattarai P, Thomas AK, Cosacak MI, Papadimitriou C, Mashkaryan V, Froc C, Reinhardt S, Kurth T, Dahl A, Zhang Y, Kizil C (2016) IL4/STAT6 signaling activates neural stem cell proliferation and neurogenesis upon amyloid-β42 aggregation in adult zebrafish brain. Cell Rep 17(4):941–948

Bhattarai P, Cosacak MI, Mashkaryan V, Demir S, Popova SD, Govindarajan N, Brandt K, Zhang Y, Chang W, Ampatzis K, Kizil C (2020) Neuron-glia interaction through serotonin-BDNF-NGFR axis enables regenerative neurogenesis in Alzheimer's model of adult zebrafish brain. PLoS Biol 18(1):e3000585

Bielen H, Houart C (2014) The Wnt cries many: Wnt regulation of neurogenesis through tissue patterning, proliferation, and asymmetric cell division. Dev Neurobiol 74(8):772–780

Boghdadi AG, Teo L, Bourne JA (2020) The neuroprotective role of reactive astrocytes after central nervous system injury. J Neurotrauma 37(5):681–691

Brafman D, Willert K (2017) Wnt/β-catenin signaling during early vertebrate neural development. Dev Neurobiol 77(11):1239–1259

Callahan R, Smith GH (2000) MMTV-induced mammary tumorigenesis: gene discovery, progression to malignancy and cellular pathways. Oncogene 19(8): 992–1001

Cardona AE, Pioro EP, Sasse ME, Kostenko V, Cardona SM, Dijkstra IM, Huang D, Kidd G, Dombrowski S, Dutta R, Lee JC, Cook DN, Jung S, Lira SA, Littman DR, Ransohoff RM (2006) Control of microglial neurotoxicity by the fractalkine receptor. Nat Neurosci 9(7):917–924

Caricasole A, Copani A, Caraci F, Aronica E, Rozemuller AJ, Caruso A, Storto M, Gaviraghi G, Terstappen GC, Nicoletti F (2004) Induction of Dickkopf-1, a negative modulator of the Wnt pathway, is associated with neuronal degeneration in Alzheimer's brain. J Neurosci 24(26):6021–6027

Caruso S, Calatayud AL, Pilet J, La Bella T, Rekik S, Imbeaud S, Letouzé E, Meunier L, Bayard Q, Rohr-Udilova N, Péneau C, Grasl-Kraupp B, de Koning L, Ouine B, Bioulac-Sage P, Couchy G, Calderaro J, Nault JC, Zucman-Rossi J, Rebouissou S (2019) Analysis of liver cancer cell lines identifies agents with likely efficacy against hepatocellular carcinoma and markers of response. Gastroenterology 157(3): 760–776

Catala M (2019) Development of the central nervous system. In: Di Rocco C, Pang D, Rutka JT (eds) Textbook of pediatric neurosurgery. Springer International Publishing, Cham, pp 1–99

Cerpa W, Farías GG, Godoy JA, Fuenzalida M, Bonansco C, Inestrosa NC (2010) Wnt-5a occludes Abeta oligomerinduced depression of glutamatergic transmission in hippocampal neurons. Mol Neurodegener 5:3

Chacón MA, Varela-Nallar L, Inestrosa NC (2008) Frizzled-1 is involved in the neuroprotective effect of Wnt3a against Abeta oligomers. J Cell Physiol 217 (1):215–227

Chapouton P, Jagasia R, Bally-Cuif L (2007) Adult neurogenesis in non-mammalian vertebrates. BioEssays 29(8):745–757

Chavali M, Ulloa-Navas MJ, Pérez-Borredá P, Garcia-Verdugo JM, McQuillen PS, Huang EJ, Rowitch DH (2020) Wnt-dependent oligodendroglial-endothelial interactions regulate white matter vascularization and attenuate injury. Neuron 108(6):1130–1145

Chen J, Chen Z, Yu D, Yan Y, Hao X, Zhang M, Zhu T (2023) Neuroprotective effect of hydrogen sulfide subchronic treatment against TBI-induced ferroptosis and cognitive deficits mediated through Wnt signaling pathway. Cell Mol Neurobiol 43(8):4117–4140

Chiareli RA, Carvalho GA, Marques BL, Mota LS, Oliveira-Lima OC, Gomes RM, Birbrair A, Gomez RS, Simão F, Klempin F, Leist M, Pinto MCX (2021) The role of astrocytes in the neurorepair process. Front Cell Dev Biol 9:665795

Clevers H (2006) Wnt/beta-catenin signaling in development and disease. Cell 127(3):469–480

Dai ZM, Sun S, Wang C, Huang H, Hu X, Zhang Z, Lu QR, Qiu M (2014) Stage-specific regulation of oligodendrocyte development by Wnt/β-catenin signaling. J Neurosci 34(25):8467–8473

Dash PK, Johnson D, Clark J, Orsi SA, Zhang M, Zhao J, Grill RJ, Moore AN, Pati S (2011) Involvement of the glycogen synthase kinase-3 signaling pathway in TBI pathology and neurocognitive outcome. PLoS One 6(9):e24648

De Ferrari GV, Chacón MA, Barría MI, Garrido JL, Godoy JA, Olivares G, Reyes AE, Alvarez A, Bronfman M, Inestrosa NC (2003) Activation of Wnt signaling rescues neurodegeneration and behavioral impairments induced by beta-amyloid fibrils. Mol Psychiatry 2:195–208

De Ferrari GV, Papassotiropoulos A, Biechele T, Wavrant De-Vrieze F, Avila ME, Major MB, Myers A, Saez K, Henriquez JP, Zhao A, Wollmer MA, Nitsch RM, Hock C, Morris CM, Hardy J, Moon RT (2007) Common genetic variation within the low-density lipoprotein receptor-related protein 6 and late-onset Alzheimer's disease. Proc Natl Acad Sci USA 104(22):9434–9439

Demirci Y, Cucun G, Poyraz YK, Mohammed S, Heger G, Papatheodorou I, Ozhan G (2020) Comparative transcriptome analysis of the regenerating zebrafish telencephalon unravels a resource with key pathways during two early stages and activation of Wnt/β-catenin signaling at the early wound healing stage. Front Cell Dev Biol 8:584604

Di Giaimo R, Durovic T, Barquin P, Kociaj A, Lepko T, Aschenbroich S, Breunig CT, Irmler M, Cernilogar FM, Schotta G, Barbosa JS, Trumbach D, Baumgart EV, Neuner AM, Beckers J, Wurst W, Stricker SH, Ninkovic J (2018) The aryl hydrocarbon receptor pathway defines the time frame for restorative neurogenesis. Cell Rep 25(12):3241–3251

Diaz Verdugo C, Myren-Svelstad S, Aydin E, Van Hoeymissen E, Deneubourg C, Vanderhaeghe S, Vancraeynest J, Pelgrims R, Cosacak MI, Muto A, Kizil C, Kawakami K, Jurisch-Yaksi N, Yaksi E (2019) Glia-neuron interactions underlie state transitions to generalized seizures. Nat Commun 10(1):3830

Dickins EM, Salinas PC (2013) Wnts in action: from synapse formation to synaptic maintenance. Front Cell Neurosci 7:162

Ding Y, Qiao A, Fan GH (2010) Indirubin-3′-monoxime rescues spatial memory deficits and attenuates beta-amyloid-associated neuropathology in a mouse model of Alzheimer's disease. Neurobiol Dis 39(2):156–168

Diotel N, Rodriguez Viales R, Armant O, Marz M, Ferg M, Rastegar S, Strahle U (2015) Comprehensive expression map of transcription regulators in the adult zebrafish telencephalon reveals distinct neurogenic niches. J Comp Neurol 523(8):1202–1221

Dong F, Liu D, Jiang F, Liu Y, Wu X, Qu X, Liu J, Chen Y, Fan H, Yao R (2021) Conditional deletion of Foxg1 alleviates demyelination and facilitates remyelination via the Wnt signaling pathway in cuprizone-induced demyelinated mice. Neurosci Bull 37(1):15–30

Elliott C, Rojo AI, Ribe E, Broadstock M, Xia W, Morin P, Semenov M, Baillie G, Cuadrado A, Al-Shawi R, Ballard CG, Simons P, Killick R (2018) A role for APP in Wnt signalling links synapse loss with β-amyloid production. Transl Psychiatry 8(1):179

Ernst C (2016) Proliferation and differentiation deficits are a major convergence point for neurodevelopmental disorders. Trends Neurosci 39(5):290–299

Ettle B, Schlachetzki JCM, Winkler J (2016) Oligodendroglia and myelin in neurodegenerative diseases: more than just bystanders? Mol Neurobiol 53(5): 3046–3062

Evgrafov OV, Armoskus C, Wrobel BB, Spitsyna VN, Souaiaia T, Herstein JS, Walker CP, Nguyen JD, Camarena A, Weitz JR, Kim JMH, Lopez Duarte E, Wang K, Simpson GM, Sobell JL, Medeiros H, Pato MT, Pato CN, Knowles JA (2020) Gene expression in patient-derived neural progenitors implicates WNT5A signaling in the etiology of schizophrenia. Biol Psychiatry 88(3):236–247

Fancy SP, Baranzini SE, Zhao C, Yuk DI, Irvine KA, Kaing S, Sanai N, Franklin RJ, Rowitch DH (2009) Dysregulation of the Wnt pathway inhibits timely myelination and remyelination in the mammalian CNS. Genes Dev 23(13):1571–1585

Farkhondeh T, Samarghandian S, Pourbagher-Shahri AM, Sedaghat M (2019) The impact of curcumin and its modified formulations on Alzheimer's disease. J Cell Physiol 234(10):16953–16965

Farr SA, Niehoff ML, Kumar VB, Roby DA, Morley JE (2019) Inhibition of glycogen synthase kinase 3β as a treatment for the prevention of cognitive deficits after a traumatic brain injury. J Neurotrauma 36(11): 1869–1875

Fleisch VC, Fraser B, Allison WT (2011) Investigating regeneration and functional integration of CNS neurons: lessons from zebrafish genetics and other fish species. Biochim Biophys Acta 1812(3):364–380

Fortress AM, Frick KM (2016) Hippocampal Wnt signaling: memory regulation and hormone interactions. Neuroscientist 22(3):278–294

Fujimura N (2016) WNT/β-catenin signaling in vertebrate eye development. Front Cell Dev Biol 4:138

Galli S, Lopes DM, Ammari R, Kopra J, Millar SE, Gibb A, Salinas PC (2014) Deficient Wnt signalling triggers striatal synaptic degeneration and impaired motor behaviour in adult mice. Nat Commun 5(1):4992

Gao K, Shen Z, Yuan Y, Han D, Song C, Guo Y, Mei X (2016) Simvastatin inhibits neural cell apoptosis and promotes locomotor recovery via activation of Wnt/β-catenin signaling pathway after spinal cord injury. J Neurochem 138(1):139–149

Gao J, Xu H, Rong Z, Chen L (2022) Wnt family member 1 (Wnt1) overexpression-induced M2 polarization of microglia alleviates inflammation-sensitized neonatal brain injuries. Bioengineered 13(5):12409–12420

Gao K, Shao W, Wei T, Yan Z, Li N, Lv C (2024) Wnt-3a improves functional recovery after spinal cord injury by regulating the inflammatory and apoptotic response in rats via wnt/beta-catenin signaling pathway. Brain Res 1822:148637

Gazestani VH, Pramparo T, Nalabolu S, Kellman BP, Murray S, Lopez L, Pierce K, Courchesne E, Lewis NE (2019) A perturbed gene network containing PI3K-AKT, RAS-ERK and WNT-β-catenin pathways in leukocytes is linked to ASD genetics and symptom severity. Nat Neurosci 22(10):1624–1634

Gemberling M, Bailey TJ, Hyde DR, Poss KD (2013) The zebrafish as a model for complex tissue regeneration. Trends Genet 29(11):611–620

Godyń J, Jończyk J, Panek D, Malawska B (2016) Therapeutic strategies for Alzheimer's disease in clinical trials. Pharmacol Rep 68(1):127–138

Hayat R, Manzoor M, Hussain A (2022) Wnt signaling pathway: a comprehensive review. Cell Biol Int 46(6): 863–877

Homem CC, Repic M, Knoblich JA (2015) Proliferation control in neural stem and progenitor cells. Nat Rev Neurosci 16(11):647–659

Hoseth EZ, Krull F, Dieset I, Mørch RH, Hope S, Gardsjord ES, Steen NE, Melle I, Brattbakk HR, Steen VM, Aukrust P, Djurovic S, Andreassen OA, Ueland T (2018) Exploring the Wnt signaling pathway in schizophrenia and bipolar disorder. Transl Psychiatry 8(1):55

Hussaini SM, Choi CI, Cho CH, Kim HJ, Jun H, Jang MH (2014) Wnt signaling in neuropsychiatric disorders: ties with adult hippocampal neurogenesis and behavior. Neurosci Biobehav Rev 47:369–383

Inestrosa NC, Varela-Nallar L (2015) Wnt signalling in neuronal differentiation and development. Cell Tissue Res 359(1):215–223

Jankovic J, Tan EK (2020) Parkinson's disease: etiopathogenesis and treatment. J Neurol Neurosurg Psychiatry 91(8):795–808

Ji Y, Hao H, Reynolds K, McMahon M, Zhou CJ (2019) Wnt signaling in neural crest ontogenesis and oncogenesis. Cells 8(10)

Jia L, Piña-Crespo J, Li Y (2019) Restoring Wnt/β-catenin signaling is a promising therapeutic strategy for Alzheimer's disease. Mol Brain 12(1):104

Joshi NJ, Reddy ARS (2024) Navigating the GSK-3β inhibitors as versatile multi-target drug ligands in Alzheimer's disease intervention – a comprehensive review. Res Chem 7:101500

Kalueff AV, Stewart AM, Gerlai R (2014) Zebrafish as an emerging model for studying complex brain disorders. Trends Pharmacol Sci 35(2):63–75

Karabicici M, Azbazdar Y, Iscan E, Ozhan G (2021) Misregulation of Wnt signaling pathways at the plasma membrane in brain and metabolic diseases. Membranes (Basel) 11(11)

Karve IP, Taylor JM, Crack PJ (2016) The contribution of astrocytes and microglia to traumatic brain injury. Br J Pharmacol 173(4):692–702

Kawakami K, Asakawa K, Hibi M, Itoh M, Muto A, Wada H (2016) Gal4 driver transgenic zebrafish: powerful tools to study developmental biology, organogenesis, and neuroscience. Adv Genet 95:65–87

Kawamura Y, Kikuchi A, Takada R, Takada S, Sudoh S, Shibamoto S, Yanagisawa K, Komano H (2001) Inhibitory effect of a presenilin 1 mutation on the Wnt signalling pathway by enhancement of β-catenin phosphorylation. Eur J Biochem 268(10):3036–3041

Killick R, Ribe EM, Al-Shawi R, Malik B, Hooper C, Fernandes C, Dobson R, Nolan PM, Lourdusamy A, Furney S, Lin K, Breen G, Wroe R, To AW, Leroy K, Causevic M, Usardi A, Robinson M, Noble W, Williamson R, Lunnon K, Kellie S, Reynolds CH, Bazenet C, Hodges A, Brion JP, Stephenson J, Simons JP, Lovestone S (2014) Clusterin regulates β-amyloid toxicity via Dickkopf-1-driven induction of the wnt-PCP-JNK pathway. Mol Psychiatry 19(1):88–98

Knopman DS, Amieva H, Petersen RC, Chételat G, Holtzman DM, Hyman BT, Nixon RA, Jones DT (2021) Alzheimer disease. Nat Rev Dis Prim 7(1):33

Knotek T, Janeckova L, Kriska J, Korinek V, Anderova M (2020) Glia and neural stem and progenitor cells of the healthy and ischemic brain: the workplace for the Wnt signaling pathway. Genes (Basel) 11(7)

Kobylarek D, Iwanowski P, Lewandowska Z, Limphaibool N, Szafranek S, Labrzycka A, Kozubski W (2019) Advances in the potential biomarkers of epilepsy. Front Neurol 10:685

Kroehne V, Freudenreich D, Hans S, Kaslin J, Brand M (2011) Regeneration of the adult zebrafish brain from neurogenic radial glia-type progenitors. Development 138(22):4831–4841

Kumar S, Reynolds K, Ji Y, Gu R, Rai S, Zhou CJ (2019) Impaired neurodevelopmental pathways in autism spectrum disorder: a review of signaling mechanisms and crosstalk. J Neurodev Disord 11(1):10

Kuwahara A, Hirabayashi Y, Knoepfler PS, Taketo MM, Sakai J, Kodama T, Gotoh Y (2010) Wnt signaling and its downstream target N-myc regulate basal progenitors in the developing neocortex. Development 137(7): 1035–1044

Kwan V, Unda BK, Singh KK (2016) Wnt signaling networks in autism spectrum disorder and intellectual disability. J Neurodev Disord 8:45

L'Episcopo F, Serapide MF, Tirolo C, Testa N, Caniglia S, Morale MC, Pluchino S, Marchetti B (2011a) A Wnt1 regulated Frizzled-1/β-catenin signaling pathway as a candidate regulatory circuit controlling mesencephalic dopaminergic neuron-astrocyte crosstalk: therapeutical relevance for neuron survival and neuroprotection. Mol Neurodegener 6:49

L'Episcopo F, Tirolo C, Testa N, Caniglia S, Morale MC, Cossetti C, D'Adamo P, Zardini E, Andreoni L, Ihekwaba AE, Serra PA, Franciotta D, Martino G, Pluchino S, Marchetti B (2011b) Reactive astrocytes and Wnt/β-catenin signaling link nigrostriatal injury to repair in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine model of Parkinson's disease. Neurobiol Dis 41(2): 508–527

L'Episcopo F, Tirolo C, Testa N, Caniglia S, Morale MC, Deleidi M, Serapide MF, Pluchino S, Marchetti B (2012) Plasticity of subventricular zone neuroprogenitors in MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) mouse model of Parkinson's disease involves cross talk between inflammatory and Wnt/β-catenin signaling pathways: functional consequences for neuroprotection and repair. J Neurosci 32(6):2062–2085

L'Episcopo F, Tirolo C, Testa N, Caniglia S, Morale MC, Impagnatiello F, Pluchino S, Marchetti B (2013) Aging-induced Nrf2-ARE pathway disruption in the subventricular zone drives neurogenic impairment in parkinsonian mice via PI3K-Wnt/β-catenin dysregulation. J Neurosci 33(4):1462–1485

Leeds PR, Yu F, Wang Z, Chiu CT, Zhang Y, Leng Y, Linares GR, Chuang DM (2014) A new avenue for lithium: intervention in traumatic brain injury. ACS Chem Neurosci 5(6):422–433

Li X, Shan J, Chang W, Kim I, Bao J, Lee HJ, Zhang X, Samuel VT, Shulman GI, Liu D, Zheng JJ, Wu D (2012) Chemical and genetic evidence for the involvement of Wnt antagonist Dickkopf2 in regulation of glucose metabolism. Proc Natl Acad Sci USA 109 (28):11402–11407

Li M, Gao W, Ji L, Li J, Jiang W, Ji W (2020a) Methane saline ameliorates traumatic brain injury through anti-inflammatory, antiapoptotic, and antioxidative effects by activating the Wnt signalling pathway. Biomed Res Int 2020:3852450

Li X, Ortiz MA, Kotula L (2020b) The physiological role of Wnt pathway in normal development and cancer. Exp Biol Med (Maywood) 245(5):411–426

Licht-Murava A, Paz R, Vaks L, Avrahami L, Plotkin B, Eisenstein M, Eldar-Finkelman H (2016) A unique type of GSK-3 inhibitor brings new opportunities to the clinic. Sci Signal 9(454):ra110

Liddelow SA, Barres BA (2017) Reactive astrocytes: production, function, and therapeutic potential. Immunity 46(6):957–967

Liu B, Hunter DJ, Rooker S, Chan A, Paulus YM, Leucht P, Nusse Y, Nomoto H, Helms JA (2013) Wnt signaling promotes Müller cell proliferation and survival after injury. Invest Ophthalmol Vis Sci 54(1): 444–453

Liu CC, Tsai CW, Deak F, Rogers J, Penuliar M, Sung YM, Maher JN, Fu Y, Li X, Xu H, Estus S, Hoe HS, Fryer JD, Kanekiyo T, Bu G (2014) Deficiency in LRP6-mediated Wnt signaling contributes to synaptic abnormalities and amyloid pathology in Alzheimer's disease. Neuron 84(1):63–77

Liu C, He D, Zhao Q (2020) Licoricidin improves neurological dysfunction after traumatic brain injury in mice via regulating FoxO3/Wnt/β-catenin pathway. J Nat Med 74(4):767–776

Llorens-Martín M, Jurado J, Hernández F, Avila J (2014) GSK-3β, a pivotal kinase in Alzheimer disease. Front Mol Neurosci 7:46

Lv Q, Lan W, Sun W, Ye R, Fan X, Ma M, Yin Q, Jiang Y, Xu G, Dai J, Guo R, Liu X (2014) Intranasal nerve growth factor attenuates tau phosphorylation in brain after traumatic brain injury in rats. J Neurol Sci 345(1–2):48–55

Ly PT, Wu Y, Zou H, Wang R, Zhou W, Kinoshita A, Zhang M, Yang Y, Cai F, Woodgett J, Song W (2013) Inhibition of GSK3β-mediated BACE1 expression reduces Alzheimer-associated phenotypes. J Clin Invest 123(1):224–235

Lyons DA, Talbot WS (2014) Glial cell development and function in zebrafish. Cold Spring Harb Perspect Biol 7(2):a020586

Marchetti B (2018) Wnt/β-catenin signaling pathway governs a full program for dopaminergic neuron survival, neurorescue and regeneration in the MPTP mouse model of Parkinson's disease. Int J Mol Sci 19(12)

Marchetti B, Pluchino S (2013) Wnt your brain be inflamed? Yes, it Wnt! Trends Mol Med 19(3):144–156

Marzo A, Galli S, Lopes D, McLeod F, Podpolny M, Segovia-Roldan M, Ciani L, Purro S, Cacucci F, Gibb A, Salinas PC (2016) Reversal of synapse degeneration by restoring Wnt Signaling in the adult hippocampus. Curr Biol 26(19):2551–2561

Mercurio D, Fumagalli S, Schafer MK, Pedragosa J, Ngassam LDC, Wilhelmi V, Winterberg S, Planas AM, Weihe E, De Simoni MG (2022) Protein expression of the microglial marker Tmem119 decreases in association with morphological changes and location in a mouse model of traumatic brain injury. Front Cell Neurosci 16:820127

Miyaoka T, Seno H, Ishino H (1999) Increased expression of Wnt-1 in schizophrenic brains. Schizophr Res 38(1): 1–6

Mo Z, Zeng Z, Liu Y, Zeng L, Fang J, Ma Y (2022) Activation of Wnt/Beta-catenin signaling pathway as a promising therapeutic candidate for cerebral ischemia/reperfusion injury. Front Pharmacol 13:914537

Morsch M, Radford R, Lee A, Don EK, Badrock AP, Hall TE, Cole NJ, Chung R (2015) In vivo characterization of microglial engulfment of dying neurons in the zebrafish spinal cord. Front Cell Neurosci 9:321

Mudher A, Chapman S, Richardson J, Asuni A, Gibb G, Pollard C, Killick R, Iqbal T, Raymond L, Varndell I, Sheppard P, Makoff A, Gower E, Soden PE, Lewis P, Murphy M, Golde TE, Rupniak HT, Anderton BH, Lovestone S (2001) Dishevelled regulates the metabolism of amyloid precursor protein via protein kinase C/mitogen-activated protein kinase and c-Jun terminal kinase. J Neurosci 21(14):4987–4995

Ng SY, Lee AYW (2019) Traumatic brain injuries: pathophysiology and potential therapeutic targets. Front Cell Neurosci 13:528

Nusse R (2008) Wnt signaling and stem cell control. Cell Res 18(5):523–527

Nusse R, Clevers H (2017) Wnt/β-catenin signaling, disease, and emerging therapeutic modalities. Cell 169(6): 985–999

Nusse R, Varmus HE (1992) Wnt genes. Cell 69(7): 1073–1087

Osakada F, Ooto S, Akagi T, Mandai M, Akaike A, Takahashi M (2007) Wnt signaling promotes regeneration in the retina of adult mammals. J Neurosci 27(15):4210–4219

Ozhan G, Weidinger G (2014) Restoring tissue homeostasis: Wnt signaling in tissue regeneration after acute injury. In: Hoppler SP, Moon RT (eds) Wnt signaling in development and disease: molecular mechanisms and biological functions. Wiley-Blackwell

Ozhan G, Weidinger G (2015) Wnt/β-catenin signaling in heart regeneration. Cell Regen 4(1):3

Palomer E, Buechler J, Salinas PC (2019) Wnt signaling deregulation in the aging and Alzheimer's brain. Front Cell Neurosci 13:227

Paolicelli RC, Bolasco G, Pagani F, Maggi L, Scianni M, Panzanelli P, Giustetto M, Ferreira TA, Guiducci E, Dumas L, Ragozzino D, Gross CT (2011) Synaptic pruning by microglia is necessary for normal brain development. Science 333(6048):1456–1458

Park G, Jang WE, Kim S, Gonzales EL, Ji J, Choi S, Kim Y, Park JH, Mohammad HB, Bang G, Kang M, Kim S, Jeon SJ, Kim JY, Kim KP, Shin CY, An JY, Kim MS, Lee YS (2023) Dysregulation of the Wnt/β-catenin signaling pathway via Rnf146 upregulation in a VPA-induced mouse model of autism spectrum disorder. Exp Mol Med 55(8):1783–1794

Parr C, Mirzaei N, Christian M, Sastre M (2015) Activation of the Wnt/β-catenin pathway represses the transcription of the β-amyloid precursor protein cleaving enzyme (BACE1) via binding of T-cell factor-4 to BACE1 promoter. FASEB J 29(2):623–635

Patel AK, Park KK, Hackam AS (2017) Wnt signaling promotes axonal regeneration following optic nerve injury in the mouse. Neuroscience 343:372–383

Pei J-J, Braak E, Braak H, Grundke-Iqbal I, Iqbal K, Winblad B, Cowburn RF (1999) Distribution of active glycogen synthase kinase 3β (GSK-3β) in brains staged for Alzheimer disease neurofibrillary changes. J Neuropathol Exp Neurol 58(9):1010–1019

Poewe W, Seppi K, Tanner CM, Halliday GM, Brundin P, Volkmann J, Schrag A-E, Lang AE (2017) Parkinson disease. Nat Rev Dis Prim 3(1):17013

Pöschl J, Grammel D, Dorostkar MM, Kretzschmar HA, Schüller U (2013) Constitutive activation of β-catenin in neural progenitors results in disrupted proliferation and migration of neurons within the central nervous system. Dev Biol 374(2):319–332

Prajapat M, Singh H, Chaudhary G, Sarma P, Kaur G, Prakash Patel A, Medhi B (2023) A novel inhibitor of DKK1/LRP6 interactions against the Alzheimer disease: An Insilco approach. Bioinform Biol Insights 17:11779322231183762

Purro SA, Dickins EM, Salinas PC (2012) The secreted Wnt antagonist Dickkopf-1 is required for amyloid β-mediated synaptic loss. J Neurosci 32(10): 3492–3498

Qin K, Yu M, Fan J, Wang H, Zhao P, Zhao G, Zeng W, Chen C, Wang Y, Wang A, Schwartz Z, Hong J, Song L, Wagstaff W, Haydon RC, Luu HH, Ho SH, Strelzow J, Reid RR, He T-C, Shi LL (2024) Canonical and noncanonical Wnt signaling: multilayered mediators, signaling mechanisms and major signaling crosstalk. Genes Dis 11(1):103–134

Quintanilla RA, Muñoz FJ, Metcalfe MJ, Hitschfeld M, Olivares G, Godoy JA, Inestrosa NC (2005) Trolox and 17betaestradiol protect against amyloid beta-peptide neurotoxicity by a mechanism that involves modulation of the Wnt signaling pathway. J Biol Chem 280 (12):11615–11625

Reimer MM, Sörensen I, Kuscha V, Frank RE, Liu C, Becker CG, Becker T (2008) Motor neuron regeneration in adult zebrafish. J Neurosci 28(34):8510–8516

Ren C, Gu X, Li H, Lei S, Wang Z, Wang J, Yin P, Zhang C, Wang F, Liu C (2019) The role of DKK1 in Alzheimer's disease: a potential intervention point of brain damage prevention? Pharmacol Res 144:331–335

Rodriguez JP, Coulter M, Miotke J, Meyer RL, Takemaru K, Levine JM (2014) Abrogation of β-catenin signaling in oligodendrocyte precursor cells reduces glial scarring and promotes axon regeneration after CNS injury. J Neurosci 34(31):10285–10297

Rong Y, Liu W, Zhou Z, Gong F, Bai J, Fan J, Li L, Luo Y, Zhou Z, Cai W (2019) Harpagide inhibits neuronal apoptosis and promotes axonal regeneration after spinal cord injury in rats by activating the Wnt/β-catenin signaling pathway. Brain Res Bull 148:91–99

Rosi MC, Luccarini I, Grossi C, Fiorentini A, Spillantini MG, Prisco A, Scali C, Gianfriddo M, Caricasole A, Terstappen GC, Casamenti F (2010) Increased Dickkopf-1 expression in transgenic mouse models of neurodegenerative disease. J Neurochem 112(6): 1539–1551

Ross SP, Baker KE, Fisher A, Hoff L, Pak ES, Murashov AK (2018) miRNA-431 prevents amyloid-β-induced synapse loss in neuronal cell culture model of Alzheimer's disease by silencing Kremen1. Front Cell Neurosci 12:87

Rosso SB, Inestrosa NC (2013) WNT signaling in neuronal maturation and synaptogenesis. Front Cell Neurosci 7:103

Sakr R, Mohamed HE, Abo-El-Matty D, Wahba N, Wahba AS (2023) Therapeutic potential of targeting wingless-integrated/β-catenin/(Wnt/β-catenin) signaling pathway in Alzheimer's disease. Rec Pharm Biomed Sci 7(3):71–80

Salcedo-Tello P, Hernández-Ortega K, Arias C (2014) Susceptibility to GSK3β-induced tau phosphorylation differs between the young and aged hippocampus after Wnt signaling inhibition. J Alzheimers Dis 39(4): 775–785

Saleem S, Kannan RR (2018) Zebrafish: an emerging real-time model system to study Alzheimer's disease and neurospecific drug discovery. Cell Death Discov 4:45

Salinas PC (2012) Wnt signaling in the vertebrate central nervous system: from axon guidance to synaptic function. Cold Spring Harb Perspect Biol 4(2)

Scali C, Caraci F, Gianfriddo M, Diodato E, Roncarati R, Pollio G, Gaviraghi G, Copani A, Nicoletti F, Terstappen GC, Caricasole A (2006) Inhibition of Wnt signaling, modulation of tau phosphorylation and induction of neuronal cell death by DKK1. Neurobiol Dis 24(2):254–265

Sellers KJ, Elliott C, Jackson J, Ghosh A, Ribe E, Rojo AI, Jarosz-Griffiths HH, Watson IA, Xia W, Semenov M, Morin P, Hooper NM, Porter R, Preston J, Al-Shawi R, Baillie G, Lovestone S, Cuadrado A, Harte M, Simons P, Srivastava DP, Killick R (2018) Amyloid β synaptotoxicity is Wnt-PCP dependent and blocked by fasudil. Alzheimers Dement 14(3):306–317

Serafino A, Cozzolino M (2023) The Wnt/β-catenin signaling: a multifunctional target for neuroprotective and regenerative strategies in Parkinson's disease. Neural Regen Res 18(2):306–308

Serafino A, Giovannini D, Rossi S, Cozzolino M (2020) Targeting the Wnt/β-catenin pathway in neurodegenerative diseases: recent approaches and current challenges. Expert Opin Drug Discov 15(7):803–822

Serenó L, Coma M, Rodríguez M, Sánchez-Ferrer P, Sánchez MB, Gich I, Agulló JM, Pérez M, Avila J, Guardia-Laguarta C, Clarimón J, Lleó A, Gómez-Isla T (2009) A novel GSK-3β inhibitor reduces Alzheimer's pathology and rescues neuronal loss in vivo. Neurobiol Dis 35(3):359–367

Shaik MG, Joshi SV, Akunuri R, Rana P, Rahman Z, Polomoni A, Yaddanapudi VM, Dandekar MP, Srinivas N (2023) Small molecule inhibitors of NLRP3 inflammasome and GSK-3β in the management of traumatic brain injury: a review. Eur J Med Chem 259:115718

Shruster A, Ben-Zur T, Melamed E, Offen D (2012) Wnt signaling enhances neurogenesis and improves neurological function after focal ischemic injury. PLoS One 7(7):e40843

Siracusa R, Fusco R, Cuzzocrea S (2019) Astrocytes: role and functions in brain pathologies. Front Pharmacol 10:1114

Sonn I, Nakamura M, Renault-Mihara F, Okano H (2020) Polarization of reactive astrocytes in response to spinal cord injury is enhanced by M2 macrophage-mediated activation of Wnt/β-catenin pathway. Mol Neurobiol 57(4):1847–1862

Stanganello E, Zahavi EE, Burute M, Smits J, Jordens I, Maurice MM, Kapitein LC, Hoogenraad CC (2019) Wnt signaling directs neuronal polarity and axonal growth. iScience 13:318–327

Steinhart Z, Angers S (2018) Wnt signaling in development and tissue homeostasis. Development 145(11)

Stiles J, Jernigan TL (2010) The basics of brain development. Neuropsychol Rev 20(4):327–348

Strand NS, Hoi KK, Phan TMT, Ray CA, Berndt JD, Moon RT (2016) Wnt/β-catenin signaling promotes regeneration after adult zebrafish spinal cord injury. Biochem Biophys Res Commun 477(4):952–956

Tapia-Rojas C, Inestrosa NC (2018) Loss of canonical Wnt signaling is involved in the pathogenesis of Alzheimer's disease. Neural Regen Res 13(10):1705–1710

Tayanloo-Beik A, Rabbani Z, Soveyzi F, Alavi-Moghadam S, Rezaei-Tavirani M, Goodarzi P, Arjmand B, Larijani B (2021) Cellular therapy for treatment of spinal cord injury in zebrafish model. Mol Biol Rep 48(2):1787–1800

Topol A, Zhu S, Tran N, Simone A, Fang G, Brennand KJ (2015) Altered WNT signaling in human induced pluripotent stem cell neural progenitor cells derived from four schizophrenia patients. Biol Psychiatry 78(6):e29–e34

Van Camp JK, Beckers S, Zegers D, Van Hul W (2014) Wnt signaling and the control of human stem cell fate. Stem Cell Rev Rep 10(2):207–229

Varela-Nallar L, Inestrosa NC (2013) Wnt signaling in the regulation of adult hippocampal neurogenesis. Front Cell Neurosci 7:100

Vargas JY, Ahumada J, Arrázola MS, Fuenzalida M, Inestrosa NC (2015) WASP-1, a canonical Wnt signaling potentiator, rescues hippocampal synaptic impairments induced by Aβ oligomers. Exp Neurol 264:14–25

Vassar R, Kovacs DM, Yan R, Wong PC (2009) The beta-secretase enzyme BACE in health and Alzheimer's disease: regulation, cell biology, function, and therapeutic potential. J Neurosci 29(41):12787–12794

Wang LP, Pan J, Li Y, Geng J, Liu C, Zhang LY, Zhou P, Tang YH, Wang Y, Zhang Z, Yang GY (2022) Oligodendrocyte precursor cell transplantation promotes angiogenesis and remyelination via Wnt/β-catenin pathway in a mouse model of middle cerebral artery occlusion. J Cereb Blood Flow Metab 42(5):757–770

Wei L, Sun C, Lei M, Li G, Yi L, Luo F, Li Y, Ding L, Liu Z, Li S, Xu P (2013) Activation of Wnt/β-catenin pathway by exogenous Wnt1 protects SH-SY5Y cells against 6-hydroxydopamine toxicity. J Mol Neurosci 49(1):105–115

Wei ZZ, Zhang JY, Taylor TM, Gu X, Zhao Y, Wei L (2018) Neuroprotective and regenerative roles of intranasal Wnt-3a administration after focal ischemic stroke in mice. J Cereb Blood Flow Metab 38(3):404–421

Westphal M, Panza P, Kastenhuber E, Wehrle J, Driever W (2022) Wnt/β-catenin signaling promotes neurogenesis in the diencephalospinal dopaminergic system of embryonic zebrafish. Sci Rep 12(1):1030

Wirths O (2017) Altered neurogenesis in mouse models of Alzheimer disease. Neurogenesis (Austin) 4(1): e1327002

Xiang Z, Zhang S, Yao X, Xu L, Hu J, Yin C, Chen J, Xu H (2021) Resveratrol promotes axonal regeneration after spinal cord injury through activating Wnt/β-catenin signaling pathway. Aging (Albany NY) 13(20):23603–23619

Xiao Q, Werner J, Venkatachalam N, Boonekamp KE, Ebert MP, Zhan T (2022) Cross-talk between p53 and Wnt signaling in cancer. Biomol Ther 12(3)

Xie C, Li Z, Zhang GX, Guan Y (2014) Wnt signaling in remyelination in multiple sclerosis: friend or foe? Mol Neurobiol 49(3):1117–1125

Xu J, Patassini S, Rustogi N, Riba-Garcia I, Hale BD, Phillips AM, Waldvogel H, Haines R, Bradbury P, Stevens A, Faull RLM, Dowsey AW, Cooper GJS, Unwin RD (2019) Regional protein expression in human Alzheimer's brain correlates with disease severity. Commun Biol 2:43

Xu X, Song X, Chen F, Yan W, Meng Q, Liu J, Yao R, Liu Y, Dong F (2024) Solifenacin promotes remyelination in cuprizone mouse model by inhibiting the Wnt/β-catenin signaling pathway. J Chem Neuroanat 136:102375

Yang XT, Bi YY, Chen ET, Feng DF (2014) Overexpression of Wnt3a facilitates the proliferation and neural differentiation of neural stem cells in vitro and after transplantation into an injured rat retina. J Neurosci Res 92(2):148–161

Yu G, Su Y, Guo C, Yi C, Yu B, Chen H, Cui Y, Wang X, Wang Y, Chen X, Wang S, Wang Q, Chen X, Hu X, Mei F, Verkhratsky A, Xiao L, Niu J (2022) Pathological oligodendrocyte precursor cells revealed in human schizophrenic brains and trigger schizophrenia-like behaviors and synaptic defects in genetic animal model. Mol Psychiatry 27(12):5154–5166

Zabegalov KN, Khatsko SL, Lakstygal AM, Demin KA, Cleal M, Fontana BD, McBride SD, Harvey BH, de Abreu MS, Parker MO, Kalueff AV (2019) Abnormal repetitive behaviors in zebrafish and their relevance to human brain disorders. Behav Brain Res 367:101–110

Zhang L, Cen L, Qu S, Wei L, Mo M, Feng J, Sun C, Xiao Y, Luo Q, Li S, Yang X, Xu P (2016) Enhancing Beta-catenin activity via GSK3beta inhibition protects PC12 cells against rotenone toxicity through Nurr1 induction. PLoS One 11(4):e0152931

Zhang JY, Lee JH, Gu X, Wei ZZ, Harris MJ, Yu SP, Wei L (2018) Intranasally delivered Wnt3a improves functional recovery after traumatic brain injury by modulating autophagic, apoptotic, and regenerative pathways in the mouse brain. J Neurotrauma 35(5): 802–813

Zhao Y, Zhang Q, Xi J, Xiao B, Li Y, Ma C (2015) Neuroprotective effect of fasudil on inflammation through PI3K/Akt and Wnt/β-catenin dependent pathways in a mice model of Parkinson's disease. Int J Clin Exp Pathol 8(3):2354–2364

Zheng H, Jia L, Liu CC, Rong Z, Zhong L, Yang L, Chen XF, Fryer JD, Wang X, Zhang YW, Xu H, Bu G (2017) TREM2 promotes microglial survival by activating Wnt/β-catenin pathway. J Neurosci 37(7): 1772–1784

Zhou T, Zu G, Zhang X, Wang X, Li S, Gong X, Liang Z, Zhao J (2016) Neuroprotective effects of ginsenoside Rg1 through the Wnt/β-catenin signaling pathway in both in vivo and in vitro models of Parkinson's disease. Neuropharmacology 101:480–489