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REVIEW

The Wnt/β-catenin signaling pathway in the adult neurogenesis

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Abstract

The Wnt/β-catenin signaling pathway plays an important role in neural development, β-catenin is a central component of the Wnt/β-catenin signaling pathway, which not only performs the function of transmitting information in the cytoplasm, but also translocates to the nucleus-activating target gene transcription. The target genes in neural tissues have not been fully revealed, but the effects of the Wnt/β-catenin signaling pathway in adult neurogenesis have been demonstrated by ongoing research, which are significative to the basic research and treatment of neuronal degeneration diseases. Here, we review key findings to show the characteristics of β-catenin and its pivotal nature in the Wnt/β-catenin signaling pathway in a number of molecular studies. We also review current literature on the role of β-catenin in adult neurogenesis, which consists of an active process encompassing the proliferation, migration, differentiation and final synaptogenesis.

Introduction

The Wnt signaling pathway is a highly conserved signaling pathway. The components of this pathway reveal highly homologous from *Drosophila* to mammal. The initial finding of the Wnt gene was unexpected and provided a significant revelation for further research. In 1982, Nusse and Varmus found that the mouse int1 gene is a preferential integration site for the mouse mammary tumor virus in virally induced breast tumors. Subsequently, *Drosophila* Wingless (Wg), which controls segment polarity during larval development (Nusslein-Volhard & Wieschaus, 1980), was shown to be a fly homolog of Int1 (Rijsewijk *et al.*, 1987). Uniting the names of these two genes, this gene was renewed to Wnt, which encodes some kinds of secretary glycoprotein to activate the Wnt signaling pathway. Three different pathways are demonstrated to be activated upon Wnt receptor activation: the canonical Wnt/β-catenin cascade, the non-canonical planar cell polarity pathway and the Wnt/Ca^{2+} pathway. The canonical Wnt/β-catenin pathway is the best understood and is the primary subject of this review.

A crucial component of the canonical Wnt/β-catenin pathway is β-catenin, a multifunctional protein that can function in gene transcription and cell adhesion (Nelson & Nusse, 2004). β-Catenin was first isolated as a protein associated with the intracellular domain of E-cadherin, a component of the adherens junction (Aberle *et al.*, 1996). In the canonical Wnt/β-catenin pathway, the interaction between Wnt protein and receptors triggers recruitment of Axin to the plasma membrane, resulting in the inhibition of β-catenin phosphorylation and degradation (Cadigan & Liu, 2006; Huang & He, 2008). Consequently, β-catenin accumulates in the cytoplasm and then translocates into the nucleus where it forms a complex with the T-cell factor/lymphoid enhancer factor (TCF/LEF) family of transcription factors, leading to activation of target genes (Stadeli *et al.*, 2006; Willert & Jones, 2006).

The Wnt/β-catenin signaling pathway plays a vital role in neural development. Its signaling has been demonstrated to participate in axis formation, midbrain development and oncogenesis to name some of the most recognized functions (McMahon & Bradley, 1990; McMahon, 1993; Nusse, 2001; Miller, 2002; Logan & Nusse, 2004; Polakis, 2007). The inactivation of β-catenin results in specific developmental brain defects (Brault *et al.*, 2001). In contrast, the activation of β-catenin leads to amplification of the neural progenitor pool (Chenn & Walsh, 2002; Megason & McMahon, 2002). In several pathologies an association with the Wnt signaling pathway has been found (Moon *et al.*, 2004). The disorder of signaling is associated with several pathologies, such as Alzheimer's disease (AD; De Ferrari & Inestrosa, 2000; Inestrosa *et al.*, 2000; De Ferrari *et al.*, 2007), schizophrenia (Lovestone *et al.*, 2007), autism (De Ferrari & Moon, 2006) and cancer (Rubinfeld *et al.*, 1993; Polakis, 2007).These diseases all have a link with adult neurogenesis, thus it is obvious that the Wnt/β-catenin signaling pathway plays a role in adult neurogenesis. Subsequently we will review the literature of Wnt/β-catenin signaling, and the diverse points of connection between canonical Wnt/β-catenin signaling and adult neurogenesis.

The β-catenin and Wnt/β-catenin signaling pathway

β-Catenin, as a homologous molecule with *Drosophila* segment polarity gene armadillo (Arm), is the central protein in the Wnt signaling pathway. It was initially discovered as a component of the adherens junction, which links E-cadherin to α-catenin and then associates with cytoskeleton. Aside from this function, β-catenin is a key effector in the Wnt signaling pathway, serving as a downstream transcription factor.

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The structure and characteristics of β-catenin

The primary structure of the β-catenin protein comprises a 42-amino acid central domain (Arm repeats), a 130-amino acid amino-terminal domain and a 100-amino acid carboxy-terminal domain (Willert & Nusse, 1998). The central domain of β-catenin consists of 12 imperfect repeats, which form three α-helices that are connected by short loops, reorienting the polypeptide by 90°. The final structure of the central domain is a tightly packed series of interacting α-helices that form a rigid right-handed super helix. This generates a shallow groove lined with basic amino acids that confer on the groove an overall positive charge (Huber *et al.*, 1997). This positively charged groove may serve as a binding surface for several proteins, including TCF (Behrens *et al.*, 1996; Huber *et al.*, 1996; Molenaar *et al.*, 1996; Brunner *et al.*, 1997; van de Wetering *et al.*, 1997), adenomatous polyposis coli (APC; Rubinfeld *et al.*, 1993) and adherens junction protein E-cadherin (Hulsken *et al.*, 1994; Orsulic & Peifer, 1996).

The function of each structure of β-catenin in neuronal development of adult mammal is still unclear, and the related researches mainly concentrate on *Drosophila* and *Xenopus*. It has demonstrated that each domain of β-catenin plays an independent role in the Wnt signaling pathway. Previously, Funayama *et al.* reported that overexpression of β-catenin in the ventral side of the early *Xenopus* embryo, by injection of synthetic β-catenin mRNA, induces the formation of a complete secondary body axis. Furthermore, an analysis of β-catenin deletion constructs demonstrates that the internal Arm repeat region is both necessary and sufficient to induce axis duplication (Funayama *et al.,* 1995). It is noteworthy that nuclear accumulation of the Arm repeat domain of β-catenin retains potent signaling activity, which interacts with some downstream protein targets that leads ultimately to a change in neuronal development.

In the amino terminus of β-catenin, there are four potential glycogen-synthasekinase-3β (GSK-3β) phosphorylation sites (Cadigan & Nusse, 1997). Mutation of these sites led to a β-catenin that is more stable than wild-type β-catenin and considerably more potent in secondary axis formation in *Xenopus* (Yost *et al.*, 1996). Deletions at the amino terminus of Arm (removing the four serine/threonine residues) result in a constitutively active Arm protein (Zecca *et al.*, 1996; Pai *et al.*, 1997). Besides, the interaction of β-catenin with α-catenin occurs via the amino terminus region of β-catenin (Aberle *et al.*, 1994; Oyama *et al.*, 1994; Rubinfeld *et al.*, 1995; Orsulic & Peifer, 1996), and the amino terminal deletion, that fails to bind α-catenin, still has the potential capacity to induce axis duplication (Funayama *et al.*, 1995).

So far, the function of the carboxyl terminus has not been studied in detail, it is possible that the carboxyl terminus is required for this early upstream step in the pathway, whereas the repeat domain of β-catenin might bypass the early steps in a signaling pathway and act directly (Funayama *et al.*, 1995). Moreover, there seems to be an opinion that the carboxyl terminus contains a transcriptional activation domain (Willert & Nusse, 1998) that plays a role in activating the downstream target gene.

Although those theories have not been demonstrated in mammals, those studies form the stepping stones for further research to better understand the function of each structure of β-catenin in neuronal development and enlighten us to do further work in adult neurogenesis.

The Wnt/β-catenin signaling pathway

The first step of the activation of the Wnt/β-catenin signaling pathway is the interaction between Wnt proteins and the receptor protein Frizzled (Fzd) and the co-receptor low-density lipoprotein receptor-related protein 5/6 (LRP5/6). The classical view of the canonical Wnt/β-catenin signaling transduction pathway (Fig. 1) implies the presence of an extracellular secreted Wnt ligand that interacts with the receptor protein Fzd, which is a member of a family of seven-pass transmembrane proteins. The Wnt-Fzd receptor complex forms a ternary cell surface complex with the co-receptor LRP5/6 (Tamai *et al.*, 2000). Thus, the Wnt signaling is transduced into cytoplasm. This then activates Dishevelled (Dvl) usually by phosphorylation, which, in turn, inactivates GSK-3β – a key modulator of this pathway. Wnt signaling regulates GSK-3β activity by physically displacing complex GSK-3β from a member of regulatory binding partners, consequently preventing the phosphorylation and degradation of β-catenin (Toledo *et al.*, 2008).

In the absence of Wnt, the signaling poll of β-catenin is maintained at a low level, through degradation (Dale, 1998; Logan & Nusse, 2004). β-Catenin is targeted for ubiquitination by the β-transducing repeat-containing protein and is then degraded by the proteosome. β-Catenin is phosphorylated by the serine/threonine kinases casein kinase 1 and GSK-3β. Phosphorylation of β-catenin occurs in a multiprotein complex (the destruction complex; Chen *et al.*, 2000), comprising Axin, APC and diversin. Upon receipt of a Wnt signal, Dvl prevents degradation of β-catenin through recruitment of GSK-3β-binding proteins/Frat-1, which displace GSK-3β from the destruction complex (Toledo *et al.*, 2008). As a consequence, stable, non-phosphorylated β-catenin accumulates and translocates into the nucleus.

Stabilized β-catenin enters the nucleus and associates with TCF/LEF transcription factors via physically displaced Groucho from TCF/LEF (Daniels & Weis, 2005), leading to the transcription of Wnt target genes, such as cyclin D1, PPARδ and engrailed (Logan & Nusse, 2004), and many others (http://www.stanford.edu/~rnusse/pathways/targets.html). In the CNS, these targets include proteins involved in neural patterning, such as the caudal-type homeodomain transcription factors 1 (CDX1; Ikeya & Takada, 2001) and engrailed-1 (Danielian & McMahon, 1996) during mid-brain development and EMX2 dorsal telencephalic development (Theil *et al.*, 1999), and may also include proliferation-promoting genes such as c-myc and cyclin D1 (He *et al.*, 1998; Shtutman *et al.*, 1999; Tetsu & McCormick, 1999; Coyle-Rink *et al.*, 2002).

Furthermore, β-catenin may also be actively transported back to the cytoplasm by either an intrinsic export signal or as cargo of Axin (Cong & Varmus, 2004) or APC (Rosin-Arbesfeld *et al.*, 2000) that shuttle between cytoplasm and nucleus (Clevers, 2006). Although the mechanism of the Wnt/β-catenin signaling pathway is detailed and complete, the subsequent expression of the target genes which impact on human biology is unclear, and the molecule involved in this pathway also requires further investigation.

Wnt/β-catenin signaling in adult neurogenesis

Adult neurogenesis is generally considered an active process encompassing the proliferation and cell fate specification of adult neural progenitors, and their subsequent differentiation, maturation, navigation and functional integration into the existing neuronal circuitry (Duan *et al.*, 2008). In the adult CNS, active neurogenesis occurs in two discrete 'neurogenic' regions: the subgranular zone (SGZ) of the dentate gyrus (DG) in the hippocampus and the subventricular zone (SVZ) of the lateral ventricles in the forebrain (Alvarez-Buylla & Lim, 2004; Lie *et al.*, 2004). In this section we will review evidence for the role of the Wnt/β-catenin signaling in adult neurogenesis, including

studies concerning neural stem cells proliferation, migration of precursor cells, differentiation and synaptic development (Fig. 2).

Wnt/β-catenin signaling in the proliferation of neural stem cells

The effects of Wnt/β-catenin signaling depend on which Wnt family members are involved, as well as on the specific time point and cellular localization of activation. In the early stages of embryonal development, activation of the Wnt/β-catenin signaling pathway supports precursor cells in a pluripotent state and maintains their self-renewal (Scholzke & Schwaninger, 2007). It is well known that β-catenin is both a component of the transmission and a transcription factor in this pathway. Its nuclear (transcription) actions induce proliferation of undifferentiated precursor cells by making them re-enter the cell cycle rather than differentiate (Brembeck *et al.*, 2006). If stabilized β-catenin is overexpressed in transgenic mice, the brain is enlarged, and the neural precursor population is expanded (Chenn & Walsh, 2002).

Strong evidence is accumulating for a role of Wnt/β-catenin signaling in adult neurogenesis, in particular the proliferation of neural stem cells. Lie *et al.* tested whether Wnt/β-catenin signaling regulates

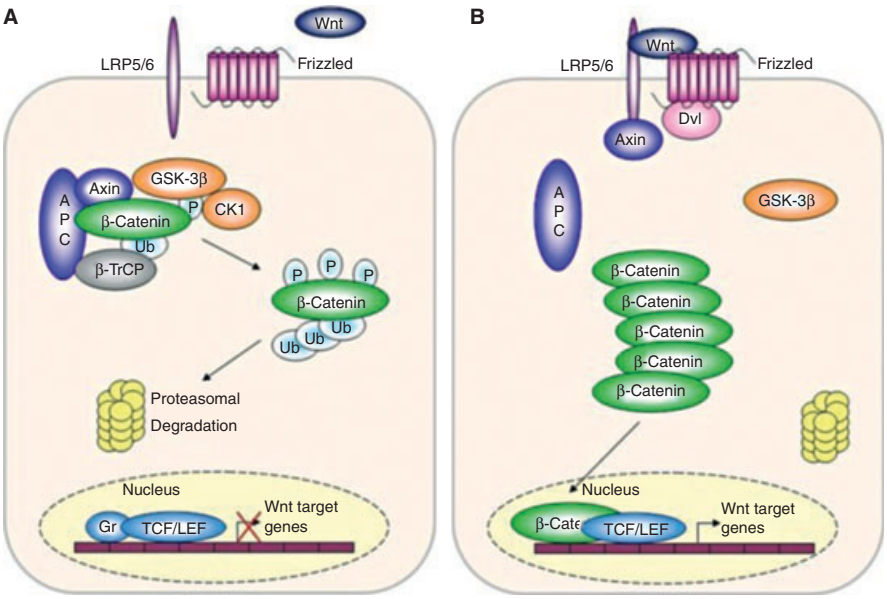

FIG. 1. The canonical Wnt signaling pathway. (A) In the absence of Wnt protein, the degradation complex, comprising Axin, adenomatous polyposis coli (APC), glycogen-synthasekinase-3β (GSK-3β) and casein kinase 1 (CK1) maintains β-catenin in a low level. GSK-3β phosphorylates β-catenin molecules. β-Transducing repeat-containing protein (β-TrCP) degrades β-catenin, and it is eventually degraded by the proteosome. Wnt target genes are inhibited through the action of the T-cell factor/lymphoid enhancer factor (TCF/LEF)–Groucho (Gr) complex by the lack of β-catenin in the nucleus. (B) In the presence of Wnt protein, Wnt binds to the seven-transmembrane-domain protein Frizzled (Fzd) and to its co-receptors, low-density lipoprotein receptor-related protein (LRP)5/6 triggers activation of the cytoplasmic scaffold protein Dishevelled (Dvl); then the activated Dvl interacts with Axin/APC/GSK-3β and leads to the inhibition of GSK-3β. Inhibition of GSK-3β results in the accumulation of stabilized β-catenin in the cytoplasm and translocation to the nucleus. In the nucleus, β-catenin interacts with the TCF/LEF and forms the transcriptional complex leading to the transcriptional activation of Wnt target genes which are involved in cell fate and/or proliferation.

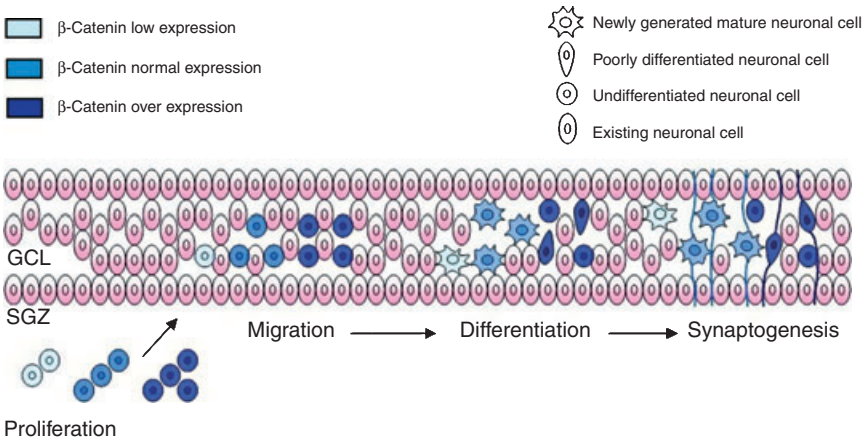

FIG. 2. Model of neurogenesis affected by β-catenin in the adult hippocampal dentate gyrus. In the subgranular zone (SGZ) of the dentate gyrus, compared with stem cells normally expressed with β-catenin (sky blue), cells overexpressed with β-catenin (deep blue) promote the proliferation of themselves. The low expression of β-catenin in stem cells (light blue) inhibits its proliferation. In the granule cell layer (GCL), the migration of light blue low-expressed β-catenin reveals deficiency. In the following events, the differentiation of deep blue cells overexpressed β-catenin is inhibited, and in the stage of syanptogenesis, light blue cell low-expressed β-catenin reveals deficiency in aspects of axonal and dendritic development.

neurogenesis *in vivo* by way of injecting a single dose of BrdU into adult BATGAL mice. It was indicated that Wnt/β-catenin pathway activity was observed in BrdU-positive cells with morphological features of proliferating neuroblasts (Lie *et al.*, 2005). By contrast, using a secreted mutant Wnt1 protein (dnWnt), which non-autonomously blocks Wnt signaling *in vivo* (Hoppler *et al.*, 1996; Garcia-Castro *et al.*, 2002), Lie *et al.* (2005) found that blockade of Wnt signaling reduces neurogenesis from adult hippocampal stem/progenitor cells (AHPs) *in vitro*, and abolishes neurogenesis almost completely *in vivo*. In addition, Qu *et al.* (2010) took cell cycle analysis to reveal that the β-catenin activation promoted neural stem cell proliferation, resulting in an increase in cell population, which further suggests that the β-catenin promotes neural stem cell proliferation and self-renewal. Furthermore, Qu *et al.* (2010) transduced the β-catenin inhibitor Axin into the SVZ of adult wild-type brains, and detected decreased numbers of GFP+BrdU+ cells compared with that in the control vector-transduced brains. These results all support the concept that the effect of Wnt/β-catenin signaling plays a role in promoting neural stem cell proliferation in adult brains.

This view has been specially demonstrated in the studies for proliferation of hippocampal progenitors. So far, the central importance of the Wnt/β-catenin signaling during development of the hippocampus has been demonstrated. In the hippocampus, Machon *et al.* (2003) observed with the D6-Cre/β-catenin$^{flox/flox}$ mutational mice and found that β-catenin-mediated Wnt signaling was central in controlling the expansion of the early progenitor pool in the developing hippocampus. Similarly, transgenic mice with the D6-driven Dkk1 gene, which encodes extracellular negative protein of Wnt/β-catenin pathway, exhibited reduced canonical Wnt signaling in the cortex and hippocampus. As a result, inhibition of the canonical Wnt signaling by the ectopic expression of Dkk1 extends the cell cycle and reduces proliferation of neurogenic progenitor cells. Therefore, all hippocampal fields were reduced in size (Solberg *et al.*, 2008). Furthermore, they indicated that although Wnt/β-catenin signaling could not be sufficiently inhibited in the adult DG of D6-Dkk1 mice, the affected progenitor pool was not able to rebuild a normal size of the DG (Solberg *et al.*, 2008). Recently, Eric *et al.* studied the participation of Wnt/β-catenin in hippocampal neurogenesis. It was found that autonomous Wnt signaling is a conserved feature of the neurogenic niche that preserves the delicate balance between neural stem cell maintenance and differentiation (Wexler *et al.*, 2009). Wexler *et al.* (2009) demonstrate that inhibition of the canonical Wnt pathways depletes multipotent progenitors from the AHP population.

Wnt/β-catenin signaling in the migration of precursor cells and the differentiation of neurons

Prenatal development of the mammalian brain involves a complex series of precisely timed events that can be divided into four phases: (i) generation of precursor cells from stem cells; (ii) migration of precursor cells to target brain regions; (iii) differentiation of new neurons into mature synaptically active cells; and (iv) pruning of new neurons by apoptosis. The discovery that these events continue into adulthood in discrete regions of the adult brain of rats (Altman & Das, 1965) and humans (Eriksson *et al.*, 1998) overthrew the dogma of a fixed neuronal complement at birth or soon after (Toro & Deakin, 2007). So, it is significant that we discuss adult neurogenesis and the aspects of migration and differentiation in mammalian brain.

It is well known that neurogenesis occurs primarily in two areas of the mammalian brain, the SGZ and the SVZ. In the DG, newly generated precursor cells in the SGZ migrate to the granular layer where they differentiate into neuronal cells of the granular layer and extend axonal projections to the CA3 area of the Ammon's horn (Markakis & Gage, 1999). Newborn cells in the anterior part of the SVZ migrate through the rostro-migratory stream to the olfactory bulb (OB), where they differentiate into interneurons, granule and periglomerular neurons (Lois & Alvarez-Buylla, 1994). Regarding the role of β-catenin in migration of precursor cells, Chenn & Walsh (2003) observed that adult transgenic mice, which expressed lower levels of β-catenin, indicated that the OBs of adult transgenic animals are not increased in size relative to those of normal mice, suggesting that the normal migratory behavior of these neurons may be impaired or misdirected. They concluded that the brains from adult transgenic mice that expressed lower levels of β-catenin in neural precursors show an apparent arrest of migration. This suggests that β-catenin has been related to its role in migration of precursor cells. Unfortunately, detailed and strong research has not been provided to demonstrate how β-catenin plays a role in migration of precursor cells in adult neurogenesis, but it is indicated that performance of further studies in this field would be beneficial.

Neuronal differentiation is controlled by both intrinsic and extrinsic regulators (Inestrosa & Arenas, 2010). Regarding intrinsic regulators, not surprisingly, the Wnt/β-catenin signaling pathway is important in regulating neural development but also appears to be involved in adult neurogenesis (Malaterre *et al.*, 2007). Apart from the Wnt ligands to regulate this process, β-catenin plays a role in neurogenesis. The activation of β-catenin leads to the proliferation of the neural progenitor pool, resulting in the expansion of the entire neural tube (Chenn & Walsh, 2002). In addition, a GSK-3β inhibitor, which phosphorylates β-catenin, was found to induce the selective differentiation of stem cells into neurons (Ding *et al.*, 2003). By contrast, treatment with an inhibitor of GSK-3β was shown to inhibit the differentiation of progenitor cells in the SVZ into neuroblasts (Adachi *et al.*, 2007). Other similar studies utilizing conditional knockout and transgenic mice with overexpressed β-catenin have shown that β-catenin plays an important role in neuronal progenitor proliferation and neural crest cell survival and differentiation (Zechner *et al.*, 2003; Lee *et al.*, 2004). Furthermore, analysis of whether precursors differentiated into neurons or remained as precursors after inhibition of β-catenin signaling has indicated that inhibition of β-catenin signaling increases the proportion of cells that exit the ventricular zone and differentiate into neurons (Woodhead *et al.*, 2006). Following those findings, it has been proposed that β-catenin may inhibit neuronal differentiation in the process of adult neurogenesis. Unfortunately, it is still unclear how the stem cells with overexpressed β-catenin are inhibited to differentiate into mature neural cells, and the exact patterning of these inhibited cells is also unknown.

Wnt/β-catenin signaling in synapse

Neurons are continuously added to the brain throughout life. These neurons develop dendritic arbors, set up functional connections with existing neurons, and integrate into neuronal circuitry. It is known that the components of Wnt signaling in early stages of neural development have been linked to their role in neurite patterning and in synaptogenesis; furthermore, the appearance of these components in the mature nervous system suggests a role of this pathway in synaptic and functional maintenance. It is noteworthy that β-catenin, as a most crucial component in this pathway, may also perform some functions in synapse.

In axonal development, β-catenin participates in axonal localization of presynaptic proteins (Bamji *et al.*, 2003) in early and late

development. Many studies show that mutant embryos for Wnt signaling components, such as β-catenin, perform defects in the precise projection of the axonal growth cone within the nerve cord (Loureiro & Peifer, 1998; Yoshikawa *et al.*, 2003; Sato *et al.*, 2006; Bhat *et al.*, 2007). *In vitro* experiments with cultures of cerebellar granule neurons show that an inhibition of GSK-3β with lithium induce axonal spreading and branching by the remodeling of axonal microtubules (Lucas & Salinas, 1997; Hall *et al.*, 2000). In dendritic development, there are studies that have shown that β-catenin is critical for dendritic morphogenesis (Yu & Malenka, 2003); in fact, increasing the levels of neuronal β-catenin improves the dendritic arborization without requiring gene transcription mediated by Wnt/β-catenin. Neuronal activity participates in dendritic arborization (Lohmann *et al.*, 2002), with the requirement of β-catenin. Gao *et al.* (2007) show that specific knockout of β-catenin in newborn neurons, without affecting β-catenin expression in neural progenitor cells, led to defects in dendritic morphology of these newborn neurons *in vivo*, and that the majority of newborn neurons that cannot extend dendrites survive < 1 month after they were born. Moreover, in mammals, depolarization induces dendritogenesis, which requires Wnt and β-catenin release (Yu & Malenka, 2003). The above results indicate that β-catenin participates in dendritic development of postnatal-born neurons, and therefore it is essential for neurogenesis in the postnatal brain.

Regarding the function of β-catenin in synaptic assembly, some studies show that the mechanism involved in presynaptic assembly is transcription independent. In cultured neurons, Wnt signaling increases the number and size of synaptic vesicle proteins without affecting presynaptic protein expression, before stabilization of β-catenin and its translocation into the nucleus (Cerpa *et al.*, 2008). *In vivo*, Wnt deficiency also affects the localization of presynaptic proteins without affecting their levels (Ahmad-Annuar *et al.*, 2006). Similarly, it was observed in conditional mutant mice for β-catenin that this protein is required for the proper localization of synaptic vesicles along the axon, but through a mechanism independent of TCF-mediated transcription (Bamji *et al.*, 2003). In addition, the presynaptic clustering of α7-nAChR induced by Wnt-7α depends on APC but is independent of β-catenin stabilization (Farias *et al.*, 2007). These findings suggest that β-catenin may not be crucial in the stage of synaptic assembly, which is transcription independent.

The Wnt/β-catenin signaling pathway in neuronal degeneration diseases

Studies on neurodegenerative diseases in humans indicate that Wnt/β-catenin signaling is altered or involved in the pathophysiology of these diseases, such as AD and Huntington's disease (HD), and is directly related to neurogenesis.

In patients with AD, active GSK-3β has been found in brains staged for AD neurofibrillary changes (Pei *et al.*, 1999). Consequently, a decrease in β-catenin levels and an increase in tau hyperphosphorylation have been revealed in AD. Also, neurodegeneration and spatial learning deficits have been observed in GSK-3β conditional transgenic mice (Lucas *et al.*, 2001; Hernandez *et al.*, 2002). Furthermore, studies show that familial AD-linked PS proteins form multiprotein complexes with the cell adhesion/Wnt signaling β-catenin protein α-catenin and GSK-3β (Toledo *et al.*, 2008).

Alzheimer's disease is characterized by the accumulation of the amyloid-β-peptide (Aβ), which is believed to induce apoptosis in newly generated neurons (He & Shen, 2009) and have a key function in the cognitive deficits observed in AD (Selkoe, 2001), and there is evidence that shows that Aβ-dependent neurotoxicity induces a loss of function of Wnt signaling components (De Ferrari *et al.*, 2003; Alvarez-Buylla & Lim, 2004; Fuentealba *et al.*, 2004). In primary cultures of hippocampal and cortical neurons exposed to Aβ neurotoxicity, an increased activation of GSK-3β, the hyperphosphorylation of tau proteins, together with the loss of the microtubule network have all been observed (Busciglio *et al.*, 1995; Takashima *et al.*, 1998). Exposure of neurons in culture to Aβ induces apoptosis and promotes tau hyperphosphorylation, through GSK-3β activity (Toledo *et al.*, 2008). In contrast, Toledo *et al.* (2008) studied the relationship between Aβ-induced neurotoxicity and lower cytoplasmatic levels of β-catenin in early years, showing that inhibition of GSK-3β by lithium protects rat neurons from Aβ-induced damage. More recently, it was found that the upregulation of β-catenin during tau hyperphosphorylation prevents the cell from going into apoptosis. Moreover, the knockdown of β-catenin produces an increase in the numbers of apoptotic cells; and also antagonizes the anti-apoptotic effects of tau (Li *et al.*, 2007). In addition, a loss of Wnt signaling through the β-catenin–TCF pathway increases neuronal vulnerability to apoptosis induced by Aβ (Zhang *et al.*, 1998), and possible defects in Wnt signaling could contribute to the pathogenesis of AD (De Ferrari & Inestrosa, 2000; Mudher & Lovestone, 2002; Caricasole *et al.*, 2003). However, β-catenin transfection led to restoration of neurogenesis (He & Shen, 2009). In AD, it has been demonstrated that neurotoxicity of Aβ in neurons is linked to increased levels of GSK-3β and loss of β-catenin, and that β-catenin is required for human restoration of injured brain.

Impaired Wnt/β-catenin signaling has also been observed in cellular models of HD (Carmichael *et al.*, 2002). β-Catenin levels and impairment of TCF-mediated transcription have been observed in HD mutation, and overexpression of β-catenin results in protection against the HD mutation (Caricasole *et al.*, 2005).

In summation, the role of β-catenin has been described in aspects of neurodegenerative disease, and a restoration of normal Wnt/β-catenin activity has also been shown to protect against neurodegeneration in cellular disease models.

Conclusions

Great progress has already been made in deciphering the characteristics of β-catenin and the network of Wnt/β-catenin signaling pathways by a number of researches. In recent years, adult neurogenesis has become one of the most rapidly growing areas in neuroscience research. It is interesting to find the relationship between the Wnt/β-catenin signaling pathway and adult neurogenesis. In the adult brain, stabilized β-catenin modulates the proliferation of neural stem cells, induces newly generated neuronal cells migration into relevant regions accurately, and then mediates them to differentiate to mature neurons and ultimately plays a role in synaptogenesis. In particular, in the process of adult neurogenesis, increased β-catenin promotes stem cells proliferation and inhibits the differentiation of new neurons, which is attractive for the research and treatment of neuronal degeneration and oncology in the CNS. Although plenty of evidence has been provided in this field, much remains to be investigated with regard to other fundamental biological functions and the interactive effects of Wnt signaling with other signaling networks in the adult brain. Further work is necessary to elucidate the exact molecular mechanisms of biological effects of Wnt/β-catenin signaling, in order to provide some basic methods toward treatments for neurodegeneration diseases and tumors in the CNS.

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Abbreviations

AD, Alzheimer's disease; AHPs, adult hippocampal stem/progenitor cells; APC, adenomatous polyposis coli; Arm, armadillo; Aβ, amyloid-β-peptide; DG, dentate gyrus; Dvl, Dishevelled; Fzd, Frizzled; GSK-3β, glycogen-synthasekinase-3β; HD, Huntington's disease; LRP5/6, low-density lipoprotein receptor-related protein 5/6; OB, olfactory bulb; SGZ, subgranular zone; SVZ, subventricular zone; TCF/LEF, T-cell factor/lymphoid enhancer factor; Wg, Wingless.

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