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Role of Wnt/β-Catenin pathway in the Pathophysiology of Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) is a progressive neurological disorder mainly affecting the elderly. AD demonstrates a gradual deterioration in cognitive functions. Alzheimer's disease is marked by the existence of intracellular flame-shaped neurofibrillary tangles (NFTs) and extracellular plaques of β-amyloid (Aβ) deposition known as amyloid plaques. Degeneration of synapses correlates to cognitive decline in patients with AD along with two hallmarks of AD. Inhibition in the Wnt signaling pathway contributes to AD pathogenesis by triggering synaptic dysfunction and neuronal degeneration. Suppression of Wnt/β-catenin signaling induced by an increase of GSK-3β activation and degradation of β-catenin. Furthermore, it was suggested that Aβ initiates the deregulation of Wnt signaling with a consequent inhibition of synapses. The binding of Wnt protein to Fzd/LRP causes inhibition of GSK3β and consequent activation of Wnt/β-catenin signalling. The activation of Wnt/β-catenin signaling prevents Aβ deposition and tau hyperphosphorylation in the brain. Therefore, restoring Wnt/β-catenin signaling could be a therapeutic opportunity to prevent the development of AD deterioration.

Keywords: Alzheimer's disease, β-amyloid (Aβ), β-catenin, Wnt signaling, synapse dysfunction.

1. Alzheimer's Disease

Alzheimer's disease (AD) is the most prevalent type of dementia, accounting for at least two-thirds of people with dementia 65 years or older. AD is a neurodegenerative disease marked by the presence of extracellular β-amyloid (Aβ) plaques and tau aggregation with intracellular flame-shaped neurofibrillary tangles (NFTs) **(Murphy and LeVine, 2010) (Figure 1)**.

AD usually presents with an obvious cognitive deficiency. Short-term memory difficulty is the most common feature of AD, but other symptoms such as deterioration in visuospatial processing, impaired expressive speech, and retrograde mental
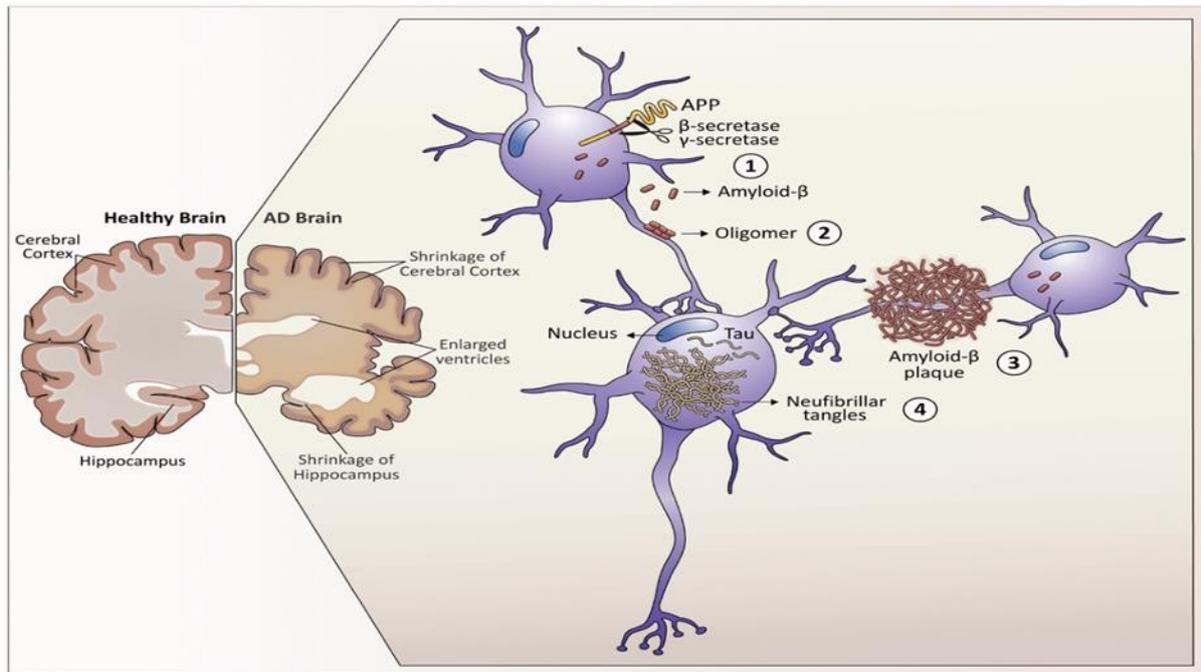
Figure 1. Pathological hallmarks of Alzheimer's disease **(Gomez et al., 2020)**. AD Brain: Alzheimer's Disease Brain; APP: Amyloid Precursor Protein.

agility are also involved **(Ferris and Farlow, 2013)**. There is no doubt that there is a complex relationship with genetics in many people with AD, but most cases of AD are not inherited dominantly.

Synapse dysfunction seems to be a further essential feature of AD. Synaptic degeneration and dysfunction are initiated by Aβ which is responsible for the negative regulation of signalling pathways that are essential for synaptic stability **(Forner et al., 2017)**. Investigation of AD patients' brains augments the hypothesis that Aβ deposition has a substantial role in synaptic failure. These are consistent with evidence suggesting that Aβ initiates deregulation of Wnt signaling with a consequent inhibition of synapses. These changes in the Wnt pathway could involve in synaptic dysfunction and degeneration, thus promoting the evolution of AD **(Palop and Mucke, 2010)**.

2. Wnt Signaling

One of the substantial signaling pathways that is closely related to AD **(De Ferrari et al., 2014)**. This pathway regulates many vital roles in the adult brain, modulating processes of synaptic plasticity and memory **(Inestrosa and Varela-Nallar, 2014)**.

Wnt proteins are a group of excreted lipoproteins that stimulate different intracellular signaling pathways by binding to numerous receptors and co-

receptors at the cell surface. The Wnt signaling may be triggered by 19 Wnt ligands **(Toledo et al., 2008)**. They could be allocated into two types: canonical or β-catenin-dependent signalling (Wnt/β-catenin) and non-canonical or β-catenin-independent signalling that could be subdivided into the planar cell polarity pathway (Wnt/PCP) and the Wnt/Ca2+ pathway. They could produce transformations in gene expression **(Wang et al., 2021) (Figure 2)**.

The Wnt signaling pathway has various contributions during the outgrowth of the nervous system that have been associated with synaptogenesis. Different Wnt signaling components are modified in AD such as β-catenin which is decreased in AD patients' brains carrying presenilin-1 (PS-1) inherited mutations and Dickkopf Wnt signaling pathway inhibitor- 1 (Dkk-1) that is enhanced in AD brains or from AD models e.g. transgenic mice **(Yang et al., 2023)**.

2.1. Antagonizing Canonical Wnt Signaling in Alzheimer's Disease

Several neurodegenerative disorders including AD are usually accompanied with synapse loss and dysfunction. Synapse vulnerability strongly associates with cognitive decline followed with neuronal death **(Colom-Cadena et al., 2020)**.
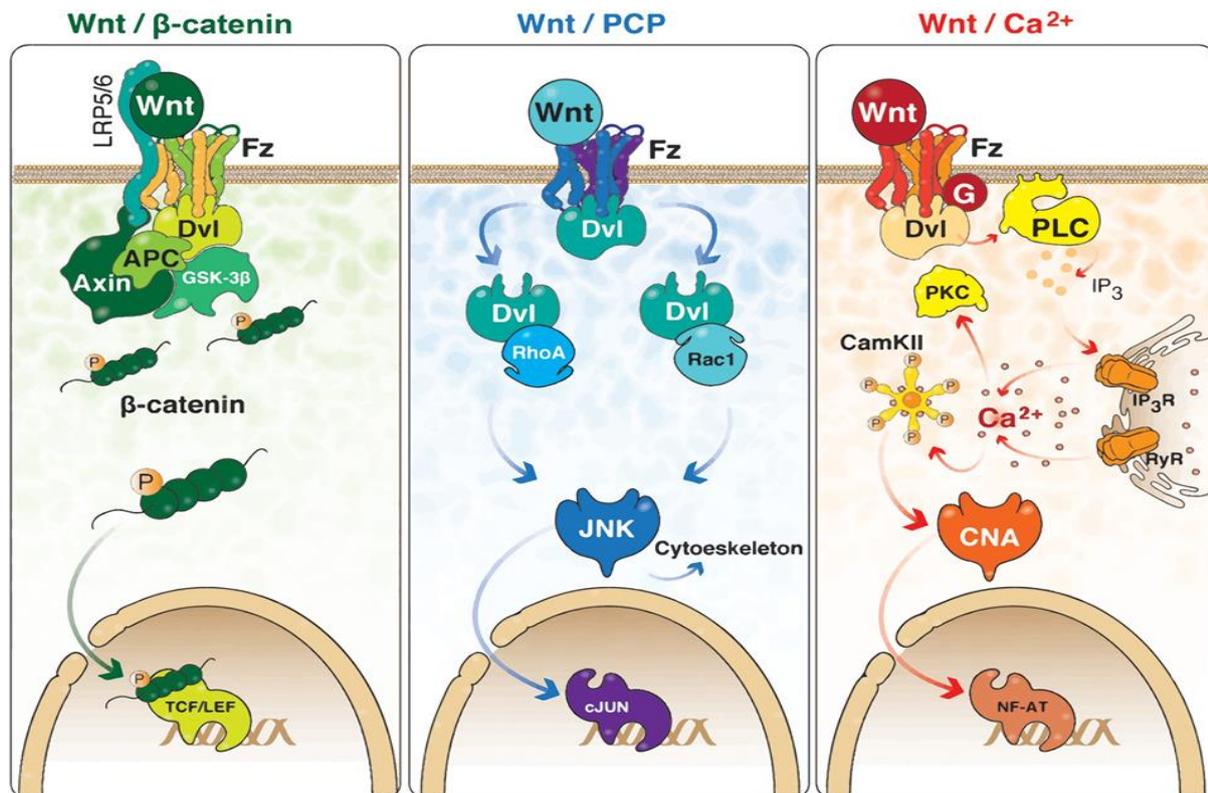
Figure 2. Types of Wnt signalling pathways (**Inestrosa and Varela-Nallar 2014**). LRP5/6: low-density lipoprotein receptor-related protein 5 and 6; Fz: Frizzled; Dvl: Dishevelled; APC: Adenomatous Polyposis Coli; GSK-3β: Glycogen Synthase Kinase-3β; TCF: T Cell-Specific Transcription Factor; LEF: Lymphoid Enhancer-Binding Factor; PCP: Planar Cell Polarity; RhoA: Ras Homolog Family Member A; Rac 1: Ras-Related C3 Botulinum Toxin Substrate 1; JNK: c-Jun N-terminal kinase; PLC: Phospholipase C; PKC: Protein Kinase C; CamkII: Calmodulin-Dependent Protein Kinase II; CNA: Calcineurin A; NF-AT: Nuclear Factor of Activated T-cells.

In a previous study, AD patients were shown to have a loss of Wnt activity, such as suggested by declined β-catenin levels and elevated tyrosine-216 phosphorylation of glycogen synthase kinase-3β (GSK-3β) compared with age-matched controls in AD brains (**Folke et al., 2019**). Therefore, Wnt signalling activity plays a key role in the development of AD.

Several evidences suggest that there is a link between Wnt signalling deficiency and AD (**Liu et al., 2014; Buechler and Salinas, 2018; Jia et al., 2019**). The Wnt antagonist Dickkopf-1 (Dkk-1) contributes to β-amyloid mediated synaptic damage, is elevated in AD. Elevated expression of Dkk-1 has been detected in post-mortem AD brain and in animal models of Aβ pathology (**Elliott et al., 2018**). Expression of Dkk-1 in the hippocampus was initiated using a transgenic mouse model. Dkk-1 was shown to initiate synapse loss, damage long-term potentiation, and generate learning and memory deficits (**Marzo et al., 2016**).

Suppression of Wnt signalling by Dkk-1 leads to

increased GSK-3β activity and reduced cytoplasmic β-catenin levels, both characteristics that were detected in the brains of AD patients. This mechanism could be prevented by combined inhibition of the GSK-3β and RhoA-Rock pathways. Reactivation of the Wnt pathway by inhibition of Dkk-1 expression completely restores synaptic plasticity, synapse number, and long-term memory (**Palomer et al., 2019**).

Increased activity of GSK-3β has been observed in the brain of AD patients. This was due to the up-regulation of Dkk-1 and the downregulation of LRP6 in the brain of AD. A significant decrease in β-catenin protein levels has been demonstrated to be inversely associated with increased activation of GSK-3β in the prefrontal cortical lobe of human AD brains (**Folke et al., 2019**) (**Figure 3**).

It was shown that the increased expression of the negative regulatory secretory protein Dkk-1 was closely related to the development of some CNS diseases, such as AD, brain ischemia, temporal lobe epilepsy. Dkk-1 could cause neuronal
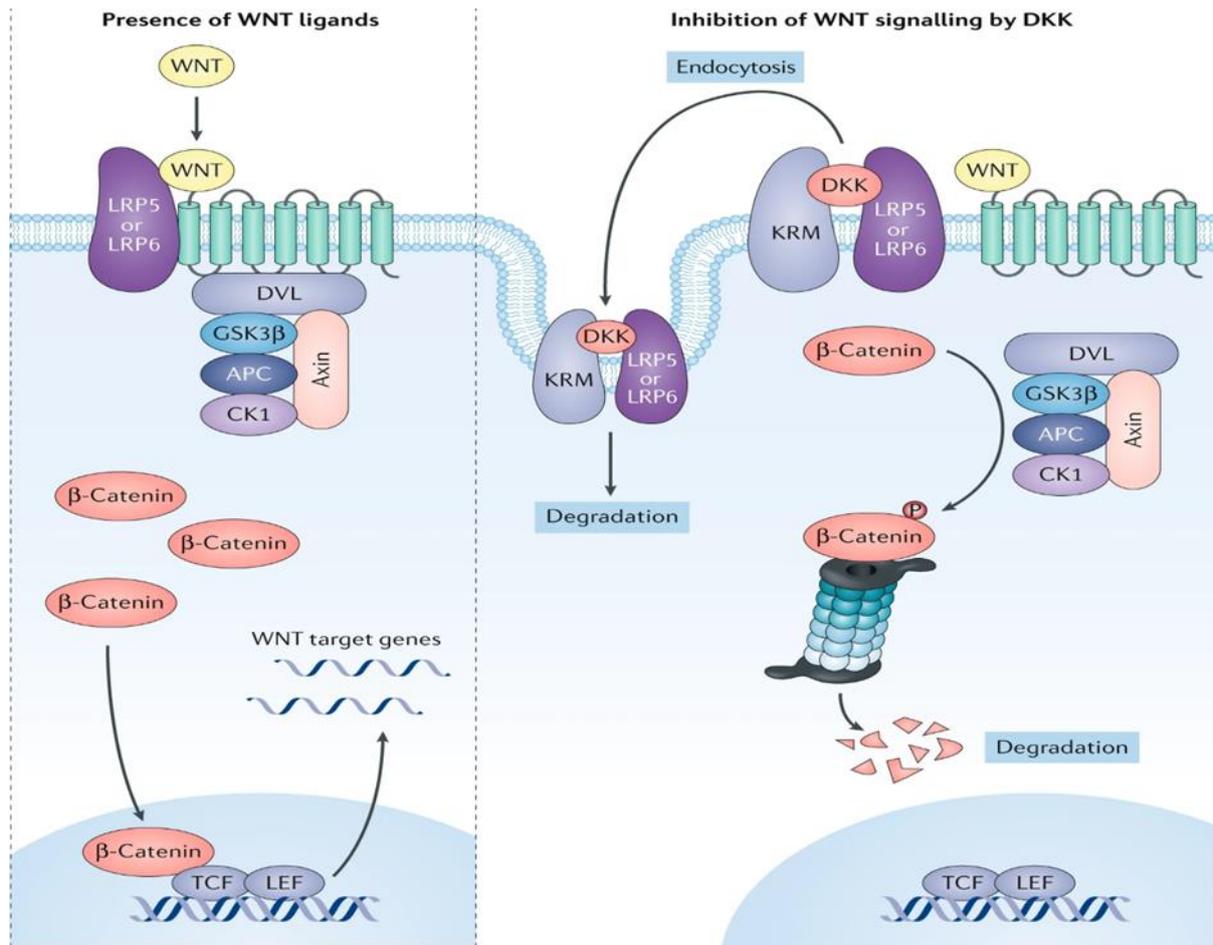
Figure 3. Canonical Wnt signalling and its inhibition by Dkk-1 proteins **(Schunk et al., 2021)**. LRP5/6: low-density lipoprotein receptor-related protein 5 and 6; Dvl: Dishevelled; APC: Adenomatous Polyposis Coli; GSK-3β: Glycogen Synthase Kinase-3β; CK1: Casein kinase 1; TCF: T Cell-Specific Transcription Factor; LEF: Lymphoid Enhancer-Binding Factor; DKK: Dickkopf; KRM: Kremen.

apoptosis in the cell and animal models of the above diseases. Thus, the expression level of Dkk-1 was reduced in a healthy human brain but increased in the brain of AD and temporal epilepsy in patients with hippocampal sclerosis **(Ren et al., 2019)**.

2.2. Wnt Signalling Promotes Amyloid β-plaques Production

Deficiency of Wnt signalling could contribute to indirect effects on synapses by activating the amyloidogenic pathway or by interfering with microglial survival **(Zheng et al., 2017)**. The Aβ peptide is generated by processing the amyloidogenic amyloid precursor protein (APP). APP protein is chopped up by β-secretase enzyme and followed by γ-secretase complex to produce 39–43 amino acids that are particularly toxic to neurons **(Chen et al., 2017)**.

It was suggested that there is a link between

deficiency in Wnt signalling and AD pathogenesis. The canonical co-receptor LRP6 modulates the processing of APP, and its depletion leads to amplified Aβ production in an AD mouse model. In vitro studies were shown that downregulation of canonical Wnt signalling or upregulation of the Wnt-PCP pathway induces the amyloidogenic processing of APP, leading to enhanced production of Aβ through a feedback loop mechanism **(Elliott et al., 2018; Tapia-Rojas and Inestrosa, 2018)**. Furthermore, other components of the Wnt pathway, including β-catenin, Tcf4, GSK-3β, and Dvl1, have been involved in modulating APP processing **(Liu et al., 2014; Tapia-Rojas and Inestrosa, 2018)**.

The amyloid plaques were promoted by an imbalance between Aβ production and clearance. Microglia has an important role in Aβ clearance through a variety of phagocytic and digestive mechanisms. One of these mechanisms, Triggering

Receptor Expressed in Myeloid Cells 2 (TREM2 an innate immune receptor and a Type I transmembrane protein) regulates phagocytosis and induces microglial survival, contributing to Aβ elimination. TREM2 promotes this survival by activating the Wnt/β-catenin signalling pathway, suggesting that this pathway is essential to the correct clearance of amyloid deposits **(Tapia-Rojas and Inestrosa, 2018)**.

Wnt signalling is essential in APP processing, as Wnt dysfunction results in Aβ production and aggregation in vitro. In vivo studies were informed that loss of canonical Wnt signalling resulted in amyloid deposition in a transgenic (Tg) mouse model of AD **(Tapia-Rojas and Inestrosa, 2018)**.

Beta (β) and γ-secretase cleave the APP to release the β-amyloid plaques (Aβ) and the APP intracellular domain (AICD). Aβ has been believed to initiate pathogenic cascades in AD while AICD was detected to interact with GSK-3β and initiate the consequent kinase activity. The subsequent AICD-strengthened Axin-GSK-3β complex potentiates down regulation of β-catenin-mediated transcription **(Zhou et al., 2012) (Figure 4)**.

Activation of Wnt/β-catenin signalling is protective against amyloid toxicity in vitro. Subsequently, the neuroprotective role of Wnt signalling against damage was produced by Aβ species, preventing tau phosphorylation and maintaining cognitive abilities in vivo using mouse models of AD **(Toledo and Inestrosa, 2010; Vargas et al., 2014; Rivera et al., 2016) (Figure 4)**.

2.3. Wnt Signalling Regulates Tau Phosphorylation

The major histopathological AD-associated changes include the deposition of extracellular amyloid plaques (Aβ) which enhances the phosphorylation of tau protein that produces intracellular filament. The misfolding, hyper-phosphorylation of tau protein, neural loss and severe destructive in cognitive were detected in AD **(Liu et al., 2014)**.

Tau phosphorylation, which is one of the hallmarks of AD, was modified by various protein kinases. These protein kinases can phosphorylate tau at different sites. GSK-3β is one of these enzymes which phosphorylates practically all tau residues
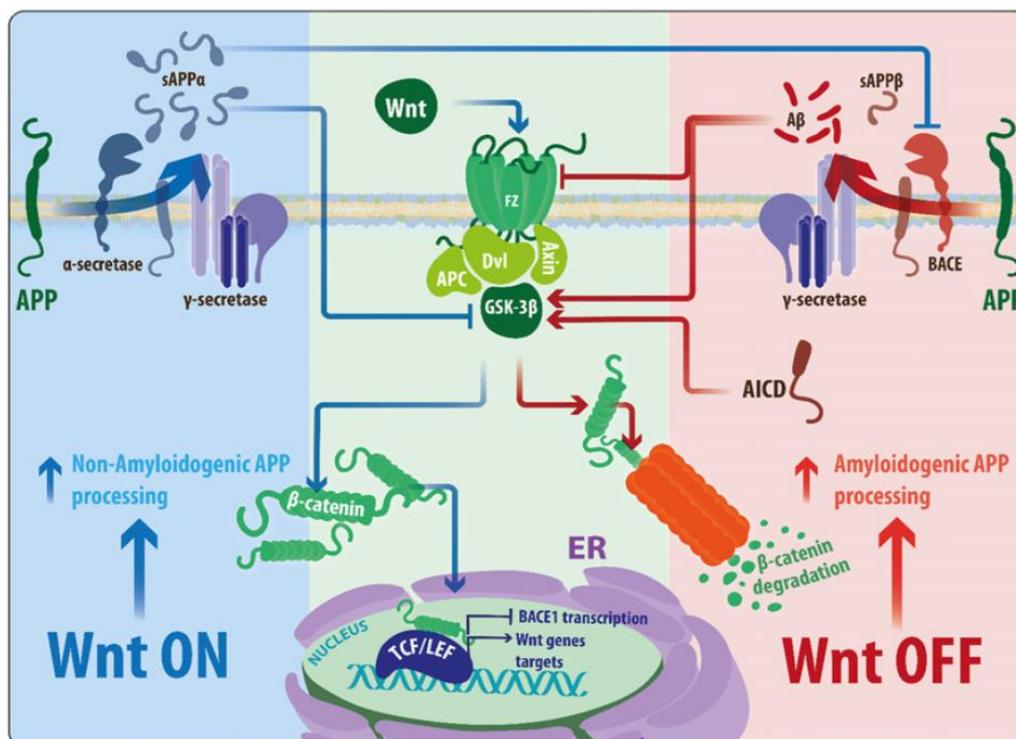
Figure 4. Effect of Wnt signalling on APP **(Tapia-Rojas et al., 2016)**. Fz: Frizzled; Dvl: Dishevelled; APC: Adenomatous Polyposis Coli; GSK-3β: Glycogen Synthase Kinase-3β; APP: Amyloid Precursor Protein; Aβ: Amyloid β; BACE: β-site Amyloid Precursor Protein Cleaving Enzyme; AICD: Amyloid Precursor Protein intracellular domain; TCF: T Cell-Specific Transcription Factor; LEF: Lymphoid Enhancer-Binding Factor; ER: Endoplasmic Reticulum.

detected in AD. Phosphorylated tau was shown in the pre-tangle of the neurons in the initial stage of neurodegenerative diseases (**Figure 5**). GSK-3β is considered as a central component of Wnt signalling and its activity is triggered by the function of the Wnt/β-catenin pathway. Inhibition of GSK-3β impedes the formation of NFTs (**Jembrek et al., 2013**).

GSK-3β activity is correlated with Wnt/β-catenin signalling in AD brain. Overactivation of GSK-3β is responsible for modulating of tau hyperphosphorylation, β-amyloid deposition, and Aβ-associated microglial-mediated inflammatory responses that ends up with memory impairment (**Lauretti et al., 2020**).

Inhibition of Wnt signalling could enhance GSK-3β activity with consequent tau hyperphosphorylation, which is a key pathological hallmark of AD. GSK-3β overexpression leads to learning deficiency with neurodegeneration. Wnt signalling could be inhibited by Aβ-mediated increase in Dkk-1 expression that promotes the aggravation of AD pathology (**Salcedo-Tello et al., 2014**).

2.4. Alzheimer's Disease Associated Genes Are Linked to Reduced Wnt Signalling

Several AD vulnerability genes (including *APOE*, *TREM2*, and *Clusterin*) are linked to abnormal Wnt signalling. ApoE4, a main genetic risk factor for late-onset AD (LOAD), inhibits canonical Wnt signalling in cell lines. Another study showed that TREM2, which is linked to LOAD, promotes microglia proliferation through Wnt signalling (**Zheng et al., 2017**).

Clusterin, is also involved in Aβ-driven Dkk-1 expression with help of soluble Aβ which promotes the intracellular accumulation of Clusterin and subsequent Dkk-1 upregulation. While inhibition of Clusterin prevents induction of Dkk-1 expression and protects against Aβ neurotoxicity (**Killick et al., 2014**).

Wnt signalling induces the expression of RE1-Silencing Transcription factor (REST) normally during aging. REST has a vital role in blocking the apoptotic genes and protection against oxidative stress and Aβ neurotoxicity. While abolished Wnt signalling could participate in reduction of REST levels observed in AD which resulted in increased susceptibility to Aβ toxicity (**Lu et al., 2014**).

Wnt signalling was detected to be impaired in different AD mouse models (**Scali et al., 2006; Toledo and Inestrosa, 2010**). More important, familial Alzheimer's disease (FAD) patients with PS1 mutations have reduced β-catenin levels, greatly indicating Wnt signalling loss. More important, an allele of low-density lipoprotein receptor-related protein-6 (LRP6) combined with a loss of function of Wnt signalling is a susceptibility gene for LOAD (**De Ferrari et al., 2007**).

3. Wnt Signalling Pathway Activation as Therapeutic Opportunities for Alzheimer's Disease

Activation of Wnt signalling improves spatial memory loss, diminishes the activation of inflammatory processes, and reduces the levels of Aβ species and tau phosphorylation in the hippocampus of a natural model of AD (**Tapia-Rojas et al., 2015**).
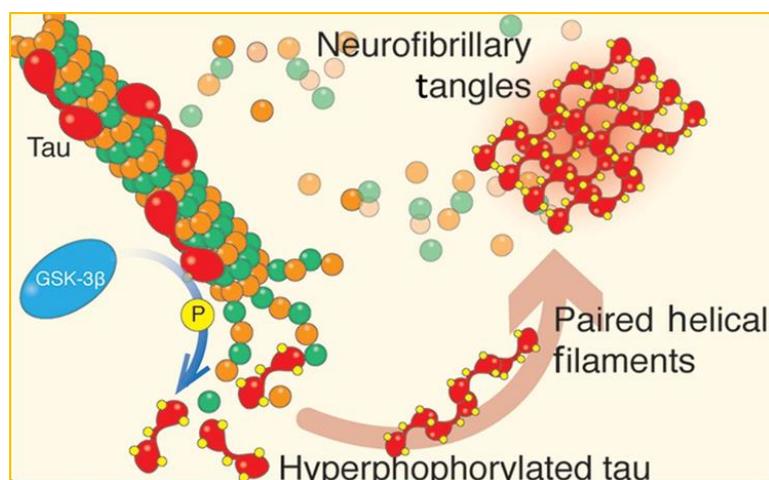
Figure 5. Neurofibrillary tangles formation with GSK-3β (**Inestrosa and Varela-Nallar, 2014**). GSK-3β: Glycogen Synthase Kinase-3β.

The binding of Wnt protein to Fzd/LRP causes inhibition of GSK-3β and consequent activation of Wnt/β-catenin signalling. GSK-3β is one of two major kinases responsible for β-catenin phosphorylation, so, activation of GSK-3β provokes β-catenin phosphorylation and degradation (**Liu et al., 2002; Nusse and Clevers, 2017**) (**Figure 6**).

In vivo, treatment with the GSK-3β inhibitor activated Wnt signalling in the hippocampus with the increase in β-catenin level and inhibition of GSK-3β. This resulted in a reduction in spatial memory impairment and, a decrease in Aβ aggregates and oligomers (**Toledo and Inestrosa, 2010**). The activation of this pathway may be a therapeutic strategy for the treatment of AD.

4. Conclusion

Wnt signalling was deregulated in aging brains and in AD, which could contribute to synapse degeneration and cognitive decline. The deficiency in Wnt signalling can further exacerbate key pathological processes, including Aβ production and tau hyperphosphorylation. The Wnt antagonist Dkk-1 induces AD-related synaptic loss and cognitive impairment. The Wnt signalling pathway contributes to neuronal survival and is closely related to central nervous system (CNS) homeostasis. Activation of the Wnt/β-catenin pathway has a positive significance in the treatment of AD.
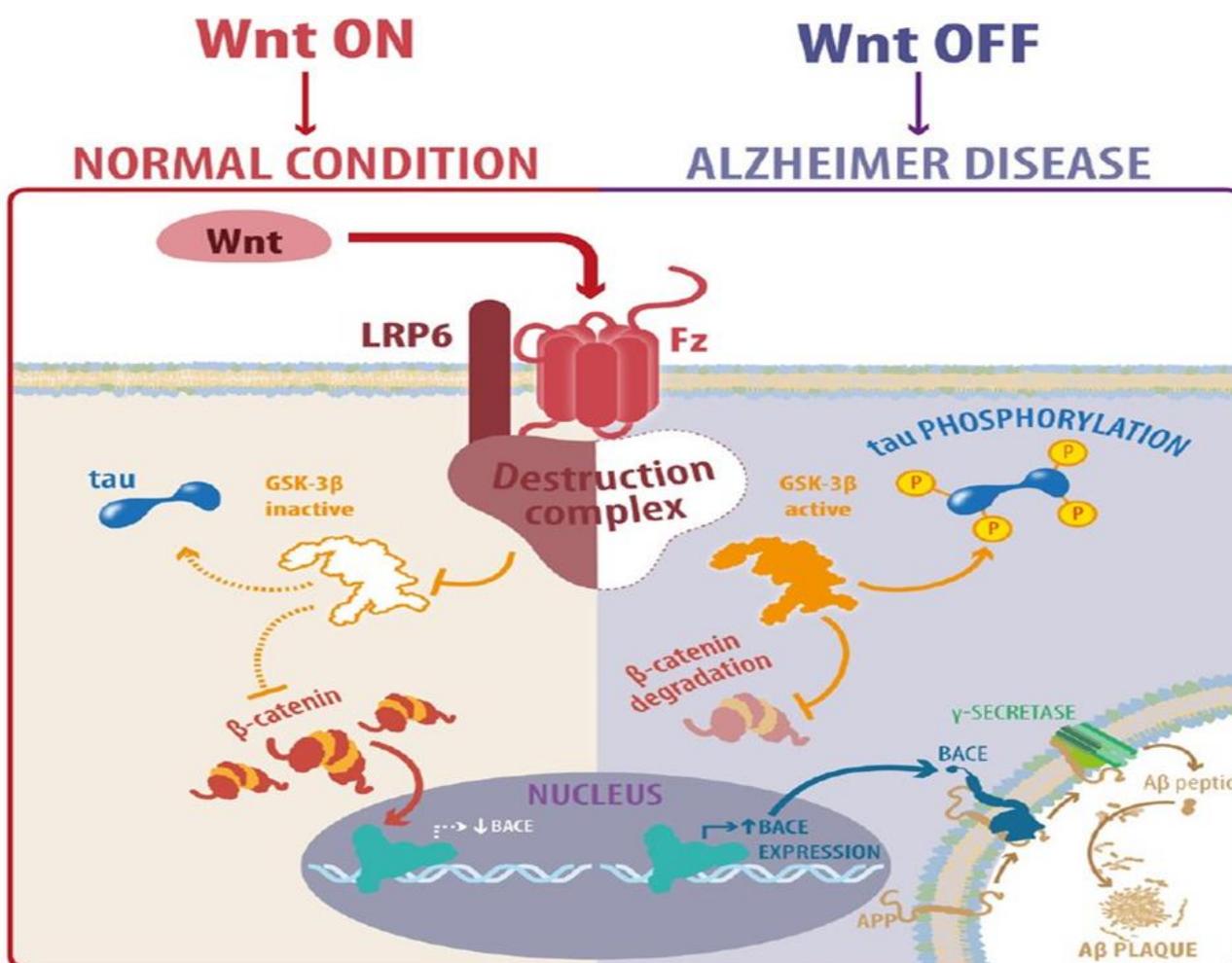
Figure 6. Wnt/β-catenin signalling activity in pathogenesis of Alzheimer's disease (**Tapia-Rojas and Inestrosa, 2018**). LRP6: low-density lipoprotein receptor-related protein 6; Fz: Frizzled; GSK-3β: Glycogen Synthase Kinase-3β; APP: Amyloid Precursor Protein; Aβ: Amyloid β; BACE: β-site Amyloid Precursor Protein Cleaving Enzyme.

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