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Review

Targeting Wnt signaling in Alzheimer's disease: mechanisms and therapeutic opportunities

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ABSTRACT

This review examines the roles and mechanisms of Wnt signaling in Alzheimer's disease (AD). AD is pathologically defined by extracellular amyloid-β (Aβ) plaque deposition and neurofibrillary tangles composed of hyperphosphorylated tau, accompanied by synaptic loss, neuroinflammation, blood–brain barrier (BBB) dysfunction, and progressive brain atrophy. Growing evidence identifies Wnt signaling as a central regulatory system that maintains neuronal survival, synaptic plasticity, and neurovascular unit homeostasis. Disruption of Wnt signaling intersects with and amplifies AD pathology at multiple levels. Attenuated Wnt activity can derepress amyloidogenic pathways, including BACE1 expression, and compromise cellular environments that support Aβ clearance. Aberrant activation of glycogen synthase kinase-3β (GSK-3β) promotes tau hyperphosphorylation, while altered Wnt-dependent synaptic protein homeostasis and excitatory–inhibitory balance destabilize neuronal networks. In parallel, Wnt signaling modulates microglial and astrocytic inflammatory state transitions and contributes to BBB integrity and repair. Key regulators—including LRP5/6, LRP1, the Dickkopf (DKK) family (particularly DKK1 and the atypical DKK3), sFRP1, Kremen, Notum, and R-spondins—collectively shape Wnt signal strength, receptor availability, and antagonistic tone, forming a pathogenic network characterized by receptor gating, antagonist amplification, and clearance cross-talk. We summarize three major Wnt-oriented therapeutic strategies: enhancing canonical Wnt/β-catenin signaling, reducing antagonistic pressure on Wnt receptors, and modulating LRP family functions to coordinate synaptic protection, BBB repair, and Aβ clearance. Overall, Wnt signaling represents a promising disease-modifying axis centered on synaptic and network resilience; however, successful clinical translation will require refined understanding of cell-type specificity, disease-stage dependence, context-dependent effects of regulators such as DKK3, and the development of robust pharmacodynamic biomarkers.

KEYWORDS

Wnt pathway, Alzheimer's disease, Dickkopf (DKK), lipoprotein receptor-related protein (LRP)

1 Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder defined by the accumulation of two hallmark proteinopathies—extracellular amyloid-β (Aβ) plaques and intracellular neurofibrillary tangles composed of hyperphosphorylated tau—together with widespread synaptic loss and neuronal degeneration. Aβ is generated by sequential cleavage of amyloid precursor protein (APP) through the amyloidogenic pathway and readily aggregates into insoluble plaques, often surrounded by dystrophic neurites [1]. In addition to parenchymal deposition, Aβ accumulates within cerebral vessel walls, contributing to cerebrovascular dysfunction and increasing the risk of microhemorrhage [2]. According to the amyloid cascade hypothesis, Aβ accumulation represents an early pathogenic event that initiates downstream tau pathology and neurodegeneration [3]. Tau pathology constitutes the second core lesion in AD. Under physiological conditions, tau stabilizes neuronal microtubules; however, excessive phosphorylation causes tau to detach, aggregate into paired helical filaments, and form neurofibrillary tangles [4]. This process disrupts axonal transport [5], impairs synaptic integrity, and ultimately leads to neuronal death [6]. The regional distribution of tau pathology closely correlates with cognitive decline, progressing in a stereotypical pattern from the entorhinal cortex to limbic and neocortical regions (Braak staging) [7]. These proteinopathies converge on synaptic dysfunction, neuronal loss, and progressive brain atrophy, accompanied by chronic neuroinflammation driven by activated microglia and astrocytes. While initially protective, sustained glial activation exacerbates neuronal injury through persistent cytokine

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release [8]. Degeneration of cholinergic neurons in the basal forebrain further contributes to memory and learning deficits, underscoring the multifactorial nature of AD pathogenesis [9].

Recent evidence positions the Wnt signaling pathway as a central regulator of brain homeostasis and a critical modulator of AD pathology. Wnt signaling supports neuronal survival, synaptic structure, and plasticity, while restraining neuroinflammatory responses. Importantly, it directly influences APP processing, favoring non-amyloidogenic pathways, and promotes Aβ clearance through both microglial phagocytosis and blood–brain barrier (BBB) transport, processes that critically involve low-density lipoprotein receptor-related protein (LRP) family members, including LRP5/6 as Wnt co-receptors and LRP1 as a major mediator of Aβ clearance and BBB efflux [10].

Disruption of canonical Wnt/β-catenin signaling is increasingly recognized as a pathogenic driver rather than a secondary consequence of AD. Wnt inactivation leads to synaptic destabilization and impaired memory formation, derepresses amyloidogenic APP processing, and results in hyperactivation of GSK-3β, a key kinase responsible for tau hyperphosphorylation [11]. These pathological effects are strongly shaped at the receptor level by altered LRP receptor availability and signaling competence, as well as by increased activity of extracellular Wnt antagonists such as members of the DKK family, which fine-tune Wnt–LRP interactions and downstream signal strength [12]. In parallel, Wnt dysfunction compromises BBB integrity and biases microglia and astrocytes toward pro-inflammatory states, establishing a feed-forward loop that amplifies Aβ accumulation, tau pathology, and neuroinflammation [13]. Thus, decline in Wnt signaling reflects dysregulation of a receptor-centered network involving LRP receptors and their antagonists, representing a convergent mechanistic node linking the major pathological axes of AD and highlighting the Wnt pathway—and its regulation by DKK–LRP interactions—as a promising target for disease-modifying intervention.

2 Overview of the Wnt signaling pathway

2.1 Canonical Wnt/β-catenin pathway

The canonical Wnt/β-catenin pathway is the most extensively characterized branch of Wnt signaling and has the most clearly defined mechanistic relevance to AD pathology. Its central function is to regulate the stability, cytoplasmic accumulation, and nuclear translocation of β-catenin, thereby controlling context-dependent transcriptional programs [14]. In the absence of Wnt ligands, cytoplasmic β-catenin is constitutively targeted for degradation by the "destruction complex", composed of Axin, adenomatous polyposis coli (APC), casein kinase 1 (CK1), and GSK-3β. Within this complex, CK1 and GSK-3β sequentially phosphorylate β-catenin, leading to its ubiquitination and proteasomal degradation. Upon Wnt ligand binding to Frizzled (FZD) receptors and the co-receptors LRP5/6, LRP5/6 becomes phosphorylated and functions as a scaffold to recruit Dishevelled (DVL) and Axin to the membrane receptor complex. This process disrupts the destruction complex and suppresses GSK-3β activity, thereby preventing β-catenin degradation. Stabilized β-catenin subsequently accumulates in the cytoplasm and translocates into the nucleus, where it acts as a transcriptional co-activator by associating with T-cell factor/lymphoid enhancer factor (TCF/LEF) family members to drive gene expression programs involved in cell survival, differentiation, synaptic function, and metabolic regulation

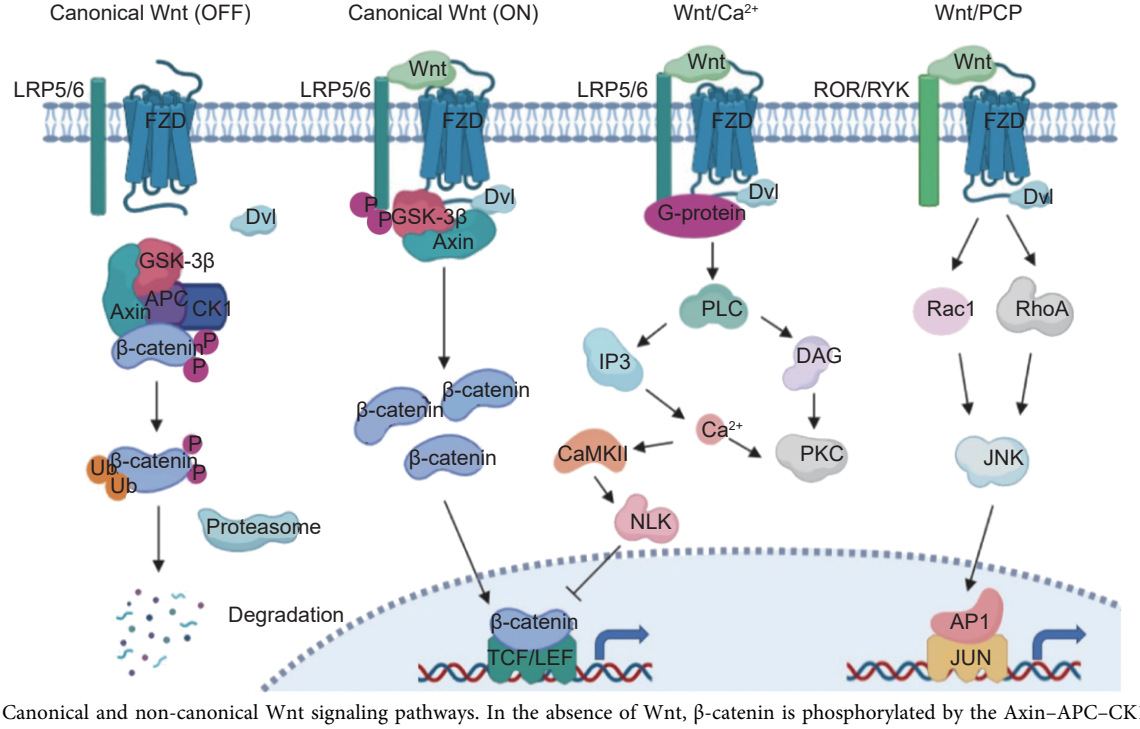

Figure 1 Canonical and non-canonical Wnt signaling pathways. In the absence of Wnt, β-catenin is phosphorylated by the Axin–APC–CK1–GSK-3β complex and degraded. Wnt binding to FZD and LRP5/6 stabilizes β-catenin, enabling its nuclear translocation and TCF/LEF-mediated transcription. Non-canonical pathways include Wnt/Ca^{2+} signaling via PLC–Ca^{2+}–CaMKII/PKC and Wnt/PCP signaling via ROR/RYK, Rac1/RhoA, and JNK, regulating cytoskeletal dynamics and gene expression.

(Fig. 1).

2.2 Non-canonical Wnt pathway

Non-canonical Wnt signaling operates independently of β-catenin–mediated transcription and primarily regulates cell polarity, cytoskeletal dynamics, and directional migration. In the nervous system, these pathways play important roles in synaptic regulation, neuroinflammatory responses, and glial function. The two principal non-canonical branches are the Wnt/Ca^{2+} pathway and the planar cell polarity (Wnt/PCP) pathway. The Wnt/Ca^{2+} pathway modulates gene expression and cellular behavior by regulating intracellular calcium dynamics and is essential for embryonic neural development, cell polarity, and glial differentiation [15]. Following Wnt binding to FZD receptors, downstream activation of heterotrimeric G proteins and phospholipase C (PLC) leads to the production of inositol trisphosphate (IP_3) and diacylglycerol (DAG), triggering the release of Ca^{2+} from intracellular stores. Elevated intracellular Ca^{2+} levels activate calcium-dependent effectors such as calmodulin-dependent kinase II (CaMKII) and protein kinase C (PKC), thereby influencing cell adhesion, transcriptional responses, and inflammatory signaling [16] (Fig. 1). The Wnt/PCP pathway primarily governs cell polarity and tissue organization and also contributes to neuronal migration and synaptic architecture. Signaling through FZD receptors and co-receptors such as receptor tyrosine kinase–like orphan receptors (RORs) and RYK activates downstream Rho family small GTPases (including RhoA and Rac1) and c-Jun N-terminal kinase (JNK) (Fig. 1). These effectors regulate actin cytoskeletal remodeling, cell adhesion, and directional signaling processes critical for neural circuit formation and maintenance [17].

Together, the canonical and non-canonical branches of Wnt signaling constitute a highly versatile regulatory network whose dysregulation can have broad consequences for neuronal, glial, and vascular functions relevant to AD.

3 Wnt pathway in AD pathogenesis

AD is characterized by several interrelated pathological hallmarks, including extracellular Aβ accumulation, intracellular tau hyperphosphorylation, progressive synaptic dysfunction, and chronic neuroinflammation. These processes do not occur in isolation but instead form a tightly interconnected pathological network driving cognitive decline. Accumulating evidence indicates that Wnt signaling intersects with each of these core features at multiple mechanistic levels. In this section, we systematically discuss how dysregulation of Wnt signaling contributes to Aβ pathology, tau phosphorylation, synaptic failure, and neuroinflammatory responses, highlighting Wnt signaling as a unifying regulatory axis in AD pathogenesis.

3.1 Wnt signaling and Aβ pathology

Under physiological conditions, intact Wnt/β-catenin signaling suppresses amyloidogenic Aβ production. Activation of the Wnt/β-catenin pathway has been shown to repress transcription of β-site APP–cleaving enzyme 1 (BACE1), the rate-limiting protease responsible for amyloidogenic APP processing. Mechanistically, β-catenin–TCF4 complexes can bind regulatory elements within the BACE1 gene, thereby restraining its expression. When Wnt signaling is attenuated—such as in the presence of elevated levels of the antagonist DKK1—this transcriptional repression is relieved, resulting in increased BACE1 expression and enhanced Aβ generation [18] (Fig. 2).

In addition to limiting Aβ production, Wnt signaling positively regulates Aβ clearance. The Wnt/β-catenin pathway is essential for maintaining BBB integrity and endothelial repair capacity, both of which are critical for Aβ efflux from the brain. Using the optogenetic tool OptoLRP6 to selectively activate upstream LRP6 and canonical Wnt signaling, it has

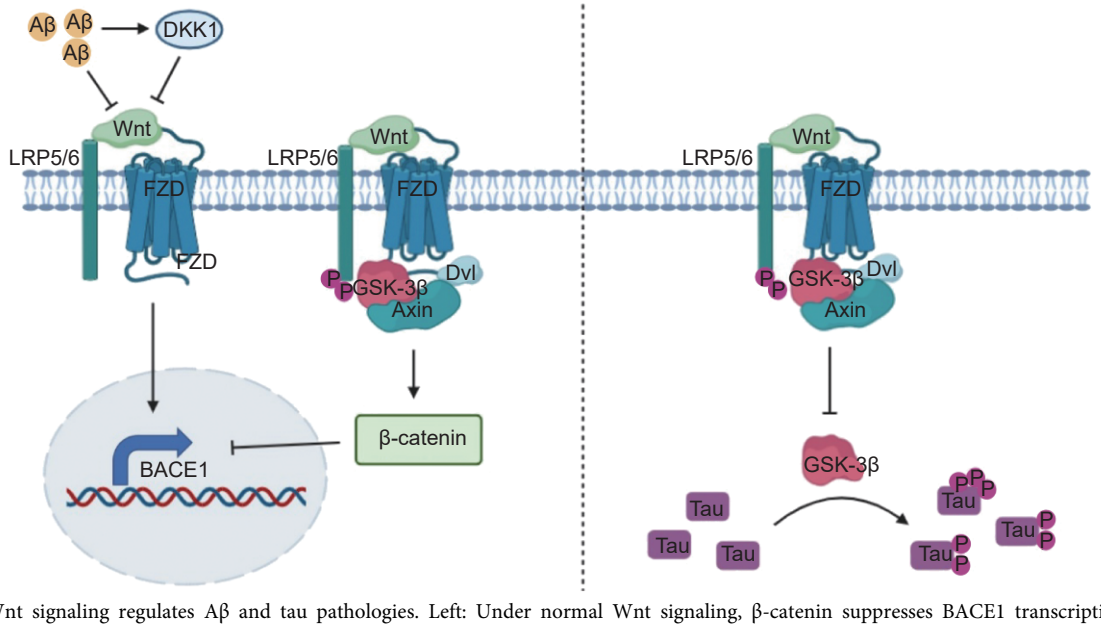

Figure 2 Wnt signaling regulates Aβ and tau pathologies. Left: Under normal Wnt signaling, β-catenin suppresses BACE1 transcription, limiting amyloidogenic Aβ production. Aβ and DKK1 inhibit Wnt signaling, relieving BACE1 repression. Middle: Canonical Wnt activation stabilizes β-catenin via LRP5/6–FZD receptor complexes, inhibiting GSK-3β and maintaining neurovascular and neuronal homeostasis. Right: Wnt inhibition allows GSK-3β activation, promoting tau hyperphosphorylation and contributing to AD pathology.

been demonstrated that Aβ-induced endothelial damage can be attenuated and BBB repair significantly enhanced, highlighting a direct role for Wnt signaling in preserving neurovascular function and facilitating Aβ clearance [19]. Supporting this, our recent work revealed that DKK1 and DKK3 form a functional complex with LRP1, a key endocytic receptor mediating Aβ clearance, and that disruption of DKK-LRP1 interactions impairs Aβ uptake by endothelial cells and astrocytes [20]. This identifies DKK-LRP1 as a previously unrecognized Wnt-linked mechanism that facilitates Aβ removal and preserves neurovascular homeostasis.

Conversely, Aβ can directly and indirectly inhibit Wnt signaling, establishing a pathogenic positive feedback loop. Aβ has been reported to bind the cysteine-rich domain of FZD receptors, interfering with Wnt ligand engagement and suppressing canonical Wnt/β-catenin signaling at the receptor level [21]. In parallel, soluble Aβ oligomers induce the expression of the secreted Wnt antagonist DKK1, which further inhibits canonical signaling by disrupting the LRP-associated receptor complex [22]. Together, these mechanisms amplify Wnt signaling suppression, promoting sustained Aβ accumulation and disease progression.

3.2 Wnt pathway and tau phosphorylation

Aberrant tau hyperphosphorylation and the formation of neurofibrillary tangles represent a second core pathological hallmark of AD. The Wnt/β-catenin pathway plays a pivotal role in this process through its regulation of GSK-3β [23]. GSK-3β is a central component of the β-catenin destruction complex and one of the principal kinases responsible for pathological tau phosphorylation. Activation of canonical Wnt signaling suppresses GSK-3β activity, thereby exerting dual neuroprotective effects. On one hand, inhibition of GSK-3β stabilizes β-catenin and supports transcriptional programs essential for neuronal survival and synaptic maintenance. On the other hand, reduced GSK-3β activity limits excessive tau phosphorylation, mitigating the formation of neurofibrillary tangles (Fig. 2). In the AD brain, attenuation of Wnt signaling removes this inhibitory constraint on GSK-3β, leading to simultaneous β-catenin degradation and unchecked tau phosphorylation [24]. This convergence positions Wnt pathway dysfunction as a central mechanistic link between amyloid pathology and tau-driven neurodegeneration.

3.3 Wnt pathway and synaptic plasticity

Synapses are key structures for information transmission and storage between neurons, with their functional plasticity and structural stability forming the biological basis of learning and memory. In AD, early synaptic loss represents the most direct pathological change associated with cognitive impairment. Extensive research indicates that the Wnt signaling pathway, particularly the canonical Wnt/β-catenin pathway, serves as a core signaling network regulating synaptic formation, maturation, maintenance, and plasticity. Electrophysiological recordings in rat hippocampal slices demonstrate that blocking Wnt signaling impairs long-term potentiation (LTP), highlighting the pathway's critical role in synaptic plasticity [25]. Furthermore, activation of Wnt signaling has been demonstrated to protect against Aβ-induced synaptic damage. Activation of Wnt signaling also rescues memory loss and improves synaptic dysfunction in APP/PS1 transgenic mice that mimic the amyloid pathology of Alzheimer's disease [26].

Wnt signaling directly regulates the expression and localization of synapse-associated proteins, playing a crucial role in the morphogenesis of postsynaptic dendritic spines and the release of neurotransmitters from presynaptic terminals. The Wnt5a ligand enhances synaptic transmission by promoting postsynaptic protein clustering and stimulating dendritic spine morphogenesis. Postsynaptic scaffold proteins, such as PSD-95—the primary scaffold protein in excitatory postsynaptic dense areas—are crucial for recruiting glutamate receptors (e.g., NMDA receptors, AMPA receptors) to the postsynaptic membrane, directly determining synaptic strength [27]. Wnt5a signaling upregulates PSD-95 expression while reducing spine density, miniature excitatory postsynaptic currents (mEPSCs), and field excitatory postsynaptic potential (fEPSP) amplitude [28]. Wnt7a ligand enhances synaptic transmission by increasing the probability of neurotransmitter release at synapses in the cerebellum and hippocampus [29]. Presynaptic proteins such as synapsin I participate in regulating synaptic vesicle recycling and neurotransmitter release. Wnt7a modulates the aggregation of the synaptic vesicle protein synapsin I [30]. In cultured hippocampal neurons and slices, neuronal activity coupled with NMDAR-mediated calcium-dependent signaling pathways enhances Wnt2 expression, while Wnt2 expression promotes dendritic branching. This indicates that Wnt2 participates in the dynamic remodeling of dendritic architecture induced by neuronal activity [31]. When the Wnt signaling pathway functions normally, it continuously provides essential "nutritional" support to synapses, maintaining the homeostasis of synaptic proteins and thereby ensuring the stability and plasticity of neural network connections.

Wnt proteins are critical regulators of neural circuit assembly, maintenance, and plasticity in the central nervous system. Studies by Salinas PC in African clawed frogs and mice showed that Wnt proteins secreted by motor neurons (e.g., Wnt3a) orchestrate the assembly of presynaptic components. In the hippocampus and cerebellum, Wnt signaling (e.g., Wnt7a) promotes the recruitment of synaptic vesicles and active zone proteins. For example, Wnt7a increases levels of synaptic protein I by engaging the receptor FZD-5 and the scaffolding protein DVL, thereby facilitating presynaptic differentiation [32]. Concurrently, Wnt7a induces clustering of PSD-95 and glutamate receptors, shaping the postsynaptic density and highlighting the role of Wnt-mediated presynaptic–postsynaptic intercellular signaling. Beyond development, Wnt signaling is essential for the functional regulation of mature synapses. Wnt5a promotes dendritic spine growth via noncanonical pathways, while Wnt7a/7b expression is upregulated during LTP, engaging the canonical β-catenin pathway to regulate genes necessary for sustained synaptic enhancement. Consistently, blocking Wnt signaling impairs LTP, whereas exogenous Wnt application potentiates it [33].

3.4 Wnt pathway and neuroinflammation

Microglia- and astrocyte-mediated neuroinflammation is a

key driver of AD pathology. A bidirectional, complex dialogue exists between Wnt signaling and neuroinflammation. In neurons and glial cells, moderate Wnt/β-catenin signaling exerts anti-inflammatory effects. Wnt3a suppresses the production of pro-inflammatory cytokines in microglia and enhances the expression of anti-inflammatory factors [34]. This shift toward an anti-inflammatory state helps reduce neuroinflammation and protect neurons. Mechanistically, inhibition of GSK-3β enhances canonical Wnt/β-catenin signaling and reduces pro-inflammatory outputs, leading to decreased expression of cytokines such as IL-6, IL-12, and TNF-α [35]. In addition, Wnt signaling can suppress NF-κB activation, thereby alleviating the neuroinflammatory milieu [36] (Fig. 3). Wnt3a and Wnt5a individually induce upregulation of cyclooxygenase-2 (COX-2), a universal proinflammatory microglial marker, but LPS's proinflammatory effect far exceeds theirs. However, combined administration of LPS and Wnts resulted in a dose-dependent decrease in LPS-induced COX-2 protein and mRNA expression. This indicates that Wnts exert dual and context-dependent effects on microglia, exhibiting both pro-inflammatory and anti-inflammatory homeostatic actions [37]. It should be noted that the classical M1/M2 paradigm represents a simplified functional framework for describing microglial activation and does not fully capture the dynamic and heterogeneous nature of microglial states observed during AD progression [38]. More recent single-cell and spatial transcriptomic studies have revealed that microglial responses to neurodegeneration occur along a continuous spectrum of activation states rather than as discrete phenotypes. Among these, disease-associated microglia (DAM) have been described as transcriptional programs that emerge in close association with amyloid burden and disease stage, reflecting coordinated changes in inflammatory signaling, lipid metabolism, phagocytic capacity, and cell survival pathways [39]. Within this context, Wnt signaling is increasingly recognized not as a background pathway confined to neuronal or synaptic regulation, but as a modulatory axis that intersects with key microglial state-defining pathways [40]. By influencing microglial survival, metabolic adaptation, and inflammatory tone, Wnt-related signaling may contribute to the regulation or functional bias of DAM-like states under chronic pathological conditions, although the precise directionality and context dependence of these interactions remain to be fully elucidated [41].

Wnt signaling also influences the production of inflammatory mediators by astrocytes, thereby regulating the inflammatory environment within the central nervous system. Pathological stimuli (e.g., Aβ) induce astrocytes to overexpress non-canonical Wnt ligands (e.g., Wnt5a), activating Wnt/Ca^{2+} or Wnt/JNK pathways. This drives astrocytes toward a pro-inflammatory phenotype, leading to massive release of inflammatory mediators such as IL-1β and TNF-α, thereby exacerbating neuroinflammation and injury. Following injury, a protective astrocyte subpopulation is activated, shifting to high secretion of canonical Wnt ligands

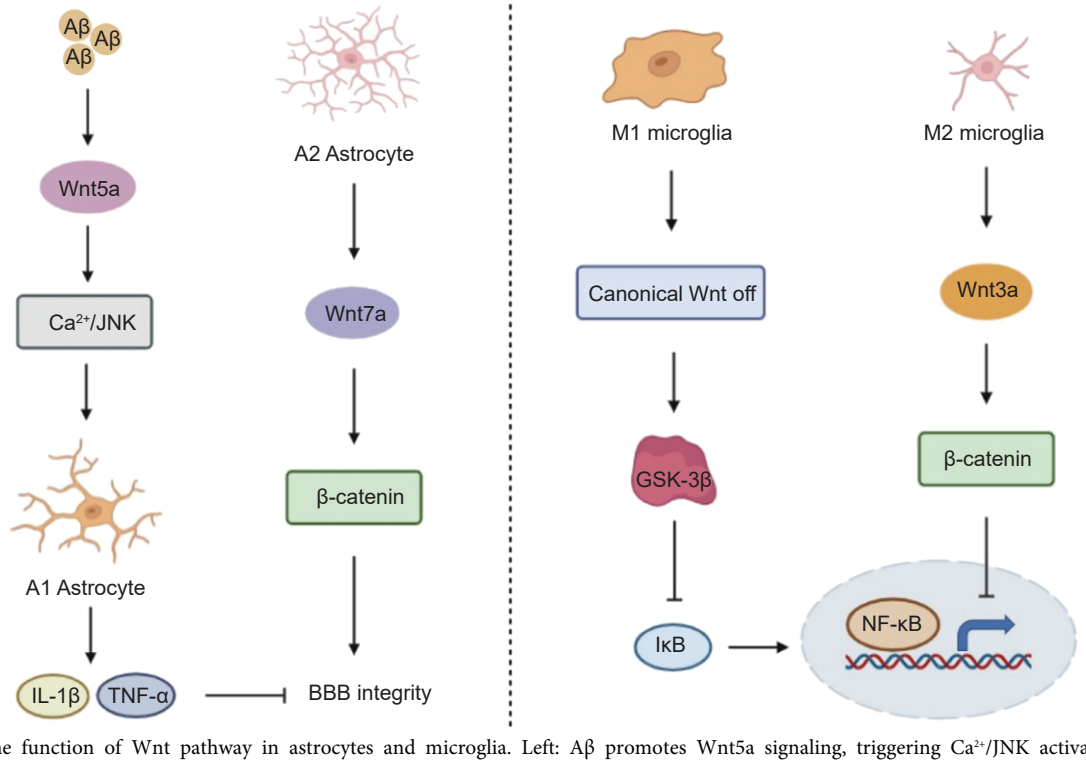

Figure 3 The function of Wnt pathway in astrocytes and microglia. Left: Aβ promotes Wnt5a signaling, triggering Ca^{2+}/JNK activation and the formation of A1 reactive astrocytes, which release pro-inflammatory cytokines (IL-1β and TNF-α) and contribute to BBB disruption. In contrast, A2 astrocytes secrete Wnt7a to activate β-catenin, supporting BBB maintenance. Right: Microglial polarization differentially shapes inflammation: M1 microglia suppress canonical Wnt signaling ("canonical Wnt off"), leading to increased GSK-3β activity, inhibition of IκB, and activation of NF-κB–driven pro-inflammatory responses; M2 microglia activate Wnt3a/β-catenin, which suppresses NF-κB signaling and favors an anti-inflammatory state. Overall, activation of Wnt/β-catenin signaling antagonizes inflammatory cascades and is associated with preserved BBB integrity. The M1/M2 classification is shown here as a simplified functional framework; however, microglial activation in AD is increasingly recognized as a dynamic spectrum that includes disease-associated microglia (DAM).

(e.g., Wnt7a). Astrocyte-derived Wnt7a acts on receptors (FZD/LRP) in adjacent cerebral vascular endothelial cells, activating the Wnt/β-catenin signaling pathway within them. Upon activation, this pathway upregulates tight junction protein expression in endothelial cells while inhibiting the destructive effects of matrix metalloproteinases. This repairs the damaged blood-brain barrier structure, reduces vascular leakage and inflammatory cell infiltration, and creates a microenvironment conducive to tissue repair [42] (Fig. 3). Astrocytes comprise distinct functional subpopulations (e.g., pro-inflammatory A1, protective A2), which secrete different categories of Wnt ligands in response to specific microenvironmental stimuli, thereby directing signaling toward entirely different outcomes.

Together, these observations underscore that the contribution of Wnt signaling to AD pathogenesis is highly context-dependent and tightly controlled at multiple regulatory levels, necessitating a closer examination of the key molecular regulators that shape Wnt signal strength, receptor availability, and pathway output.

4 Key regulatory molecules of Wnt signaling in Alzheimer's disease

Wnt signaling is regulated through coordinated control at the plasma membrane and in the extracellular environment. In AD, this balance is frequently shifted toward reduced pro-survival canonical signaling together with heightened extracellular inhibitory tone, thereby increasing vulnerability of synapses and neurovascular units and promoting downstream cascades linked to neuroinflammation and Aβ accumulation [43, 44].

4.1 Receptor nodes shaping Wnt signaling and AD vulnerability

Wnt pathway activation relies on the assembly of receptor complexes composed of Wnt ligands, FZD receptors, and pathway-selective co-receptors. FZD proteins provide the core ligand-binding platform through their extracellular cysteine-rich domains, and preferential Wnt–FZD pairing contributes to signaling selectivity and pathway specification [45]. In the canonical Wnt/β-catenin pathway, LRP5/6 functions as the indispensable co-receptor. Wnt ligands simultaneously engage FZD and LRP5/6, promoting receptor clustering and phosphorylation of the LRP5/6 intracellular domain. Phosphorylated LRP5/6 recruits Axin to the plasma membrane, destabilizes the β-catenin destruction complex, and enables β-catenin stabilization as a prerequisite for transcriptional activation [46]. In AD, impaired LRP6 expression and function is a prominent vulnerability point. LRP6 variants are associated with late-onset AD risk [44], and neuron-specific LRP6 deletion results in synaptic abnormalities, exacerbated Aβ pathology, and enhanced glial neuroinflammation [47]. Canonical Wnt/β-catenin signaling in BBB endothelial cells is also critical for maintaining barrier integrity, and enhancing endothelial canonical signaling through LRP6 can alleviate Aβ-induced BBB dysfunction [19], highlighting the importance of receptor competence within the neurovascular unit.

Non-canonical Wnt signaling is specified by alternative co-receptors such as ROR1/2 and RYK, particularly within the PCP and Wnt/Ca^{2+} branches [48]. Ligands such as Wnt5a preferentially signal through FZD–ROR2 receptor complexes to activate JNK, ROCK, or Ca^{2+}-dependent cascades, largely independent of β-catenin–mediated transcription [49]. This receptor architecture provides a mechanistic basis for branch bias under pathological conditions, in which weakened canonical receptor competence can shift Wnt outputs toward β-catenin–independent programs that remodel cytoskeletal dynamics and synaptic structure.

Beyond LRP5/6, LRP1 represents a major AD-relevant receptor node that couples Wnt-related regulation to Aβ homeostasis. Although LRP1 does not function as a canonical co-receptor, it is a dominant receptor mediating Aβ clearance across the BBB and contributes to receptor-mediated endocytic clearance in neurons [50–53] (Fig. 4). Impaired endothelial LRP1 accelerates brain Aβ accumulation [53], and neuron-specific LRP1 deletion increases brain Aβ levels and plaque deposition without substantially altering Aβ production [51], supporting a clearance-centered role. LRP-family interactions can also influence Wnt receptor complex behavior and non-canonical ligand handling. For example, LRP-related mechanisms have been shown to modulate the formation of functional Wnt receptor complexes [54] and to regulate trafficking of non-canonical ligands such as Wnt5a, thereby influencing PCP pathway activity [55]. Metabolic factors relevant to AD can further converge on this receptor layer. High cholesterol regulates LRP1 and RAGE expression via Wnt/β-catenin signaling [56], while LRP1 itself can influence non-canonical signaling with implications for cholesterol homeostasis [57]. Together, these observations position LRP6 and LRP1 as complementary determinants of AD vulnerability, with LRP6 primarily shaping canonical signaling competence and neurovascular integrity and LRP1 linking receptor dynamics to Aβ clearance.

4.2 Extracellular inhibitors and their contribution to Wnt imbalance in AD

To prevent excessive diffusion and ectopic activation, Wnt ligands are constrained by secreted extracellular inhibitors that regulate ligand availability and receptor engagement with strong spatial and temporal precision. Secreted frizzled-related proteins (sFRP1–5) represent a broad inhibitory class capable of modulating both canonical and non-canonical pathways. sFRPs share structural homology with the FZD extracellular cysteine-rich domain [58] and inhibit signaling by sequestering Wnt ligands as soluble decoys and by directly associating with FZD to competitively block ligand binding [59]. Although sFRPs are frequently discussed in cancer contexts, where their silencing can release Wnt repression and sustain β-catenin activity [60, 61], the same principle underscores their relevance to neurodegeneration, as extracellular buffering of ligand–receptor engagement can decisively tune Wnt tone within vulnerable brain microenvironments.

The DKK family (DKK1–4) constitutes a potent inhibitory system with strong relevance to AD. Canonical members, especially DKK1, bind LRP5/6 to prevent productive Wnt–FZD–LRP5/6 complex formation [62] (Fig. 4) and can cooperate with Kremen1/2 to promote LRP5/6 internalization

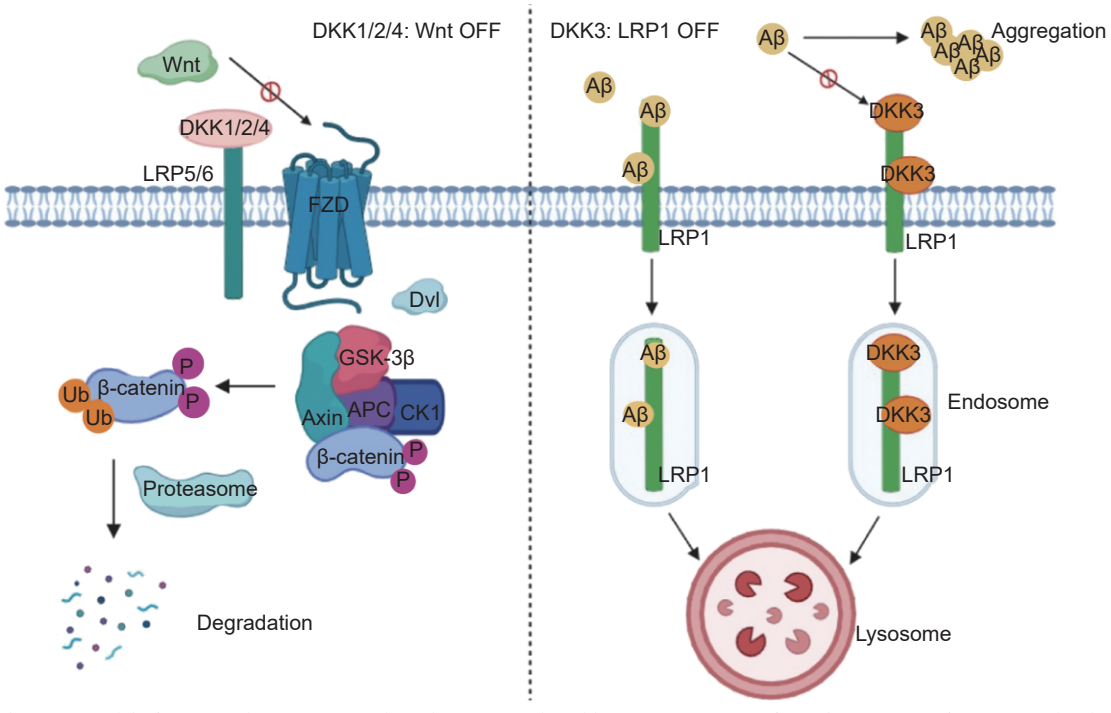

Figure 4 Schematic model of two membrane-associated mechanisms mediated by DKK proteins. Left: In the presence of DKK1/2/4, binding of Wnt to the co-receptor LRP5/6 and FZD is blocked, resulting in a Wnt-OFF state. Under these conditions, the β-catenin destruction complex (Axin/APC/GSK-3β/CK1) remains active, promoting β-catenin phosphorylation, ubiquitination, and subsequent proteasomal degradation. Right: DKK3 competes with Aβ for binding to LRP1, thereby reducing LRP1-mediated Aβ uptake and promoting extracellular Aβ aggregation. The LRP1–DKK3 complex is internalized via endocytosis into endosomes and trafficked to lysosomes for degradation, effectively turning LRP1 signaling OFF.

and lysosomal degradation, thereby enforcing durable receptor-level blockade [63]. Elevated DKK1 and DKK3 have been reported in patient cerebrospinal fluid and brain tissue [20, 64, 65], consistent with a disease-associated increase in inhibitory tone. Functionally, DKK1 has the most established causal link to AD synaptic pathology. DKK1 is upregulated early in AD brains and in AD mouse models, correlating with tau phosphorylation and synaptic loss [66]. Aβ oligomers can induce DKK1 expression in neurons and glia, and secreted DKK1 suppresses synapse-protective canonical signaling at LRP5/6-containing sites while promoting synaptic dismantling programs, leading to dendritic spine retraction and loss of synaptic proteins, with consequent impairment of plasticity and memory [67–69]. Consistent with this mechanism, DKK1 neutralization protects synapses from Aβ-mediated loss [69], supporting therapeutic strategies aimed at restoring the canonical Wnt axis by targeting the DKK1–LRP6 interface.

DKK3 is increasingly recognized as an atypical Wnt regulator in AD with multi-branch effects. DKK3 is elevated in AD brain tissue, particularly around amyloid plaques, and has been reported to suppress canonical Wnt/β-catenin–GSK-3β signaling while engaging non-canonical Wnt/JNK programs, thereby disrupting excitatory/inhibitory synaptic balance and contributing to memory impairment. Reducing DKK3 expression rescues synaptic and cognitive deficits in AD models [64]. Recent mechanistic studies further provide a direct coupling between extracellular Wnt inhibition and Aβ clearance machinery. DKK family proteins can act as ligands for LRP1, and DKK3–LRP1 interactions are proposed to compete with Aβ recognition and endocytosis and modulate Aβ metabolism and clearance-related processes [20] (Fig. 4). DKK2 extends this inhibitory network into a microglia-centered framework. DKK2 transcription is upregulated in microglia in AD models, and recombinant DKK2 antagonizes Wnt-dependent synapse formation and maintenance, suggesting that microglia-derived DKK2 can locally dampen Wnt signaling and contribute to synaptic dysfunction [41]. Together, extracellular inhibitors not only suppress canonical Wnt neuroprotection but also connect Wnt pathway imbalance to Aβ clearance failure through LRP1, integrating synaptic pathology and amyloid homeostasis within a unified regulatory framework.

Understanding how these receptor-level nodes and extracellular inhibitors reshape Wnt signaling provides a mechanistic foundation for the development of targeted therapeutic strategies in AD.

5 Therapeutic intervention strategies targeting the Wnt signaling pathway and their efficacy

5.1 Peptide interventions

Peptide-based strategies provide a means to selectively disrupt pathological protein–protein interactions within the Wnt regulatory network while preserving overall pathway integrity. A representative example is DLDP, a blocking peptide designed to target the N-terminal LRP6-binding domain of DKK1, thereby preventing formation of the inhibitory DKK1–LRP6 complex. In vitro studies demonstrated that DLDP attenuated DKK1-induced dendritic spine loss and suppressed the associated increase in endogenous Aβ levels. These protective effects were further validated *in vivo*: in rats

receiving intracerebroventricular administration of DLDP followed by Aβ oligomer challenge, DLDP treatment preserved cognitive performance and significantly mitigated Aβ-induced reductions in the synaptic marker PSD-95. Behavioral assessment using the novel object recognition task at 7 and 14 days post-challenge confirmed sustained protection of synaptic function and memory [67]. Together, these findings indicate that peptide-mediated disruption of DKK–LRP6 interactions represents a viable approach for restoring synapse-supportive Wnt signaling under amyloid stress conditions.

5.2 Small-molecule interventions

Small-molecule modulators of Wnt signaling offer practical advantages with respect to oral bioavailability, brain penetration, and translational feasibility and have been explored at multiple regulatory levels of the pathway. Recent studies identified the DKK3–LRP1 axis as a druggable interface linking Wnt regulation to Aβ metabolism. The orally available, brain-penetrant compound SJ-300 disrupts DKK3–LRP1 interactions and has been shown to improve cognitive performance and markedly reduce amyloid plaque burden in 5×FAD mice, with plaque reduction reaching approximately 73.3% [20]. Modulation of downstream Wnt signaling components has also been investigated. Lithium salts, which indirectly enhance canonical Wnt/β-catenin signaling through inhibition of GSK-3β, reversed Aβ-associated reductions in phosphorylated GSK-3β (Ser9), β-catenin, and cyclin D1 expression and improved learning and memory performance in APP/PS1 mice when administered chronically at either early or later disease stages [70]. However, clinical translation of this approach has proven challenging. Tideglusib (NP031112), a selective GSK-3β inhibitor, failed to demonstrate significant superiority over placebo in a randomized clinical trial involving patients with mild-to-moderate AD, despite comprehensive cognitive, functional, imaging, and biomarker assessments [71]. Collectively, these findings underscore both the potential and the limitations of broadly targeting downstream Wnt signaling components and highlight the need for pathway-selective and context-dependent intervention strategies.

5.3 Gene therapy interventions

Gene- and tool-based approaches enable precise spatial and temporal modulation of Wnt signaling and have provided important insights into pathway-targeted intervention, particularly within the neurovascular unit. To counteract Aβ-induced suppression of endothelial canonical Wnt/β-catenin signaling and associated BBB dysfunction, the optogenetic construct OptoLRP6 was developed to allow controllable activation of LRP6 in brain endothelial cells. In APP/PS1-related models, OptoLRP6-mediated activation of Wnt signaling upregulated tight junction and transport-related proteins, prevented Aβ-induced pathological alterations in brain endothelial cells, and restored BBB integrity [19]. In addition, gene-regulatory strategies targeting upstream inhibitory complexes have been explored. Silencing of Kremen1 via miR-431 disrupts inhibition mediated by the DKK1–Kremen1 complex and effectively blocked Aβ-induced synaptic loss in cortical–hippocampal neuronal cultures derived from 3×Tg-AD mice [72]. These studies collectively demonstrate that targeted manipulation of Wnt pathway regulators using gene- or tool-based approaches can confer synaptic and vascular protection in preclinical AD models.

Together, peptide-, small-molecule-, and gene-based studies indicate that therapeutic modulation of the Wnt signaling network can engage multiple pathological dimensions of Alzheimer's disease, including synaptic dysfunction, neurovascular impairment, and amyloid pathology, at the preclinical level. At the same time, variable outcomes in clinical translation emphasize the importance of pathway selectivity, cell-type specificity, and disease-stage dependence, suggesting that precision-guided modulation of discrete Wnt regulatory nodes is likely to be more effective than global pathway activation.

6 Perspectives

Wnt pathway modulation is increasingly regarded as a disease-relevant therapeutic axis in AD rather than a peripheral epiphenomenon. Hallmark AD features, including Aβ deposition, tau hyperphosphorylation, and synaptic dysfunction, are consistently associated with weakened canonical Wnt/β-catenin signaling and heightened extracellular inhibitory pressure [73]. Importantly, Wnt dysregulation can participate in feed-forward pathology, as Aβ-induced upregulation of antagonists further suppresses synapse-protective signaling and accelerates synaptic decline [67, 69].

A useful integrative model is receptor gating, antagonist amplification, and clearance cross-talk. LRP5/6 governs canonical signaling competence in neurons and brain endothelium, linking Wnt tone to synaptic stability and BBB integrity [19, 74], whereas LRP1 anchors Aβ transport and clearance across the BBB and within neurons, shaping amyloid flux and overall burden [53]. Secreted antagonists such as DKK proteins and sFRPs remodel extracellular Wnt availability and receptor complex formation, thereby amplifying pathway suppression and promoting AD-relevant signaling imbalance [72]. Together, these nodes provide a mechanistic bridge connecting extracellular Wnt "tension" to both synaptic vulnerability and Aβ homeostasis.

Therapeutic development should therefore prioritize localized functional restoration rather than global pathway activation. Promising directions include selectively reinforcing canonical Wnt/β-catenin signaling in protective compartments such as brain endothelium [19, 75], interrupting amplification loops by targeting inhibitory interfaces exemplified by the DKK1–LRP6 axis [67, 72], and receptor-centric strategies that combine restoration of LRP6-mediated signaling competence with enhancement of LRP1-dependent clearance capacity [53, 67]. Key translational needs include resolving cell-type and stage dependence [64] and adopting mechanism-aligned endpoints, including synaptic function, BBB permeability, Aβ clearance flux, and inflammatory phenotypes [19, 53], while ensuring adequate brain delivery and long-term safety [75, 76].

Author contributions

X.Z., R.Y., and J.W. collected the data and wrote the

manuscript; J.S. supervised and revised this work.

Conflict of interests

The authors declare no conflict of interests.

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