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Progress Research on Wnt/β-Catenin Signaling Pathway

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Abstract

The Wnt/β-catenin signaling pathway is a key signal pathway. Its occurrence and development are closely related to biological mechanisms such as inflammation and angiogenesis. This article systematically elaborates on the current research progress of the Wnt/β-catenin signaling pathway from several aspects, including the activation process of the Wnt/β-catenin signaling pathway, the controllable disease spectrum, the research status in the field of cerebrovascular disease, typical receptors, agonists, inhibitors of the signaling pathway, research progress on inflammatory effects, and the crosstalk of the NF-κB signaling pathway. In order to provide a basis for subsequent studies on the correlation between diseases or drugs in this pathway.

Keywords: *Wnt/β-catenin signaling pathway, Activation, Disease spectrum, Cerebral vascular disease, Inflammation, NF-κB*

Wnt/β-Catenin Signaling Pathway Activation

The Wnt/β-catenin signaling pathway is a classic pathway in current disease research. It plays a very important role in regulating the normal development of embryos and participating in cell proliferation and differentiation. The typical Wnt/β-catenin signaling pathway is used in the signal transmission of the cdkey cell regulator, the β-catenin protein, which is mainly found in the cytoplasm, and its level determines the activation of the pathway. The mechanism of the β-catenin dependence is regulated by the cytoplasmitic complex, including the Gsk3β \ Axin \CK1/2 \PP2A\Apc factor etc. In the absence of the Wnt ligands signal, the β-catenin in the cytoplasm is phosphorylated by Gsk3β, which in turn is modified, which is eventually degraded, so that the β-catenin in the cytoplasm remains low level. In the case of the Wnt ligands signal, they combine with the transmembrane receptors, destroy destruction complex including GSK3β, inhibit Gsk3β activity, and lost its phosphorylation to β-catenin, thus result in the accumulation of unphosphorylated β-catenin in the cytoplasm and subsequent translocation to the nucleus, where it binds to various transcription factors. This promotes the transcription of the Wnt target gene in the downstream Wnt target of the Wnt signal transduction and vascular growth.

The Disease Spectrum of Wnt/β-Catenin Signaling Pathway and the Research Status of Cerebrovascular Disease

Wnt/β-Catenin Signaling Pathway Can Regulate the Spectrum of Diseases

The Wnt/β-catenin signaling pathway is now found to be associated with a variety of diseases. ① Neurological disease: [1]. In the study of the animal model of the mice Alzheimer's disease, the mechanism of the memory and particle cells of mice may be improved by downregulating DKK1 to activate the Wnt/β-catenin pathway, which can improve the shortening and lack of cognition of neuronal dilatations. ② Hepatic disease: [2] In the study of non-alcoholic fatty liver disease, the multi-pathway analysis platform showed that the Wnt-signaling was a common biological pathway associated with non-alcoholic fatty liver disease and non-alcoholic fatty hepatitis. For the first time, the activation of the classic Wnt signal may be one of the main ways of the two diseases associated with gender type 2. ③ Renal disease: [3] Dong Xiangnan et al. found that long-chain non coding RNA-H19 mediates the fibrosis process from acute kidney injury to chronic kidney disease by regulating the miR-196a/Wnt/β-Catenin signaling pathway. ④ Tumor disease: The overactivation of β-catenin caused by mutations in APC, Axin, or β-catenin is a well-known cancer-related high-risk factor, such as colon cancer [4]. ⑤ Metabolic disease: [5-8] The imbalance of lrp6 has a strong correlation with coronary artery disease (CAD) and atherosclerosis. Through whole genome analysis of CAD patients, it was found that multiple residue mutations such as r473q in LRP6 are associated with the pathogenesis of CAD, which is

determined by the levels of hyperglycemia, hyperlipidemia, and low-density lipoprotein in blood vessels [9]. The impaired activity of lrp6 is highly correlated with coronary heart disease, mainly through pdgf signaling transduction. Studies have found that miRNA-17-92 clusters targeting LRP6 can downregulate wnt/β-catenin signal transduction, and the lack of miRNA17-92 in endothelial cells can improve blood flow and atherosclerosis. ⑥ Inflammatory disease: [10]cytokines can regulate the Wnt/lrp6 signal. For example, the cell kinetic interferon or tumor necrosis factor, which is exposed in the state of inflammation for a long period of time, induces the expression of dkk1, inhibiting the transmission of Wnt/β-catenin signaling and increasing the incidence of intestinal inflammation [11]. Dendritic cells (DCs) - Specific knockout of LRP5/6 can promote the differentiation of effector T cells, inhibit the differentiation of regulatory T cells, thereby enhancing anti-tumor immunity and inhibiting tumor growth, both of which indicate that the fine regulation of LRP6 is crucial for appropriate immune responses. ⑦ skeletal muscle disease: [12] LRP5 mutations typically lead to decreased bone mass and osteoporosis, which is caused by downregulation of the Wnt/β-catenin signaling pathway. ⑧ Blood disease: [13] Hematopoietic stem cells are the best mammal stem cells. Many studies have shown that the Wnt signaling pathway is an important regulatory factor for hematopoietic stem cells and progenocytes. The hematopoietic stem cells themselves and the bone marrow microenvironment can produce Wnt protein. The above lists some of the diseases related to the Wnt/β-catenin signaling pathway that have been discovered. In addition, there are still many related diseases that need to be explored.

Research Status of Wnt/β-Catenin Signaling Pathway in the Field of Cerebrovascular Diseases

Animal experiments have found that miR-124 can affect neuronal apoptosis during cerebral infarction through the Wnt/β-catenin signaling pathway [14]. [15] Zhizhun et al. observed abnormal activation of Wnt signaling in ischemic stroke, accompanied by blood-brain barrier disruption, neuronal apoptosis, and neuroinflammatory symptoms in the central nervous system. Through cell experiments, it has been proposed that the Wnt/β-catenin signaling pathway can serve as a therapeutic target for ischemic stroke. [16] Satchakorn et al. found through animal experiments and motor function tests that after reperfusion injury, quercetin can significantly reduce the infarct size, blood-brain barrier leakage, and apoptotic cells after injury. The main mechanism involved is angiogenesis, and the Wnt/β-catenin signaling pathway may run through it. [17] Wenyong et al. pointed out that celastrol mediates the Wnt/β-catenin signaling pathway to alleviate cerebral ischemia-reperfusion injury in rats. [18] Donya et al. believe that the FoxO1 and Wnt/β-catenin signaling pathways are molecular targets for protecting against cerebral ischemia/reperfusion injury. [19] Other studies have shown that NPD1 inhibits excessive autophagy in cerebral ischemia-reperfusion injury by targeting the RNF146 and Wnt/β-catenin pathways; [20] Dexmedetomidine hydrochloride has a protective effect on the Wnt/β-catenin signaling pathway in cerebral ischemia-reperfusion injury; [21] The involvement of Wnt/β-catenin signaling pathway in cerebral vascular reperfusion injury may be related to the transforming growth factor β 1/Smad3 signaling pathway. The Wnt/β-catenin signaling pathway is closely related to the occurrence, development, and treatment of various cerebrovascular diseases, especially ischemic cerebral perfusion injury, which can serve as a new therapeutic target.

Wnt/β-Catenin Signaling Pathway Receptors, Agonists, and Inhibitors

Wnt signaling receptors [22] can bind to frizzled (fz) proteins, which are seven transmembrane receptors characterized by an extracellular cysteine rich N-terminal domain (crd). The current research results show that the surface expression of LRP5/6 receptors is a necessary condition for initiating Wnt signaling. The transmembrane tyrosine kinase receptor Derailed is also a Wnt signaling receptor.

The main agonists of the Wnt signaling pathway have been found to be Norrin, r-spondins, and others. Norrin [23] binds with high affinity to frizzled4 and activates typical signaling pathways in an LRP5/6-dependent manner. Other factors that activate the typical Wnt signaling pathway include r-spondins, which are proteins containing thrombin reactive protein. In previous studies [24], it was confirmed that r-spondin-2 is a Wnt agonist that can synergistically activate β-catenin with Wnt. Moreover, cell experiments have shown that r-spondins can physically interact with the extracellular regions of LRP6 and frizzled8, thereby activating Wnt signaling [25].

The main inhibitors of the Wnt signaling pathway have been found to be DKK, WISE, SFRPS, and WIFS. Secretory DKK protein inhibits Wnt signaling by directly binding to LRP5/6 [26]. The secretory Wnt inhibitor WISE also acts by binding to lrp [27], such as its member SOST [28,29]. The soluble frizzled related protein (SFRPS) is similar to the ligand binding crd domain of frizzled family Wnt receptors [30]. WIF protein is a secreted molecule that is similar to the extracellular portion of Derailed/ryk transmembrane Wnt receptors [31]. SFRPS and WIFS are considered to have the function of extracellular Wnt inhibitors [32,33].

There are many receptors, agonists, and inhibitors of Wnt that have been discovered, and here are only some typical proteins. With the continuous deepening of research, more and more protein targets will be discovered in the future.

Research Progress on the Inflammatory Effects of Wnt/β-Catenin Signaling Pathway

The Wnt/β-catenin pathway has dual anti-inflammatory and pro-inflammatory effects. Its anti-inflammatory and pro-inflammatory effects vary with different conditions, and the regulatory mechanisms are also different. The anti-inflammatory effect of Wnt/β-catenin signaling pathway: On the one hand, studies have found that Wnt/β-catenin signaling can downregulate the production of pro-inflammatory cytokines such as IL-1 β and IL-6 when stimulated by lipopolysaccharides, cytokines, viruses, and bacteria [34-40]. The anti-inflammatory effect of β-catenin may be due to the induction of PI3K/Akt signaling transduction and the reduction of TLR4 driven inflammatory response in DCs. Liu Yongsheng et al. [41] found that in the process of atherosclerosis, PAR2 plays an anti-inflammatory role in ox-LDL treated macrophages through Dkk 1/Wnt/β-catenin signaling pathway.

There are also studies indicating that the deficiency of β-catenin leads to increased inflammatory response and disease onset [42]. The Wnt/β-catenin pathway not only has anti-inflammatory effects but also pro-inflammatory effects [43]. The β-catenin signal can induce inflammatory responses in liver cells, participate in direct transcriptional regulation, and activate the NF-κB pathway. This β-catenin signaling may indirectly promote tumor associated inflammatory responses by altering cellular components in the microenvironment. Another study also reported the positive effect of β-catenin on lipopolysaccharide induced production of pro-inflammatory cytokines in human bronchial epithelial cells [44].

Interference Between Wnt/β-Catenin Signaling Pathway and NF-κB Signaling Pathway

The Wnt/β-catenin and NF-κB signaling pathways are two very important inflammatory signaling pathways. Numerous literature studies have confirmed the inhibition of inflammatory response by interfering with the Wnt/β-catenin or NF-κB pathways. Zhang Tao et al. [45] found through experiments that metformin reduces inflammation and cell apoptosis by activating the Wnt/β-catenin signaling pathway. Similarly, studies have found that curcumin can alleviate asthma symptoms and inflammatory responses by activating the Wnt/β-catenin signaling pathway [46]. Puerarin inhibits atherosclerotic inflammatory response in rabbits by inhibiting NF-κB signaling pathway [47]. In addition, many effective traditional Chinese medicine monomers have been experimentally proven to rely on the NF-κB signaling pathway to exert anti-inflammatory effects, such as gastrodin, quercetin, baicalin, and so on.

The crosstalk between Wnt/β-catenin and NF-κB signals is bidirectional, indicating that these two pathways regulate each other. In the hair follicle development model [48], members of the tumor necrosis factor-α family bind to their receptor EDAR to induce NF-κB nuclear translocation and activation in developing hair follicles. EDAR is a direct target of Wnt/β-catenin and can activate the Wnt/β-catenin signaling pathway. The literature suggests that the localization expression of Wnt10b/Wnt10a requires NF-κB signaling transduction, and Wnt10b is a direct transcriptional target gene of NF-κB. In addition, Wnt/β-catenin signaling antagonist DKK4 is a target gene of the EDAR/NF-κB pathway and can act as a negative feedback to limit β-catenin signaling transduction [49]. Other studies have found that high expression of β-catenin can block NF-κB-mediated cell apoptosis, while endotoxin induced NF-κB can promote β-catenin expression and β-catenin regulated cell proliferation [50]. Xi Yang et al. [51] revealed that esomeprazole can inhibit the activation of MAPK and Wnt/β-catenin induced by IL-1 β, as well as inhibit the process of p65 entering the nucleus from the cytoplasm induced by IL-1 β. The progression of rheumatoid arthritis model in rats can be delayed in vivo, providing new treatment ideas for clinical treatment of rheumatoid arthritis. Some studies have also found that curcumin can inhibit the inflammatory response of acute lung injury by suppressing the Wnt/β-catenin and NF-κB signaling pathways. Tang Bi et al. [52] found that Circ 0001434 RNA inhibits the inflammatory response of acute lung injury models by regulating miR-625-5p, NF-κB, and Wnt/β-catenin signaling pathways. Suo Tao et al. [53] found that MicroRNA-1246 inhibits acute lung injury induced lung inflammation and apoptosis by suppressing NF-κB and Wnt/β-catenin pathway activation.

In summary, Wnt/β-catenin and NF-κB signaling are mutually regulated in various cells and tissues, and play an important role in maintaining environmental balance within cells/tissues.

The cross regulation of Wnt/β-catenin and NF-κB also links inflammation and tumorigenesis, not only within cells but also between cells. Carcinogenic inflammation has been recognized as one of the biomarkers of cancer [54]. The positive regulation of Wnt/β-catenin by the NF-κB pathway in tumor models may contribute to tumor development. For example, in colon cancer models, activated NF-κB and β-catenin/Tcf4 act as transcriptional co activators, inducing a series of stem cell genes and subsequently promoting tumor cell growth [55]. In a gastric tumor model, macrophages activated by Helicobacter pylori infection induce NF-κB-mediated TNF-α production, thereby enhancing the oncogenic Wnt/β-catenin signaling pathway [56,57]. In addition to creating favorable tumor microenvironments composed of various pro-inflammatory cells, NF-κB mediated inflammation can enhance the tumorigenic potential of cancer cells by upregulating Wnt/β-catenin signaling. Therefore, NF-κB may be a therapeutic target for inflammation related cancers.

Author Contributions

HYZ: designed this work of review; TLW: performed the literature search of the databases; YL: wrote the manuscript of this paper; YW, QNY, and CCY: revised the manuscript; All authors approved the paper for publication.

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