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Wnt/β−catenin Signaling Cascades in Cardiovascular Diseases*

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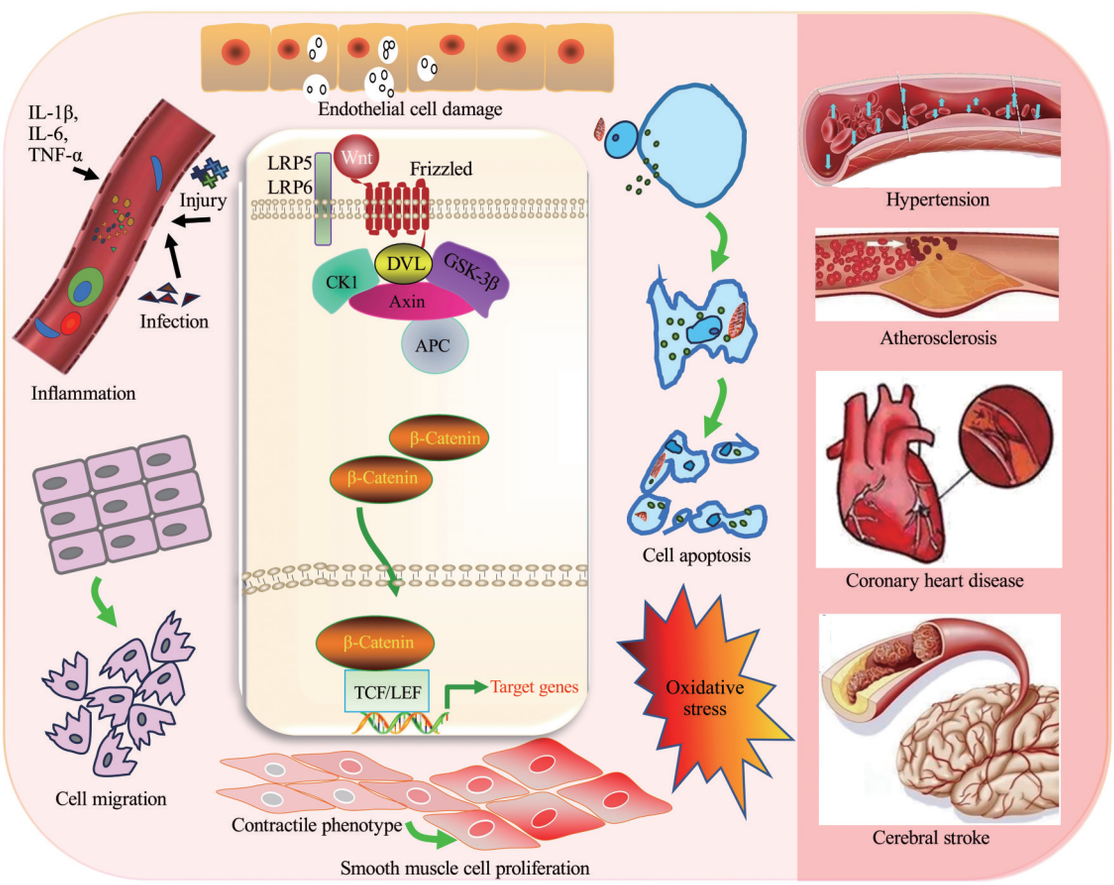
Graphical abstract



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Abstract Cardiovascular diseases are a group of disorders of the heart and blood vessels, primarily including coronary heart disease, stroke, and other diseases. It is the world's leading cause of death, and its incidence is increasing yearly. Hypertension is a major risk factor for cardiovascular disease. Wnt signaling comprises a series of highly conservative cascading events controlling fundamental biological processes. Wnt signaling pathways include the canonical Wnt pathway (or Wnt/β-catenin pathway), the non-canonical planar cell-polarity pathway, and the non-canonical calcium-dependent pathways. Abnormal Wnt signaling promotes cell proliferation and differentiation, cardiac malformations, various malignancies, so drugs targeting Wnt signaling play a great therapeutic potential. Wnt/β-catenin pathway is involved in the occurrence and development of cardiovascular diseases such as atherosclerosis and stroke by regulating cell proliferation, migration, apoptosis, blood-brain barrier permeability, inflammation, oxidative stress, and immune response. Based on the latest research progress, this review summarizes the role of Wnt/β-catenin signaling in cardiovascular diseases, in order to provide new ideas for the prevention and treatment of cardiovascular diseases.

Key words Wnt/β-catenin pathway, cardiovascular diseases, pathological process
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Wnt protein is a large family of cysteine-rich molecules encoded by 19 *Wnt* genes, which have been identified in mammals. The signaling pathway mediated by Wnt protein is highly conserved in evolution and can regulate cell proliferation, differentiation, migration, and adhesion[1]. Wnt-mediated signaling pathways can be classified into classical Wnt/β-catenin signaling pathways, non-classical Wnt/planar cell polarity (PCP) pathway, and Wnt/Ca^{2+} signaling pathways. The Wnt/PCP signaling pathway participates in cytoskeletal rearrangement by activating GTPase. The Wnt/Ca^{2+} signaling pathway activates CaMKII and PKC to release Ca^{2+} from the endoplasmic reticulum in a G protein-dependent manner, thereby regulating physiological processes such as muscle contraction and endocrine response[2]. In the Wnt/β-catenin signaling pathway, Wnt protein binds to Frizzled (FZD) and low-density lipoprotein (LDL) receptor-related protein (LRP) co-receptors, resulting in the disintegration of β-catenin destructive complex. This phenomenon enables β-catenin to accumulate in the cytoplasm and transfer into the nucleus, initiating downstream signal transcription. The Wnt/β-catenin signaling pathway is involved in the atherosclerosis process by participating in the initial inflammatory response, lipid metabolism, endothelial cell damage, and foam-cell formation[3]. Other studies have shown that the Wnt/β-catenin signaling pathway is also involved in the alteration of blood flow at the ischemic site of the heart, the transformation of endothelium-mesenchymal cells, and the angiogenesis of endothelial and smooth muscle cells (SMCs) after cardiac injury[4-5].

1 Wnt signaling pathway

Extracellular Wnt proteins activate intracellular signal transduction cascades downstream of the FZD receptor. They are classified as the Wnt/β-catenin or canonical Wnt signaling pathway and the non-canonical or β-catenin-independent pathway[1-2]. The non-canonical pathway is further divided into the Wnt-PCP and the Wnt-Ca^{2+} pathways (Figure 1). At present, research on Wnt pathway primarily focuses on the classical Wnt signaling pathway. The disorder of this pathway is closely related to the occurrence and development of many diseases[6].

1.1 Wnt−PCP pathway

Wnt signalling *via* FZD receptors directs asymmetric cytoskeleton organization and cell polarization by causing modification of the actin cytoskeleton. A key Wnt signalling protein called Disheveled (DVL) initiates two independent pathways that induce activation of two GTPases, Rho and Rac. Rho activation leads to the activation of a Rho-associated kinase called ROCK. Rac activation induces Jun Kinase activity[2].

1.2 Wnt/Ca^{2+} pathway

Activation of the Wnt signalling pathway *via* FZD receptors can also result in the release of intracellular calcium. The FZD co-receptors Knypek and Ror2 are activated in this pathway. Other activated intracellular messengers in the pathway are G-proteins, phospholipase C and protein kinase C[2]. The increase in calcium can activate a calcium/calmodulin-dependent protein phosphatase called

calcineurin, which results in dephosphorylation of a transcription factor called nuclear factor of activated T-cells (NF-AT) and its accumulation in the nucleus[7].

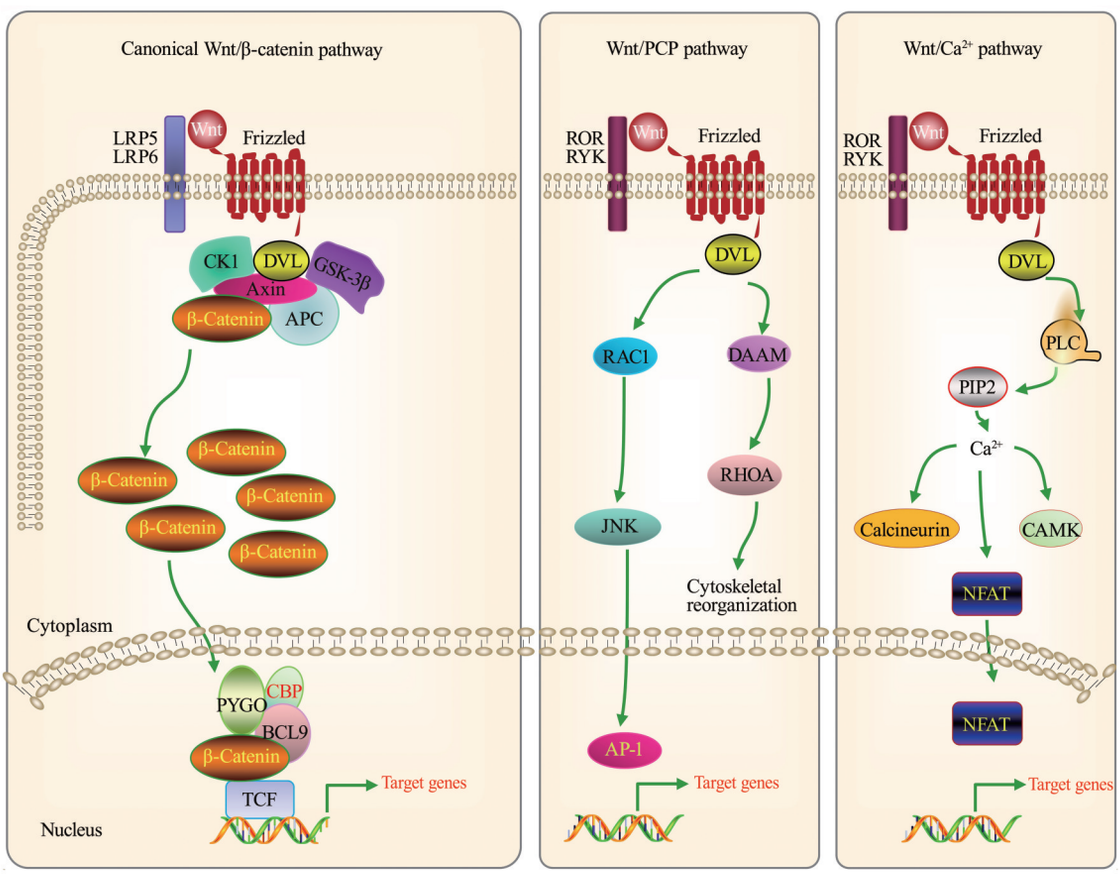

Fig. 1 Canonical and non-canonical Wnt signaling pathways

LRP: low-density lipoprotein receptor-related protein, DVL: Disheveled, CK1: casein kinase 1, GSK-3β: glycogen synthase kinse, APC: adenomatous polyposis coli, pygo: pygopus, CBP: CREB binding protein, TCF: T cell factor, LEF: lymphoid enhancer-binding factor, RAC1: Rac Family Small GTPase 1, JNK: JUN N-terminal kinase, AP-1: activator protein-1, PLC: phospholipase C, PIP2: Phosphatidylinositol 4, 5-bisphosphate, CAMK: calcium/calmodulin-dependent protein kinase, NFAT: nuclear factor of activated T cells.

1.3 Canonical Wnt/β-catenin pathway

The Wnt/β-catenin signaling pathway consists of extracellular Wnt ligand protein, membrane receptor protein, intracellular signal transduction, and transcriptional regulation.

The *Wnt* gene was first discovered in fruit flies as a mutation that causes them to be wingless, hence the name Wingless[8]. Subsequently, *Int* gene has been identified as the activated target gene inserted by mouse mammary tumor virus[9]. Considering that drosophila *wingless* is homologous to mouse *Int*, it is named *Wnt* by combining the two names. The protein encoded by the *Wnt* gene is a secreted glycoprotein with a length of 350-400 amino acids, a molecular weight of about 40 ku, and 23-24 conserved cysteine[10-12]. The Wnt protein family consists of 19 members, including Wnt1, Wnt2, Wnt3, Wnt8, and Wnt10, which activate the classical Wnt/β-catenin signaling pathway[13-14]. Wnt proteins are secreted outside the cell in an autocrine or paracrine manner and bind to about 15 corresponding receptors.

The receptor proteins on the cell membrane include FZD receptor protein and LRP5/6. FZD protein is composed of an extracellular cysteine rich region, seven helical transmembrane region, and an intracellular carboxyl terminal[12]. The cysteine-rich extracellular end is the site that binds to Wnt. LRP5/6 is also composed of 3 parts, namely, an extracellular region, a transmembrane region, and an intracellular region comprising epidermal growth factor and LDL receptor repeats[15]. The extracellular region of LRP5/6 binds to Wnt, and the intracellular region sequence

can recruit Axin and degrade it. Consequently, the classical Wnt signaling pathway is activated.

DVL protein has 3 functional domains, namely, DIX, PDZ, and DEF domains. In the presence of Wnt protein ligands, the PDZ domain of DVL is bound to the carboxyl terminal of FZD protein and activates the intracellular signal transduction[16]. Transcriptional regulation in the nucleus is realized by binding β-catenin to TCF/LEF, a complex formed by T cell factor (TCF) and lymphoid enhancer-binding factor (LEF).

As shown in Figure 2, cytoplasmic scaffold proteins Axin, casein kinase 1 (CK1), glycogen synthase kinse (GSK-3β), and adenomatous polyposis coli (APC) form destruction complexes[17]. In the absence of classical Wnt ligand, β-catenin binds to the destruction complex. CK1α first initiates the phosphorylation of β-catenin at Ser45, and then GSK-3β recognizes pSer45 and phosphorylates Thr41, with pThr41 as the recognition object of GSK3β[17-18]. Ser37 and Ser33 are phosphorylated successively[18]. The F-box protein β-TrCP recognizes p-Ser37/33 β-catenin and its neighbor Asp32[19]. The SKp1-cullins-F-box (SCF) complex binds to E2 ligase to transfer ubiquitin into Lys49 and Lys19 of β-catenin, and the ubiquitinated β-catenin is degraded by the proteasome system. The outcome is decreased intracellular and nuclear β-catenin protein content[20]. The TCF/LEF transcription factor family in the nucleus binds to the Grouch protein family, thereby inhibiting the transcription of target genes[21]. In the presence of Wnt, LRP5/6 is phosphorylated. Wnt, combined with FZD receptor and LRP5/6, can form a terpolymer complex on the cell surface, It then recruits DVL into the plasma membrane, thereby inhibiting the phosphorylation of GSK-3β to

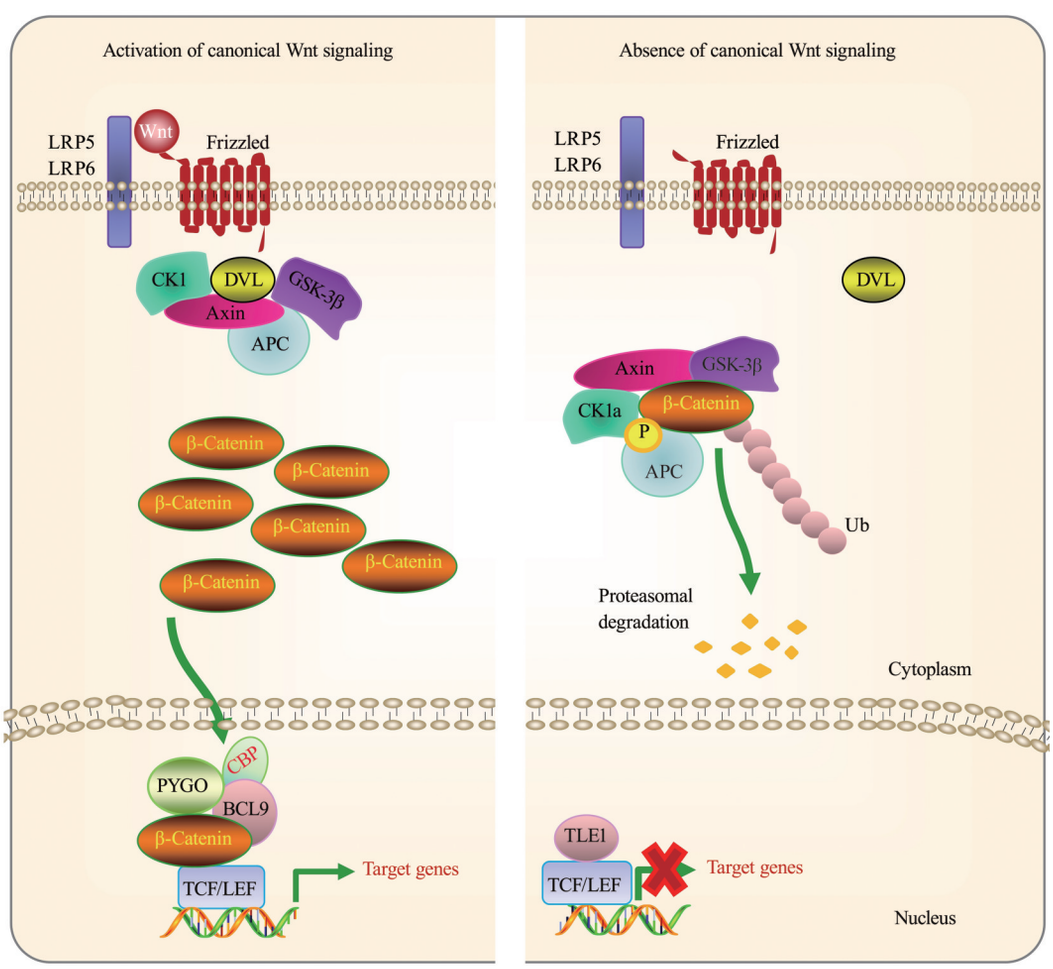

Fig. 2　Canonical Wnt/β−catenin signaling pathway off and on

LRP: low-density lipoprotein receptor-related protein, DVL: Disheveled, CK1: casein kinase 1, GSK-3β: glycogen synthase kinse, APC: adenomatous polyposis coli, pygo: pygopus, CBP: CREB binding protein, TCF: T cell factor, LEF: lymphoid enhancer-binding factor, TLE1: tasducin-likeenhancerof split 1.

β-catenin. This allows β-catenin to accumulate in the cytoplasm and transfer into the nucleus to activate TCF/LEF and subsequently regulate Wnt/β-catenin transcription factors, such as *C-Myc*, *Cyclin D1*, and matrix metalloproteinase (*MMP*) *-3*[22-23]. Changes in any component of this pathway can induce abnormal signal transduction, which can lead to disease.

2 Canonical Wnt/β-catenin pathway in cardiovascular diseases

Cardiovascular diseases are a group of diseases involving the heart and blood vessels. It primarily includes coronary heart disease, cerebrovascular diseases (such as stroke), peripheral arterial vascular diseases, congenital heart disease, deep vein thrombosis, and pulmonary embolism. The incidence of cardiovascular diseases increases yearly, with the number of cases increasing from 271 million in 1990 to 523 million in 2019. The number of deaths also steadily increased from 12.1 million in 1990 to 18.6 million in 2019[24]. Cardiovascular diseases are also the leading cause of death worldwide, with 80% of people with this disease dying from heart attacks and strokes. Atherosclerosis is a major cause of cardiovascular diseases, and acute ischemia and hypertrophy of cardiomyocytes are the most common damage to the heart caused by atherosclerotic plaques and thrombosis. Ultimately, cardiac progenitor cell death occurs[25]. The Wnt/β-catenin signaling pathway plays a crucial role in cardiovascular development, such as the formation of cardiac canals and cardiac rings, the formation of cardiac lumen, and the separation and maturation of lumen[26]. The Wnt/β-catenin pathway is highly active during embryonic development and in adulthood, and the dysfunction of this signaling pathway is closely associated with various cardiovascular diseases, such as heart failure, myocardial infarction, atherosclerosis, cerebral stroke, and high blood pressure (Table 1).

Table 1 Wnt/β−catenin signaling pathway is involved in the pathological process of cardiovascular diseases

Disease	Protein/RNA	Mode of action	Wnt/β-catenin pathway	Pathological process
Coronary artery disease	TGF-1β/Smad	Promote Wnt protein[27], promote GSK-3β phosphorylation[28]	Activate	Smooth muscle cell proliferation
	PEDF	Bind to LRP6[29], inhibit ROS generation[30-33]	Inhibit	Endothelial cell injury, oxidative stress
Cerebral stroke	Exendin-4/ shZFAS1	Inhibit GSK-3β[34-35]	Activate	Oxidative stress, blood brain barrier, cell proliferation/ migration/invasion
	lnc RNA NEAT1	Promote Wnt3a expression[36]	Activate	Apoptosis, inflammatory response
	PFT-α	Promote β-catenin expression[37]	Activate	Apoptosis, inflammatory response, blood brain barrier
High blood pressure	lnc RNA TUG1	Inhibit β-catenin expression[38]	Activate	Apoptosis, smooth muscle cell proliferation/migration

2.1 Coronary artery disease

Coronary heart disease is the full name of coronary atherosclerotic heart disease. It is sometimes called ischemic heart disease, referring to coronary atherosclerosis leading to myocardial ischemia and hypoxia caused by heart disease[39]. The pathogenesis of coronary atherosclerosis is complex, with theories including lipid infiltration, proliferation of arterial SMCs, thrombogenesis, and damage response[40-43]. Currently, “damage response theory” is generally accepted to be the main pathogenesis of atherosclerosis. Atherosclerosis is largely due to the accumulation of certain plasma lipoproteins, including the residue of LDLs and triglyceride-rich lipoproteins in the intima region of blood vessels, which lead to the activation of covered endothelial cells[44]. The permeability of endothelial cells increases so that LDLs are deposited into the intima and oxidized into OX-LDL. OX-LDL promotes mononuclear macrophages to adhere onto and migrate into the intima of blood vessels, subsequently, SMCs in the medial artery absorb lipids and also form foam cells[45-46]. These cells aggregate to produce lipid streaks, and SMCs secrete collagen fibers and other extracellular matrix form fibroplaque. OX-LDL and possibly the toxic effects of oxygen free radicals on

endothelial cells and SMCs result in cell damage and necrosis within the plaque[46-48]. Foam cells die and collapse, releasing many lysosomal enzymes that promote the necrosis and collapse of other cells[49]. With the development of these pathological processes, fibrous plaques gradually evolve into atherosclerotic plaques.

Endothelial cell injury and lipid deposition also promote the abnormal proliferation and migration of vascular SMCs (VSMCs), so inhibiting the proliferation and migration of VSMCs can help delay atherosclerosis formation[47, 50]. DiRenzo *et al.* [27] found that in rat VSMCs, increased TGF-β/Smad3 can up-regulate Wnt2b, Wnt4, Wnt5, Wnt9, and Wnt11 proteins. Among them, Wnt2b, Wnt4, Wnt5, and Wnt9 activate the classical Wnt/β-catenin signaling pathway, inducing β-catenin to enter the nucleus stably and play a role in promoting SMC proliferation. TGF-β1 can promote β-catenin stability through the rapid phosphorylation of GSK-3β, thereby promoting the proliferation of SMCs. Inhibiting β-catenin degradation can also achieve this effect[28, 51]. Tsaousi's group has also reported that Wnt4 stimulates the proliferation of VSMCs *in vivo* and *in vitro* by activating classical pathways[52].

OX-LDL is an important risk factor in the occurrence and development of coronary heart disease because it can promote the formation of atherosclerotic foam cells, damage vascular endothelial cells, promote the proliferation and migration of VSMCs, and induce the release of inflammatory cytokines[53-57]. OX-LDL is produced in response to the complex oxidative modification of LDL by reactive oxygen species (ROS)[58]. As shown in Figure 3, under normal physiological conditions, the nuclear redox protein (NRX) binds to DVL to form complexes that allow DVL to exist in the cytoplasm in an inactive manner and inhibit the Wnt/β-catenin signaling pathway[59]. The ROS derived from NAPDH oxidase NOX oxidizes and inactivates NRX, leading to the dissociation of NRX and DVL[29, 59]. The free DVL can be recruited into the plasma membrane to inhibit the formation of the destructive complex, thereby allowing β-catenin to statically exist and transfer into the nucleus, causing the transcription and activation of downstream target genes.

Pigment epithelium-derived factor (PEDF) is a glycoprotein belonging to the serine protease inhibitor

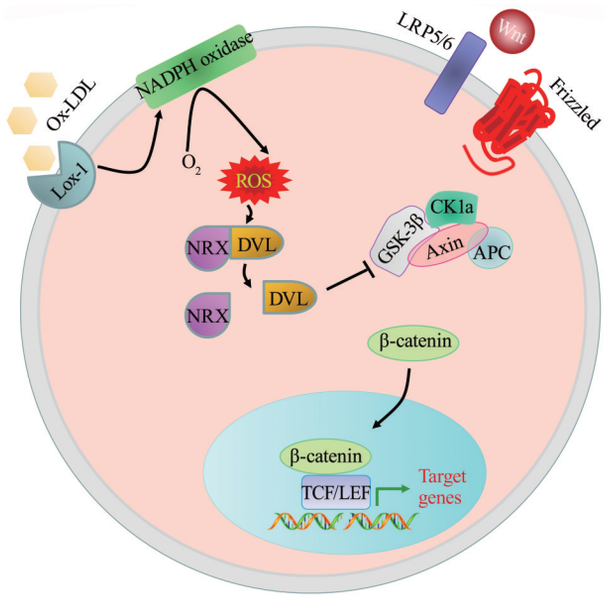

Fig. 3　The status of NRX and DVL affects the classical Wnt channel

Under normal physiological conditions, NRX binds to DVL so that DVL exists in the cytoplasm in an inactive manner, inhibiting the classical Wnt signaling pathway. ROS oxidizes and inactivates NRX, which leads to the dissociation of NRX and DVL. The free DVL can inhibit the formation of degradation complex, and β-catenin can stably exist and transfer to the nucleus, resulting in the transcription and activation of downstream target genes.

superfamily. PEDF has the characteristics of inhibiting angiogenesis and inflammation, anti-oxidative stress, anti-thrombosis, stabilizing plaque, and promoting apoptosis and immune regulation[30, 60]. Serum levels of PEDF are also considered a marker of atherosclerosis[31]. The mechanism of inhibition of the Wnt/β-catenin signaling pathway by PEDF is as follows. First, PEDF binds to Wnt coreceptor LRP6 to inhibit the activation of the Wnt/β-catenin signaling pathway; second, PEDF blocks the activation of the OX-LDL-mediated Wnt/β-catenin signaling pathway by inhibiting ROS production, alleviating endothelial cell damage and intracellular oxidative stress response[29, 32-33].

2.2　Cerebral stroke

Stroke is the world's second largest cause of death and the third largest cause of disability, with high incidence, high disability rate, high mortality, and high recurrence rate of the "four high" characteristics[61]. According to different causes, stroke can be divided into ischemic and hemorrhagic,

with ischemic stroke accounting for 87% of all stroke incidence[62]. Ischemic stroke refers to the narrowing or occlusion of the blood-supply arteries (carotid arteries and vertebral arteries) of the brain, resulting in decreased cerebral blood perfusion followed by ischemia and hypoxia. The elimination of toxic metabolites lead to ischemic injury, endangering brain tissue and even leading to cerebral infarction[63]. Due to the lack of effective treatment for ischemic stroke, thrombolysis is the main treatment at present[64]. While restoring blood flow through ischemia reperfusion, infarct tissue and blood-brain barrier dysfunction and other secondary injuries may occur[37]. The use of the thrombolytic drug rtPA in the treatment of ischemic stroke can cause neurotoxicity, such as dysfunction in the blood-brain barrier, the activation of MMP-9, the production of ROS, and the inflammatory response[34, 65-66]. MMP-9, which is expressed in vascular endothelial cells, primarily degrades collagen and tight-junction protein ZO-1 in the basal membrane, destroys the integrity of the blood-brain barrier, and leads to cerebral hemorrhage and cerebral edema[66]. Blood-brain barrier dysfunction, inflammatory response, and microglial activation are key factors that cause continued worsening of stroke.

Exendin-4, an agonist for glucagon-like peptide-1 (GLP-1) receptor, is a small-molecule drug capable of promoting insulin secretion. Exendin-4 crosses the blood-brain barrier directly into the central nervous system[34, 67-68]. By inhibiting GSK-3β, Exendin-4 weakens the expression of p-β-catenin, promotes the expression of β-catenin, activates the Wnt/β-catenin signaling pathway, inhibits the activation of MMP-9 and the production of ROS, and reduces the anti-inflammatory effect of oxidative stress[34]. It promotes the expression of ZO-1, Occludin, and Claudin-5, protects the integrity of blood-brain barrier, and thus improves the neurological deficit score. It also inhibits cerebral edema and reduces infarct size in rats[34].

Long noncoding RNA (lncRNA) is RNA greater than 200 nt[69]. Numerous studies have shown that lncRNA plays an important role in nervous system diseases, cancer, cardiovascular diseasessss, mental disorders, *etc*[70-71]. In terms of cardiovascular diseasessss, lncRNA is involved in the occurrence and development of ischemic stroke by influencing cell proliferation, migration, invasion, apoptosis, inflammatory response, and endothelial-cell injury. The expression of lncRNA NEAT1 is down-regulated in acute ischemic stroke patients and mice in oxygen glucose deprivation/re-oxygenation (OGD/R) models. Moreover, lncRNA NEAT1 promotes Wnt3a expression by binding to U2AF[36]. Wnt3a inhibits the phosphorylation of GSK-3β and then activates the Wnt/β-catein signaling pathway. Wnt3a also alleviates the OGD/R-induced decline in cell viability, decreases the expression of the pro-apoptotic proteins Bax, Bad, and caspase3/9, and increases the expression of the anti-apoptotic protein Bcl-2. Meanwhile, NEAT1 significantly reduces the expression and secretion of the pro-inflammatory factors TNF-α, IL-1β, and IL-6[72-73]. Therefore, lncRNA NEAT1 overexpression can reduce the harm of ischemia and hypoxia by inhibiting apoptosis and inflammatory response. ZNFX1 antisense RNA 1 (ZFAS1) is a novel lncRNA transcribed in the antisense direction of zinc finger NFX1-1 type[74-75]. In a myocardial infarction model, shZFAS1 activates the Wnt/β-catenin signaling pathway by inhibiting the expression of GSK-3β, thereby promoting the proliferation, migration, and invasion of fibroblasts and reducing the expansion of infarct area. The infarct rate of cells decreases, thereby preventing ventricular wall rupture[35]. Administration of XAV939, an inhibitor of the Wnt/β-catenin signaling pathway, while knocking down ZFAS expression, reverses the ameliorative effect of shZFAS on myocardial infarction. Thus, ZFAS can be a target for the treatment of ischemic stroke.

P53 reportedly acts on the Wnt/β-catenin signaling pathway, and the middle cerebral artery occlusion and reperfusion model (MCAO/R) and OGD/R in rats can simulate cerebral ischemia reperfusion injury[76]. In both models, administration of the P53 inhibitor PFT-α up-regulates β-catenin protein levels and activates the Wnt/β-catenin signaling pathway[37]. PFT-α attenuates apoptosis by down-regulating Bax and up-regulating Bcl in the classical Wnt signaling pathway. PFT-α can reduce the expression of the inflammatory cytokines IL-6 and TNF-α to weaken the inflammatory response. In MCAO/R and OGD/R models, the levels of the tight-junction proteins ZO-1, Occludin, and Claudine decrease. On this basis, the administration of PFT-α can promote the up-regulation of the expression of the three proteins, which protect the integrity of blood-brain barrier[37]. Therefore, PFT-α can significantly inhibit nerve function injury, neuronal apoptosis, and

inflammatory response in rat cerebral ischemia-reperfusion model. However, DKK, an antagonist of the Wnt/β-catenin signaling pathway, inhibits the neuroprotective effect of PFT-α[77]. In summary, the development of drugs that activate the Wnt/β-catenin signaling pathway may be a research direction for the treatment of cerebral stroke.

2.3 Hypertensive diseases

The “silent killer” high blood pressure affects more than 2 billion people worldwide, placing a heavy economic burden on the World Health Organization[78]. By 2025, the global prevalence of hypertension will increase to 20%[79]. According to whether the cause is clear, hypertension is divided into essential hypertension and secondary hypertension. When the exact cause of blood pressure rise can be found, it is called secondary hypertension. Meanwhile, when the exact cause of elevated blood pressure cannot be found, it is called essential hypertension. This type accounts for 95% of all hypertension patients[80]. Hypertension is a major risk factor for cardiovascular diseases. Although it is a major public health problem, its pathogenesis remains unclear, and its typical pathological feature is vascular remodeling[81]. Vascular remodeling is defined as a series of structural and functional abnormalities of the vascular wall caused by changes in the internal and external environment in the course of hypertension. It is primarily manifested as the thickening of the vascular wall, increased ratio of wall cavity, decreased number of tiny arteries, and induced vascular function abnormalities. VSMCs are important cells for vascular remodeling. Studies have indicated that lncRNA TUG1 is highly expressed in the aorta of spontaneously hypertensive model rats[81]. LncRNA TUG1 inhibits FGF10 expression by inhibiting miRNA-145-5P, which activates the Wnt/β-catenin signaling pathway. The activation of this pathway leads to down-regulated expression of downstream target gene *Bax*, increased expression of BCL, and increased expression of TCF/LEF, thereby inhibiting cell apoptosis and promoting the proliferation and migration of VSMCc. Another research has found that the expression of miRNA-145-5P is significantly down-regulated in the brain tissue of a model rat with hypertensive cerebral hemorrhage[38]. By targeting the 3'-untranslated region of MMP-2, miR-145-5p reduces the protein expression of MMP-2 in human brain microvascular endothelial cells, leading to the activation of the classical Wnt signaling pathway. This phenomenon promotes the expression of ZO-1 and Occludin, increases vascular permeability, alleviates brain edema, inhibits cell apoptosis, and alleviates brain tissue injury. Lowering lncRNA TUG1 can also reportedly improve atherosclerosis[82].

In Ang II-induced hypertensive models, Ang II causes increased expression of multiple Wnt ligands, which is sufficient to cause the activation of the Wnt/β-catenin signaling pathway. The outcome is the up-regulation of downstream β-MHC and α-actin genes related to ventricular hypertrophy. It also promotes the up-regulation of PAI-I and Snail I and then increases the expression of α-SMA, connexin, and collagen I, thereby promoting cardiac fibrosis[83]. Simultaneous administration of ANG II with the small-molecule compound ICG-001, which antagonizes β-catenin/TCF-mediated transcriptional activity, reduces blood pressure and inhibits hypertension-induced cardiomyocyte hypertrophy and fibrosis[84-85]. Therefore, Wnt/β-catenin may be a target for the treatment of hypertension and cardiovascular diseases caused by hypertension.

3 Conclusion

The classical Wnt/β-catenin signaling pathway plays an important role in the physiological and pathological state of the cardiovascular system. In atherosclerosis, Wnt/β-catenin is involved in pathophysiological processes, such as endothelial-cell injury, oxidative stress, inflammatory response, and atherosclerotic-plaque formation. The classical Wnt/β-catenin signaling pathway is involved in the occurrence and development of stroke by regulating the integrity of the blood-brain barrier, as well as cell proliferation, migration, and apoptosis[28, 33, 52]. Animal studies have found that activating this signaling pathway significantly improves stroke. Wnt/β-catenin regulates the proliferation and migration of SMCs and is involved in vascular remodeling, a typical pathological feature in hypertensive diseases.

Different opinions have been put forward regarding the relationship between Wnt/β-catenin and cardiovascular diseases. Most scholars believe that activating this pathway is conducive to the treatment of diseases, whereas a small number of researchers believe that antagonists inhibiting this signaling pathway are conducive to the treatment of

cardiovascular diseases. For example, Ex-4 plays an anti-inflammatory and protective role in the blood-brain barrier by activating Wnt/β-catenin signaling pathway and lncRNA NEAT1 plays an anti-inflammatory role and inhibits apoptosis by activating Wnt/β-catenin signaling pathway, shZFAS1 plays a role in cell proliferation and migration by activating Wnt/β-catenin signaling pathway to reduce the dilated tube in the infarction area[37, 72, 75]. The P53 inhibitor PFT-α protects the integrity of the blood-brain barrier by activating the Wnt/β-catenin signaling pathway[64]. GNF-6231 and tankyrase antagonists exert obvious improvement effects on cardiac injury caused by cardiovascular diseases[86-88]. Notch, TGF-β, BMP-1, and other signaling pathways can also be activated to induce cardiac response after heart damage, so the Wnt/β-catenin signaling pathway is bidirectional and complex. Although many studies have shown beneficial results in animal and cell models, the actual clinical results remain to be determined. The problems to be solved in the development of Wnt/β-catenin pathway target drugs are as follows: (1) ensure that the target drug only acts on this signaling pathway, and will not affect other signaling pathways such as Notch and TGF-β; (2) whether the drug will cause other diseases while treating cardiovascular diseases; (3) when the targeted drug is used to relieve one symptom of the disease, other symptoms are not affected. Therefore, the development of targeted drugs for Wnt/β-catenin needs to be more precise and more careful to identify targeted drugs that can achieve precise treatment.

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经典Wnt信号通路与心血管疾病*

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摘要　心血管疾病是一组累及心脏和血管的疾病，主要包括冠心病、中风等疾病。它是世界上引起死亡的主要原因之一，其发病率逐年上升。高血压是心血管疾病的主要危险因素。Wnt信号通路由一系列控制基本生物学过程的高度保守的级联事件组成。Wnt信号通路包括经典Wnt通路（或Wnt/β-catenin通路）、非经典平面细胞极性通路和非经典钙依赖通路。异常的Wnt信号通路能够引起和促进细胞增殖和分化、心脏畸形，以及各种恶性肿瘤，因此，以Wnt信号通路为靶点的药物设计具有巨大的治疗潜力。经典Wnt/β-catenin通路通过调节细胞增殖、迁移、凋亡、血脑屏障通透性、炎症、氧化应激和免疫反应等参与动脉粥样硬化、脑卒中等心血管疾病的发生发展。本文结合最新研究进展，综述Wnt/β-catenin信号通路在心血管疾病发生发展中的相关机制，希望为心血管疾病的预防和治疗提供新的思路。

关键词　Wnt/β-catenin信号通路，心血管疾病，病程
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