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Review

Wnt/β-catenin Pathway in Cardiac Hypertrophy and Arrhythmia: From Molecular Mechanisms to Therapeutic Opportunities

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Abstract

The wingless-int1/β-catenin (Wnt/β-catenin) signaling pathway plays a key role in left ventricular hypertrophy (LVH) and arrhythmias, which significantly contribute to global morbidity and mortality. Activation of Wnt/β-catenin signaling induces oxidative stress in cardiomyocytes by regulating mitochondrial function, reactive oxygen species (ROS) production, fibrosis, metabolic reprogramming, and cell death in LVH and arrhythmias. Additionally, Wnt/β-catenin signaling promotes cardiomyocyte hypertrophy and cardiac fibrosis by interacting with transforming growth factor beta (TGF-β), mitogen-activated protein kinase (MAPK), nuclear factor-kappa B (NF-κB), extracellular signal-related kinase (ERK), and other signaling pathways. In addition, activation of Wnt/β-catenin signaling can induce cardiomyocyte apoptosis by interfering with normal glucose or lipid metabolism. However, this opposing effect is evident in epicardial preadipocytes, where pathway activation may instead alleviate adipogenesis. This reflects the complexity of Wnt/β-catenin signaling in the metabolic reprogramming of cardiac cells. In this review, we discuss potential therapeutic strategies targeting the Wnt/β-catenin signaling pathway to mitigate LVH and arrhythmias.

Keywords: Wnt/β-catenin signaling pathway; cardiovascular diseases; left ventricular hypertrophy; arrhythmia; oxidative stress; fibrosis; metabolic reprogramming

1. Introduction

According to the World Health Organization, heart disease is one of the leading causes of global mortality and morbidity, accounting for approximately 17.9 million deaths annually. Heart diseases such as left ventricular hypertrophy (LVH) and arrhythmia are particularly common, which poses a significant health burden [1]. These diseases not only lead to acute illnesses such as heart attacks and strokes but also contribute to long-term complications such as heart failure (HF), placing a heavy burden on global healthcare systems. LVH is a pathological state of cardiac structural remodeling, characterized by hypertrophy and hyperplasia of the left ventricular (LV) myocardium. It typically occurs due to prolonged pressure or volume overload (such as hypertension, valve disease, or heart failure) as a compensatory response, leading to LV wall thickening, narrowing or dilation of the cavity, and eventual loss of compliance [2,3]. This pathologic change not only indicates target organ damage in patients with hypertension but is also an important risk factor for congestive heart failure (CHF), arrhythmia, and stroke [4,5]. Arrhythmia, characterized by an irregular heart rhythm due to abnormal electrical activity, usually manifests as tachycardia, bradycardia, or atrial fibrillation (AF), all of which increase the risk of stroke and CHF [6,7]. An increasing number of studies indicate that the wingless-int1 (Wnt)/β-catenin signaling pathway plays a key role in their development and progression.

The canonical Wnt/β-catenin pathway comprises four essential elements: ① Wnt proteins (ligands), ② Receptor complex, Frizzled (primary receptor), LRP5/6 (co-receptors), ③ Dishevelled (Dvl) (scaffold protein for signal transduction), ④ β-catenin (nuclear transcriptional effector). In the absence of Wnt ligands, β-catenin is phosphorylated and degraded by the "destruction complex" (Axin/APC/CK1α/GSK-3β). Upon Wnt activation, the ligand binds to the Frizzled-LRP5/6 receptor complex, leading to the recruitment of Dvl protein and the disassembly of the β-catenin destruction complex. This results in the stabiliza-

tion and nuclear accumulation of β-catenin. Subsequently, β-catenin forms a transcriptional complex with TCF/LEF factors to activate target genes [8] (Fig. 1). The Wnt/β-catenin pathway critically regulates embryonic development through cell proliferation, differentiation and migration [9,10]. Its dysregulation contributes to various diseases including cancer, stroke, myocardial infarction (MI), LVH and arrhythmias by modulating multiple cellular processes [11–14]. Aberrant activation exacerbates oxidative stress, inflammation and cell death [15,16].

Significant crosstalk exists between Wnt/β-catenin signaling and other key cellular signaling pathways, such as Notch, transforming growth factor beta (TGF-β), mitogen-activated protein kinase (MAPK), nuclear factor-kappa B (NF-κB), extracellular signal-regulated kinase (ERK), and phosphoinositide 3-kinase/Akt (PI3K/Akt), further complicating its role in regulating LVH and arrhythmia. Therefore, an in-depth study of the specific mechanisms of the Wnt/β-catenin signaling pathway in LVH and arrhythmia can help reveal its key role in disease development and provide a theoretical basis for the development of multi-target therapeutic strategies, which may open up new avenues for the precision treatment of related cardiovascular diseases.

2. Wnt/β-catenin Signaling Pathway in the Regulation of LVH

LVH is an adaptive structural change caused by prolonged pressure overload, characterized by ventricular wall thickening and changes in the ventricular cavity size [17,18]. As the condition progresses, LVH can lead to impaired cardiac function and HF [19]. The Wnt/β-catenin signaling pathway plays a critical regulatory role in the onset and progression of LVH, significantly accelerating the process through its involvement in pathological myocardial hypertrophy, fibrosis, and metabolic reprogramming [20].

2.1 Activation of the Wnt/β-catenin Signaling Pathway Promotes Cardiomyocyte Hypertrophy and Apoptosis

Moderate activation of the Wnt/β-catenin signaling pathway plays a crucial physiological protective role in cardiac repair and regeneration. In hemodialysis patients, lower serum levels of sclerostin and Dickkopf-related protein-1 (Dkk-1) are negatively correlated with LVH severity, with Dkk-1 independently predicting left ventricular mass (LVM) and LVM index (LVMI) [21]. This suggests that reduced inhibition of the Wnt/β-catenin pathway may drive cardiac remodeling, highlighting sclerostin and Dkk-1 as potential therapeutic targets. In human acute infarction tissues and rat hypertension heart tissues, activation of the Wnt/β-catenin signaling pathway triggers MAPK signaling, including extracellular signal-regulated kinase 1 and 2 (ERK1/2), c-Jun N-terminal kinase (JNK), and p38, leading to the upregulation of hypertrophic markers such as atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), nuclear factor of activated T cells 3 (NFATc3), and phosphorylated GATA-binding protein 4 (GATA4), thereby promoting cardiomyocyte hypertrophy and pathological remodeling, which may ultimately result in LVH [22]. In non-ischemic transmural samples from failing human left ventricles, increased expression of the Wnt signaling antagonists secreted frizzled-related protein (sFRP) 3 and 4 (sFRP3 and sFRP4) suppresses the Wnt/β-catenin pathway, accompanied by an elevated Fas/FasExo6Del ratio and downregulation of bcl-xL expression, promoting a proapoptotic cardiomyocyte phenotype. These changes may drive cardiac remodeling and compensatory hypertrophy, ultimately contributing to the development and progression of LVH [23]. In Angiotensin II (Ang II)-induced ventricular hypertrophy models in mice and rats, downregulation of protein arginine methyltransferase 7 (PRMT7) activates the Wnt/β-catenin pathway, leading to upregulation of hypertrophic markers such as atrial natriuretic peptide (*ANP*), brain natriuretic peptide (*BNP*), and collagen type I alpha 1 chain (*COL1A1*), thereby promoting cardiomyocyte hypertrophy and collagen deposition [24]. Such activation contributes to adaptive changes in LVH and cardiac function, highlighting the protective role of this pathway under stress conditions.

However, excessive activation of this pathway can trigger pathological myocardial hypertrophy, cardiac remodeling, and HF development. In Ang II-induced neonatal rat cardiomyocytes and C57BL/6J mouse models, increased expression of methyltransferase-like 3 (METTL3) enhances m6A methylation, promoting pri-miR-221/222 expression, and activates the Wnt/β-catenin signaling pathway by inhibiting Dickkopf2 (DKK2), thereby promoting myocardial hypertrophy [25]. In the mouse LVH model induced by transverse aortic constriction (TAC), Wnt/β-catenin signaling is activated, upregulating nuclear factor-kappa B (NF-κB), β-myosin heavy chain (β-MHC), TNF-α, fibronectin (FN), and collagen type I (Col I), leading to cardiomyocyte hypertrophy and fibrosis. As the disease progresses, it further upregulates angiotensin-converting enzyme (ACE), renin, and Ang II type 1 receptor (AT1), activates the renin–angiotensin–aldosterone system (RAAS), induces myocardial cell apoptosis, and exacerbates LVH [26].

Integrin beta-like 1 (ITGBL1) is an extracellular matrix protein associated with β-integrins that can activate the Wnt/β-catenin signaling pathway [27,28]. In TAC-induced mice, elevated ITGBL1 activates Wnt/β-catenin signaling, mediating fibroblast–cardiomyocyte crosstalk. In cardiomyocytes, this pathway upregulates β-MHC and FN, promoting hypertrophy, while in fibroblasts, it enhances TGF-β expression and interacts with the TGF-β/Smad2/3 pathway, accelerating collagen deposition and fibrosis [29]. In the isoproterenol (ISO)-induced mouse model of myocardial hypertrophy, the activation of the Wnt/β-catenin signaling pathway promotes hypertrophy by upregulating cell cycle related protein (Cyclin D1) and c-

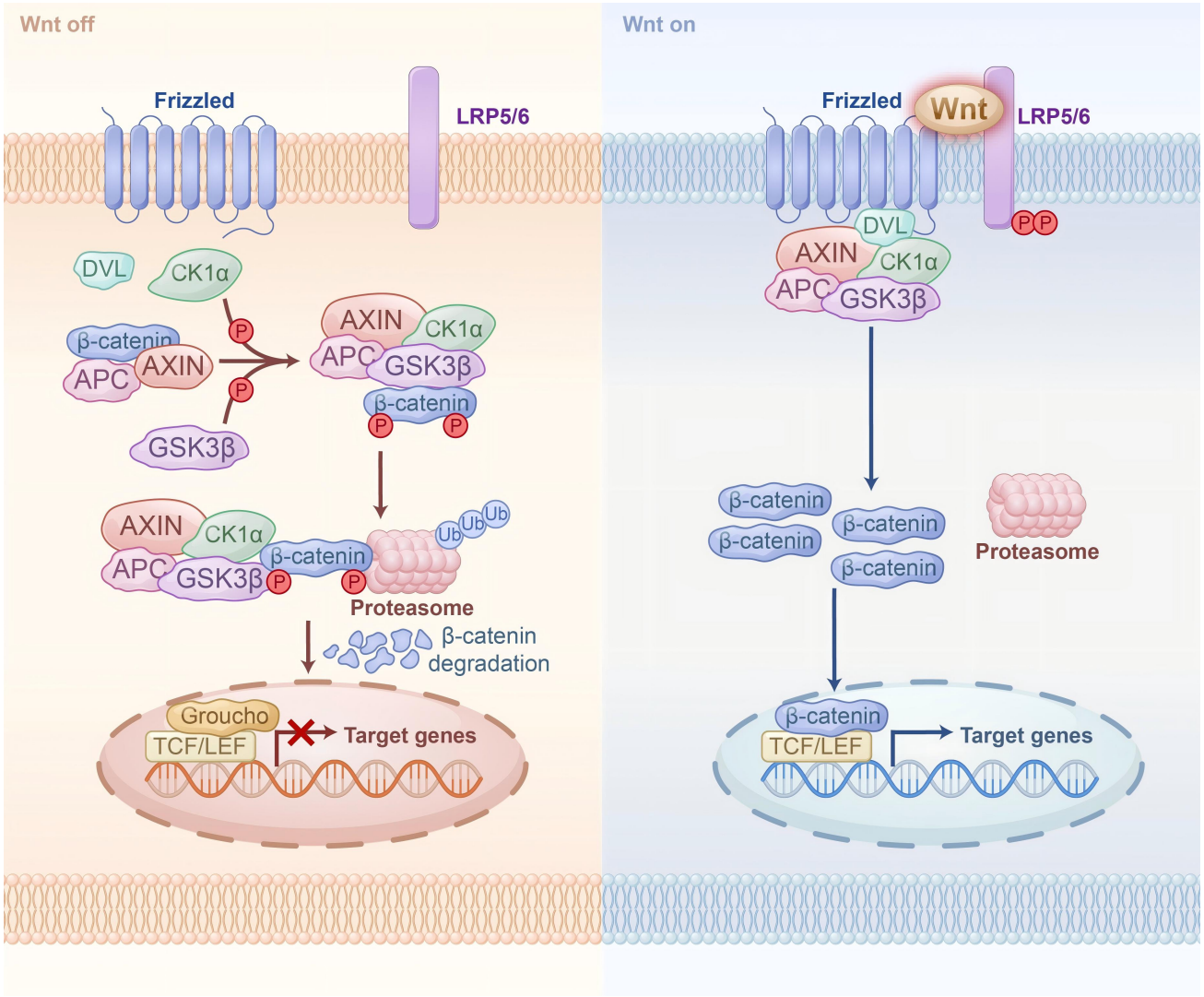

Fig. 1. Wnt/β-catenin signaling pathway. (Left) In the absence of Wnt ligands, β-catenin binds to AXIN and APC and is phosphorylated by GSK-3β and CK1α. Once the complex is formed, phosphorylated β-catenin binds to the Proteasome and is degraded, and gene transcription cannot be interrupted in the nucleus. (Right) In the present of Wnt ligands. Upon binding of Wnt ligands to LRP5/6 and Frizzled ligands, LRP5/6 phosphorylates and recruits Dvl proteins to the plasma membrane. Subsequently, Dvl recruits the destruction complex simultaneously to the cell membrane, and β-catenin dissociates in the cytoplasm and enters the nucleus, where it binds to the TCF/LEF complex and initiates gene transcription. Dvl, dishevelled; APC, adenomatous polyposis coli protein; CK1α, casein kinase 1α; GSK-3β, glycogen synthase kinase 3β; TCF, T cell factor; LEF, lymphocyte enhancer factor-1.

Myc. Concurrently, sodium/calcium exchanger-1 (NCX1) overexpression triggers Ca^{2+} overload, activating calcium–calmodulin-dependent protein kinase II (CaMKII) and calcineurin (CaN), which induces apoptosis and activates MAPK signaling via the nuclear factor of activated T-cells (NFAT)/ETS transcription factor 2 (ETS2) complex, exacerbating hypertrophy and remodeling [30,31]. Collectively, these findings highlight the dual role of Wnt/β-catenin signaling in cardiac physiology and pathology. The differences in experimental models and activation levels are likely the key factors underlying the inconsistent findings regarding the role of this pathway in cardiac function observed in previous studies.

2.2 Activation of the Wnt/β-catenin Signaling Pathway Promotes Fibroblast Fibrosis

Myocardial fibrosis (MF) is one of the main histological features of LVH and often leads to severe cardiac insufficiency [32,33]. The Wnt/β-catenin signaling pathway participates in regulating the pathological process of LVH through crosstalk with other signaling pathways such as NF-κB, TGF-β, and ERK, playing a crucial role, particularly in fibroblast-mediated fibrosis.

The synergistic interaction between Wnt/β-catenin and TGF-β signaling significantly exacerbates MF. In patients with chronic kidney disease (CKD), elevated levels of TGF-β1 suppress the cardiac expression of endogenous

Klotho, leading to activation of the Wnt/β-catenin signaling pathway. This, in turn, upregulates the expression of profibrotic markers such as fibronectin, type I collagen, PAI-1, and MMP-2/9, thereby promoting cardiac fibroblast-mediated fibrosis [34]. In TGF-β-stimulated human cardiac fibroblasts, activation of the Wnt/β-catenin signaling pathway is enhanced synergistically by exogenous WNT3a and the GSK-3β inhibitor CHIR99021, leading to increased interleukin (IL)-11 production and secretion. Concurrently, TGF-β promotes phosphorylation of TGF-β-activated kinase 1 (TAK1), which further stimulates IL-11 expression and upregulates fibrosis-related genes such as *COL1A1* and *FN1*, thereby accelerating fibroblast activation, cardiac fibrosis, and contributing to the progression of LVH [35]. In an acute myocardial infarction (AMI) rat model, Wnt2 and Wnt4 activate β-catenin by interacting with Fzd2/4 and LRP6, further activating the NF-κB signaling pathway, which upregulates fibrosis-related genes such as *COL1A1* and *FN1*, ultimately worsening cardiac fibrosis and cardiac dysfunction [36]. sFRPs, by antagonizing the Wnt/β-catenin pathway, inhibit fibroblast activation and collagen synthesis, thus slowing the progression of cardiac fibrosis [37]. In sFRP1 knockout mice, the excessive activation of the Wnt/β-catenin pathway promotes fibroblast proliferation, alpha-smooth muscle actin (α-SMA) expression, and collagen synthesis, ultimately leading to MF and LVH [38]. In a type 1 diabetes mellitus rat model induced by streptozotocin, NF-κB cooperates with the Wnt/β-catenin/GSK-3β pathway to activate the expression of pro-inflammatory cytokines tumor necrosis factor (TNF)-α and IL-2, thereby inducing myocardial hypertrophy and interstitial fibrosis [39]. In an ISO-induced MF rat model, activation of the Wnt/β-catenin pathway upregulates β-catenin, c-Myc, and Cyclin D1 expression, enhancing fibroblast proliferation and differentiation, thereby exacerbating MF and cardiac dysfunction [40]. In a high-fat diet-induced hyperlipidemia mouse model, obesity-induced hypertrophy activates the TGF-β/Wnt/β-catenin pathway, promoting α-SMA and TGF-β expression and inducing MF. Additionally, the activation of mast cells induced by obesity leads to elevated expression of serine proteases, such as tryptase and chymase, which are closely associated with cardiac fibrosis primarily by indirectly activating the TGF-β and Wnt/β-catenin signaling pathways, thereby promoting cardiac collagen deposition and myocardial fibrosis, resulting in cardiac dysfunction [41].

2.3 Activation of the Wnt/β-catenin Signaling Pathway Promotes Metabolic Reprogramming

The activation of the Wnt/β-catenin signaling pathway contributes to the development of LVH by modulating mitochondrial dynamics, lipid metabolism, glucose metabolism, and other aspects of metabolic reprogramming.

In spontaneously hypertensive rats, Wnt/β-catenin activation enhances sterol regulatory element-binding protein 1 (SREBP1), upregulates fatty acid (FA) synthesis genes (e.g., stearoyl-CoA desaturase 1 (SCD1) and acetyl-CoA carboxylase (ACC)), reduces FA transport proteins (CD36, FATP1), suppresses AMP-activated protein kinase (AMPK) and carnitine palmitoyltransferase 1 (CPT1), thereby promoting FA accumulation and impairing β-oxidation, contributing to left ventricular hypertrophy LVH [42]. In a β-catenin haploinsufficient (WT/CKO) mouse model, suppression of the Wnt/β-catenin signaling pathway reduces adipose triglyceride lipase (ATGL) and hormone-sensitive lipase (HSL) activity, leading to triglyceride (TAG) accumulation and limited fatty acid β-oxidation. Meanwhile, upregulation of glucose transporter 4 (GLUT4) and downregulation of pyruvate dehydrogenase kinase 1 (PDK1) enhance glucose utilization, elevate the NADH/NAD^+ ratio, and impair oxidative phosphorylation (OXPHOS) complex I, disrupting mitochondrial metabolism [43]. These *de novo* metabolic disturbances occur in the absence of spontaneous LVH, but directly blunt physiological cardiomyocyte growth and limit training-induced adaptive cardiac hypertrophy. This finding suggests that while Wnt/β-catenin activation is known to promote pathological cardiac remodeling, its suppression may conversely constrain the heart's adaptive growth capacity under physiological conditions and potentially restrain pathological remodeling under stress, thus affecting LVH development. In the volume overload-induced HF model, elevated TNF-α and IL-6 activate Wnt/β-catenin signaling, downregulating proliferator-activated receptor alpha (PPARα) and PPAR-gamma coactivator 1 alpha (PGC-1α), reducing CPT1B and ACADM expression, impairing FA oxidation. Simultaneously, upregulation of c-Myc enhances the activity of glycolytic enzymes hexokinase 2 (HK2) and 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3, disturbing the glucose and lipid metabolism. Furthermore, Wnt/β-catenin signaling activates the mammalian target of rapamycin (mTOR) pathway, inhibits mitophagy, promotes reactive oxygen species (ROS) production, and aggravates metabolic dysfunction and cardiomyocyte apoptosis, ultimately leading to energy imbalance and worsening cardiac function [44–46]. In hypoxia/reoxygenation rats, upregulated miR-423-5p inhibits Myb-related protein B (MYBL2), activates Wnt/β-catenin signaling, enhances caspase 3/7 activity and Bax/cleaved caspase-3 (c-casp-3) expression, while promoting Drp1-mediated mitochondrial fission, causing mitochondrial membrane potential (MMP) loss, ROS overproduction, ATP suppression, and cardiomyocyte apoptosis [47]. Therefore, Drp1 acetylation may be an early key event in LVH. In TAC-induced heart–kidney syndrome type 2 mice, Wnt/β-catenin activation inhibits antioxidant enzymes superoxide dismutase (SOD) and catalase, and activates NADPH oxidase (NOX), causing ROS accumulation,

cytochrome C release, and apoptosis. ROS suppress Bcl-2/Bcl-xL and activate Bax/Bad, aggravating mitochondrial permeability transition and promoting cardiomyocyte apoptosis [26].

The evidence suggests that activation of the Wnt/β-catenin signaling pathway contributes to ventricular hypertrophy by upregulating hypertrophy-related genes and exacerbating pathological myocardial hypertrophy through crosstalk with the MAPK and NF-κB pathways. This pathway also promotes fibrosis through interaction with TGF-β signaling, with GSK-3β acting as a key regulator (Fig. 2). Moreover, it drives metabolic reprogramming, regulating lipid and glucose metabolism as well as mitochondrial function, all of which contribute to cardiac hypertrophy and functional impairment (Fig. 3).

3. Wnt/β-catenin Signaling Pathway in the Regulation of Arrhythmia

Arrhythmias are cardiac autonomic disorders caused by abnormal electrical activity and conduction disorders of cardiomyocytes, typically manifesting as ectopic beats and impulse reentry. The most common types include AF, atrial flutter, and ventricular fibrillation [7,48]. Acute or chronic myocardial injury often leads to electrical remodeling of the heart, myocardial hypertrophy, and fibrosis. These pathological changes can interfere with the normal conduction of cardiac electrical signals and induce arrhythmia [7]. Common symptoms include sinus arrest, sinus block, bradycardia, and, in severe cases, sudden death [48,49]. The Wnt/β-catenin signaling pathway plays an important regulatory role in the occurrence and development of arrhythmia, affecting the electrical activity stability of the heart by regulating oxidative stress, atrial fibrosis, and metabolic reprogramming.

3.1 Activation of the Wnt/β-catenin Signaling Pathway Promotes Oxidative Stress

Abnormal activation of Wnt/β-catenin signaling can promote ROS production. It has been demonstrated that in the peripheral plasma of patients with persistent AF, BNP expression and the content of Diacron-reactive oxygen metabolite (dROM) are increased, and the heart undergoes oxidative stress [50]. Meanwhile, activation of Wnt/β-catenin signaling pathway and increased protein expression of ANP and BNP were found in human cardiomyocytes treated with ISO *in vitro* [51]. Therefore, the activation of Wnt/β-catenin signaling pathway in cardiac myocytes induces oxidative stress by up-regulating the expression of BNP protein, leading to the occurrence of AF. In AngII-treated rat atrial tissue, SIRT3 protein sulfhydrylation was inhibited, Wnt/β-catenin signaling pathway was activated, ROS production was increased, MDA expression was increased, while GSH and SOD expressions were decreased, leading to atrial oxidative stress [52]. Additionally, Wnt and TGF-β signaling pathways contribute to oxidative stress in alcohol-treated human pluripotent stem cell-derived cardiomyocytes, increasing susceptibility to AF [53].

3.2 Activation of the Wnt/β-catenin Signaling Pathway Promotes Cardiac Fibrosis

Cardiac fibrosis is an important pathological process of arrhythmia [54]. Previous studies have demonstrated that depolarization of fibroblasts in cardiac scar tissue can induce arrhythmias through electrical coupling between fibroblasts and cardiomyocytes [55,56]. Activation of the Wnt/β-catenin pathway is associated with increased expression of cardiac fibrosis genes [32,57]. During fibrosis, activation of cardiac fibroblasts promotes excessive deposition of the extracellular matrix (ECM) and ECM proteins (mainly col I and col III) [58,59]. The Wnt/β-catenin signaling pathway promotes AF generation by interacting with miRNA molecules or TGF-β, FRAT, and other signaling pathways.

Dvl-associated antagonist of β-catenin 2 (DACT2) expression is decreased in the right atrial cardiomyocytes of patients with AF. *In vitro*, Loss of *DACT2* resulted in the accumulation of β-catenin in HL-1 cells and the activation of TGF-β in fibroblasts. This cascade resulted in electrical remodeling of HL-1 cells, as well as increased deposition of col I and col III in fibroblasts, ultimately contributing to fibrosis. These changes induce AF [60]. This suggests that DACT2 can regulate the electrical-structural remodeling between fibroblasts and cardiomyocytes by regulating the Wnt/β-catenin and TGF-β signaling pathways and induce AF [61]. Snail1 is a key marker in epithelial-mesenchymal transition (EMT) and participates in the formation process of cardiac fibrosis [62]. A study has found that the canonical Wnt signaling pathway is activated in the myocardium of AF patients, which leads to the up-regulation of Snail1 protein level in endothelial cells, induces the expansion of cardiomyocytes and the increase of collagen tissue, and atrial fibrosis induces the occurrence of AF [63]. The expression of miR-124-3p was increased in plasma exosomes extracted from patients with AF. Notably, co-culture of these exosomes with rat fibroblasts revealed that upregulated miR-124-3p inhibited *Axin1* expression, activated the downstream Wnt/β-catenin pathway, and stimulated α-SMA expression, promoting fibroblast proliferation [64]. In the rat AF model induced by acetylcholine–$CaCl_2$, miR-27b-3p expression in the left atrium was downregulated, leading to Wnt/β-catenin pathway activation and significant upregulation of TGF-β1 and fibrotic markers Col I, Col III, and a-SMA. Furthermore, increased atrial fibrosis and decreased connexin43 (CX43) expression interfere with the electrical coupling between cardiomyocytes and promote the occurrence of AF [65]. In the same model, reported the increased expression of monocyte chemotactic protein-induced protein 1 (MCPIP1) in cardiomyocytes and decreased expression of miR-26p-5a, which activated

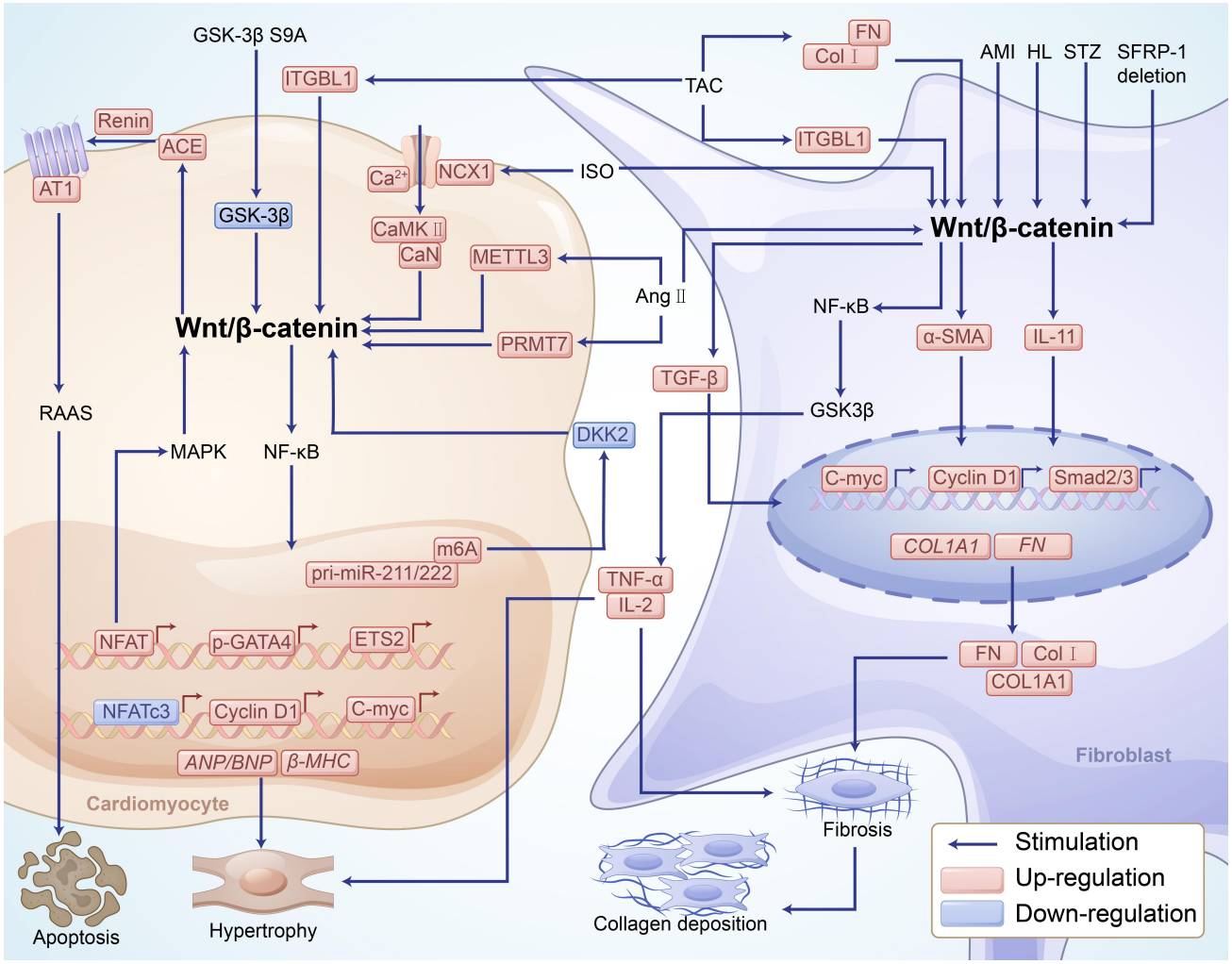

Fig. 2. Activation of the Wnt/β-catenin signaling pathway influences cardiomyocyte hypertrophy and fibroblast fibrosis through various mechanisms, thereby promoting the development of LVH. Activation of the Wnt/β-catenin signaling pathway in both cardiomyocytes and fibroblasts collectively promotes the progression of LVH. In cardiomyocytes, this pathway upregulates transcription factors such as NFAT, p-GATA4, c-Myc, NFATc3, and Cyclin D1, which promote the expression of hypertrophic markers including *ANP/BNP* and *β-MHC*, inducing myocardial hypertrophy and apoptosis. GSK-3β S9A, TAC, ISO, and Ang II activate the Wnt/β-catenin signaling pathway by inhibiting GSK-3β, METTL3, and DKK2 while upregulating NCX1, PRMT7, ITGBL1, ACE, renin, and AT1. Additionally, crosstalk between this pathway and the MAPK and NF-κB signaling pathways further amplifies the pathological process. Meanwhile, RAAS activation exacerbates cardiomyocyte apoptosis, ultimately leading to cardiac dysfunction. In fibroblasts, the Wnt/β-catenin signaling pathway interacts with the TGF-β-Smad2/3 and NF-κB pathways, upregulating the expression of α-SMA, IL-11, COL1A1, and FN1, thereby promoting interstitial fibrosis and collagen deposition. Additionally, this pathway enhances fibroblast proliferation and fibrosis through *Snail*/*Twist*-mediated endothelial-to-mesenchymal transition. Ang II, ITGBL1, and ISO activate the Wnt/β-catenin pathway in both cardiomyocytes and fibroblasts, whereas fibroblast-secreted TGF-β further amplifies myocardial hypertrophy and fibrosis. Meanwhile, NF-κB signaling is activated, increasing the production of pro-inflammatory cytokines such as TNF-α and IL-2, which promote chronic inflammation and exacerbate the progression of LVH. PRMT7, protein arginine methyltransferase 7; ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide; COL1A1, collagen type I alpha 1; METTL3, methyltransferase-like 3; m6A, N6-methyladenosine; DKK2, Dickkopf2; NF-κB, nuclear factor kappa B; β-MHC, beta-myosin heavy chain; ITGBL1, integrin beta-like 1; TGF-β, transforming growth factor beta; Smad2/3, smad family member 2/3; FN, fibronectin; ISO, isoproterenol; Cyclin D1, cell cycle-related protein D1; c-Myc, cellular Myc; NCX1, sodium/calcium exchanger 1; CaMKII, calcium–calmodulin-dependent protein kinase II; CaN, calcineurin; TAK1, TGF-β-activated kinase 1; sFRP, secreted frizzled related protein; α-SMA, alpha-smooth muscle actin; TNF-α, tumor necrosis factor alpha; IL-2, interleukin 2; T1DM, type 1 diabetes mellitus; STZ, streptozotocin; GSK-3β, glycogen synthase kinase 3 beta.

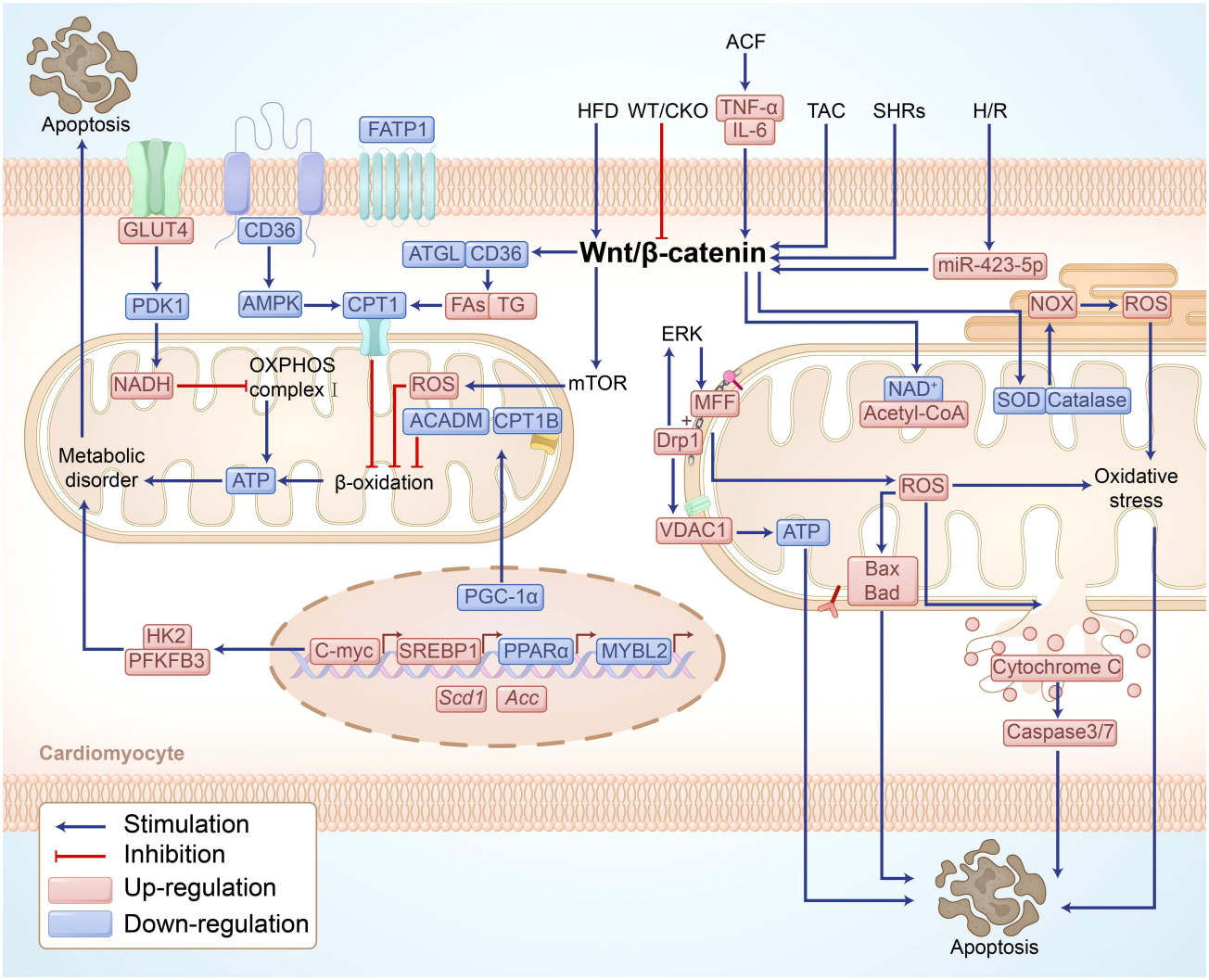

Fig. 3. Activation of the Wnt/β-catenin signaling pathway induces cardiomyocyte apoptosis and promotes the development of LVH by regulating mitochondrial dynamics, lipid metabolism, and glucose metabolism. Activation of the Wnt/β-catenin signaling pathway reprograms cardiac metabolism by regulating metabolic transcription factors (SREBP1, c-Myc, PPARα, PGC-1α, and MYBL2), promoting FA synthesis, such as *Scd1* and *Acc*, while suppressing FA oxidation, including CPT1B and ACADM. Simultaneously, it downregulates the expression of FA transport proteins (CD36, FATP1) and lipolytic enzymes (ATGL, HSL), leading to lipid accumulation, metabolic imbalance, and ultimately, cardiomyocyte apoptosis. In glucose metabolism, upregulation of GLUT4 and downregulation of PDK1 enhance pyruvate oxidation, increasing the NADH/NAD^+ ratio, thereby inhibiting OXPHOS complex I function and impairing mitochondrial metabolism. Lipid overload induces DRP1 acetylation and promotes its phosphorylation via ERK signaling, strengthening interactions with MFF and VDAC1, thereby driving mitochondrial fission, reducing ATP synthesis, and increasing oxidative stress. Additionally, Wnt/β-catenin signaling exacerbates ROS accumulation by inhibiting antioxidant enzymes (SOD, catalase) and activating NOX, triggering the caspase 3/7 cascade and upregulating pro-apoptotic proteins Bax and Bad, ultimately leading to cardiomyocyte apoptosis and contributing to LVH progression. LVH, left ventricular hypertrophy; Wnt/β-catenin, Wnt/β-catenin signaling pathway; SREBP1, sterol regulatory element-binding protein 1; c-Myc, cellular myelocytomatosis; PPARα, peroxisome proliferator-activated receptor alpha; MYBL2, Myb-related protein B; *Scd1*, stearoyl-CoA desaturase 1; *Acc*, acetyl-CoA carboxylase; FATP1, fatty acid transport protein 1; AMPK, AMP-activated protein kinase; CPT1, carnitine palmitoyltransferase 1; GLUT4, glucose transporter 4; PDK1, pyruvate dehydrogenase kinase 1; OXPHOS, oxidative phosphorylation; Drp1, dynamin-related protein 1; MFF, mitochondrial fission factor; VDAC1, voltage-dependent anion channel 1; SOD, superoxide dismutase; NOX, NADPH oxidase; complex I, oxidative phosphorylation complex I; TG, triglyceride.

the FRAT/Wnt/β-catenin signaling pathway, leading to MF [66]. In mouse cardiomyocytes with acute MI, LIM kinase 2 (LIMK2) expression is significantly increased, promoting fibroblast proliferation and activation and ventricular

remodeling through activation of the Wnt/β-catenin signaling pathway, thereby increasing susceptibility to AF [67]. Additionally, in TAC-treated mouse hearts, the activation of TGF-β signaling pathway promoted the activation of Wnt/β-catenin signaling pathway and cell activation in fibroblasts, increased collagen expression, induced cardiac fibrosis [68].

3.3 Activation of the Wnt/β-catenin Signaling Pathway Regulate Metabolic Reprogramming

Abnormal activation of Wnt/β-catenin signaling significantly impacts arrhythmias through mitochondrial dysfunction [69]. In the atrial tissue of rats treated with AngII, the sulfhydryl modification of SIRT3 protein was inhibited, the Wnt/β-catenin signaling pathway was activated, the expression of SLC7A11 and GPX4 decreased, and ferroptosis occurred in the cells, which increased the expression of fibrosis markers, and incuring atrial fibrosis [52]. At the same time, in the alcohol-treated atrial tissue of mice, decreased SIRT3 inhibited AMPK-PGC-1α signaling, up-regulated DRP1 expression, and down-regulated MFN2 and MFN1 expression, leading to atrial fibrosis [70]. These results suggest that Wnt/β-catenin signaling pathway can cross-talk with AMPK-PGC-1α signaling pathway to regulate mitochondrial homeostasis in atrial tissue. In ISO-treated mouse cardiac fibroblasts, hypermethylation of the sFRP3 promoter leads to a significant reduction in its expression, which activates Wnt/β-catenin signaling, accompanied by increased DRP1 expression and enhanced mitochondrial fission and migration [71]. The activation of the Wnt/β-catenin signaling pathway may also be involved in AF occurrence by regulating the abnormal expression of proteins related to the mitophagy pathway. In rat myocardial fibroblasts treated with ISO, the decreased expression of sirtuin 1 (Sirt1) and increased phosphorylation of forkhead box O-3a (FOXO3a) and NF-κB activates the Wnt/β-catenin signaling pathway, leading to cell fibrosis [72]. In Ang II-treated mouse fibroblasts, FOXO3a expression was upregulated, PTEN-induced putative kinase 1 (PINK) and parkin expression was increased, p62 expression was decreased, mitophagy was increased, and MMP was decreased, promoting fibroblast proliferation and increasing α-SMA, col I, and III expression, thereby elevating AF susceptibility [73]. The Wnt/β-catenin signaling pathway can activate the P38 MAPK signaling pathway, inducing the occurrence of myocardial fibrosis [74]. Meanwhile, in Ang-II-treated atrial myocytes of AF rats, it was found that MAPK14 expression was significantly increased, ROS production was elevated, Parkin protein expression was upregulated, P62 expression was significantly reduced, mitochondrial quantity decreased, vacuolation increased, mitophagy was excessively activated, Bcl2 expression was significantly decreased, and apoptosis occurred, leading to atrial fibrosis and AF [75]. Therefore, the activation of the Wnt/β-catenin signaling pathway may induce excessive mitophagy by activating the MAPK signaling pathway, thereby promoting AF. In addition, disturbance of lipid metabolism in the atrial muscle is involved in the occurrence of AF [76]. The activation of the Wnt/β-catenin signaling pathway can promote the expression of PGC-1α [77]. In high-fat diet (HFD)-treated mouse cardiomyocytes, AMPK phosphorylation is inhibited, whereas PGC-1α, ANP, and β-MHC expression are upregulated, leading to cardiomyocyte hypertrophy and increased AF susceptibility [78,79]. Although the activation of Wnt/β-catenin signaling in myocardium and fibroblasts can cause adverse effects, in epicardial cells, the activation of this signaling pathway may reduce the adipogenic process of epicardial cells. In boron-treated mouse preadipocytes, the Wnt/β-catenin signaling pathway was activated, adipogenic-related gene expression *Cebp*α, *Ppar*γ, and fatty acid-binding protein 4 (*Fabp4*) expression was downregulated, and adipogenesis was inhibited [80]. In the epicardial preadipocytes of patients undergoing cardiac surgery, significantly increased sodium-glucose cotransporter 2 (SGLT2) expression and upregulated expression of FABP4 promote adipogenesis and ROS production in cardiomyocytes, inducing AF. In the HFD-induced mice heart, ANP secreted by cardiomyocytes inhibits the Wnt/β-catenin signaling pathway, thereby inducing epicardial cell transformation into adipocytes through epithelial–mesenchymal transition and fat secretion, inducing AF [81].

The evidence suggests that activation of the Wnt/β-catenin signaling pathway plays a crucial role in the development of AF by promoting processes such as oxidative stress and fibrosis in myocardial tissue. This is achieved through the increase in ROS and MDA levels, as well as interactions with other key pathways like TGF-β and FRAT. The Wnt/β-catenin pathway has a dual role in metabolic reprogramming: in myocardial cells and fibroblasts, its activation contributes to MF and oxidative damage in myocardial cells and fibroblasts, but inhibits adipogenesis in epicardial preadipocytes, highlighting the complexity of its role in arrhythmogenesis. This multifaceted involvement in AF is summarized in Fig. 4.

4. Therapeutic Strategies Targeting Wnt/β-catenin Signaling in LVH and Arrhythmia

Accumulating evidence highlights the involvement of Wnt/β-catenin signaling in the pathological progression of LVH and arrhythmias. A range of molecular interventions—including small-molecule inhibitors, gene therapies, and bioactive natural compounds—have demonstrated the ability to modulate this pathway effectively, offering promising therapeutic avenues for the management of these cardiac conditions.

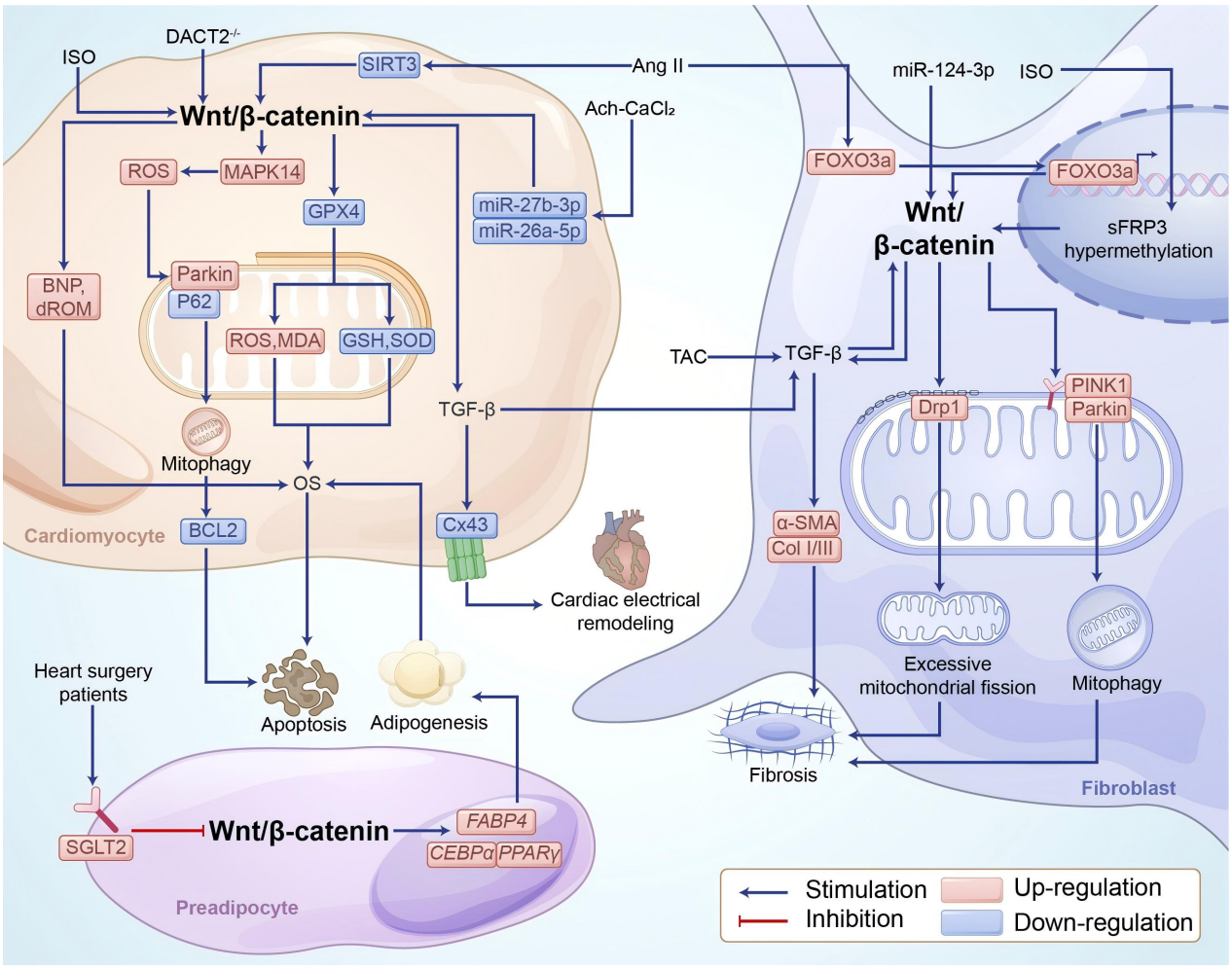

Fig. 4. Mechanisms of Wnt/β-catenin in regulating AF. In cardiomyocytes, ISO can activate Wnt/β-catenin signaling directly, promote the expression of BNP and dROM, ultimately induce OS. At the same time, Ang-II activates Wnt/β-catenin signaling pathway by reducing the expression of SIRT3, thereby decreases the expression of GPX4 and increases the expression level of MAPK protein. On the one hand, it promotes the production of ROS and the expression of MDA, and reduces the expression levels of GSH and SOD, leading to oxidative stress. On the other hand, up-regulation of Parkin and down-regulation of P62 expression could promote mitophagy, reduce the level of BCL2, and eventually lead to cell apoptosis. Absence of DACT2 and Ach–$CaCl_2$ can activate the Wnt/β-catenin signaling pathway directly or indirectly by decreasing the expression of miR-26p-5a and miR-27b-3p, induces the increase of TGF-β. Meanwhile, it decreases CX43 expression and induces cardiac electrical remodeling. Furthermore, it promotes the activation of the TGF-β signaling pathway in fibroblasts. In fibroblasts, TAC, increased miR-124-3p expression, ISO-induced hypermethylation of SFRP3, and Ang-II-induced increase in FOXO3a expression all promote the activation of Wnt/β-catenin signaling. This, in turn, directly promotes TGF-β signaling and induces upregulation of fibrosis-related proteins (α-SMA and Col-I/III). Meanwhile, by promoting the expression of PINK1, parkin, and Drp1, it promotes mitophagy and excessive mitochondrial fission, inducing fibrosis. Moreover, in preadipocytes, SGLT2 expression inhibits the Wnt/β-catenin signaling pathway, increases the gene expression of *PPAR*γ, *CEBP*α, and *FABP4*, and promotes adipogenesis, finally inducing OS in cardiomyocytes. OS, oxidative stress; ISO, isoproterenol; DACT2, dishevelled-associated antagonist of beta-catenin homolog 2; SIRT3, Sirtuin 3; MAPK, mitogen-activated protein kinase; BCL2, B cell lymphoma 2; GPX4, glutathione peroxidase 4; GSH, glutathione; SOD, superoxide dismutase; ROS, reactive oxygen species; MDA, malondialdehyde; Ach–$CaCl_2$, acetylcholine–$CaCl_2$; Ang II, angiotensin II; TGF-β, transforming growth factor-beta; α-SMA, alpha-smooth muscle actin; COL I/III, collagen I/III; CX43, connexin 43; SGLT2, sodium-glucose cotransporter 2; FABP4, fatty acid binding protein 4; TAC, transverse aortic constriction; FOXO3a, forkhead box O-3a; sFRP3, secreted frizzled-related protein 3; PINK1, PTEN-induced putative kinase 1.

4.1 Targeting of Wnt/β-catenin Signaling in LVH

Pharmacological and molecular targeting of the Wnt/β-catenin pathway has demonstrated significant potential in alleviating myocardial hypertrophy, fibrosis, and cardiac remodeling. Given that ventricular remodeling—including hypertrophy, fibrosis, and structural alterations—

is central to LVH progression, modulating these processes represents a promising therapeutic strategy.

In TAC and phenylephrine-induced LVH models, the long non-coding RNA taurine up-regulated gene 1 (TUG1) suppresses miR-34a, upregulating Dickkopf proteins and thereby inhibiting Wnt/β-catenin signaling, leading to reduced expression of hypertrophy-associated genes [82,83]. Similarly, overexpression of sFRP2 attenuates pressure overload-induced LVH by inhibiting active β-catenin, reducing fibrosis and apoptosis [84]. Targeting upstream regulators, the porcupine inhibitor CGX1321 downregulates Wnt/β-catenin target genes (Fzd2, Cyclin D1, c-Myc) in TAC-induced LVH models, while concurrently inhibiting non-canonical pathways (NFATc3 and c-Jun), thus exerting dual anti-hypertrophic and anti-fibrotic effects [85,86]. The small-molecule compound Cardiomogen 1 (CDMG1) selectively inhibits Wnt/β-catenin signaling, promoting cardiac progenitor cell formation, cardiomyocyte differentiation, and cardiac regeneration in zebrafish models [10,87]. In embryonic stem cell models, CDMG1 exerts concentration-dependent effects on cardiac lineage commitment, while minimizing off-target developmental interference [10]. Collectively, these findings highlight the therapeutic promise of Wnt/β-catenin pathway modulators in treating pathological cardiac remodeling through multilevel regulation of hypertrophy, fibrosis, and regenerative capacity.

In addition to directly inhibiting hypertrophic responses, Wnt/β-catenin pathway inhibition also ameliorates cardiac fibrosis associated with LVH. In an ISO-induced myocardial fibrosis rat model, triptolide suppresses Wnt/β-catenin activation, resulting in decreased expression of fibrosis markers such as Col I and α-SMA, thereby alleviating myocardial fibrosis and improving LV function [40]. In zebrafish heart injury models, activation of Notch signaling, suppresses Wnt/β-catenin signaling by promoting the expression of Wnt antagonists Wif1 and Notum1b, enhances cardiomyocyte proliferation, inhibits fibrosis, and facilitates cardiac regeneration, ultimately counteracting hypertrophy and apoptosis [88]. Similarly, in Ang II-induced LVH mouse models and H9c2 cardiomyocytes, nuclear protein localization protein 4 (NPLOC4) suppresses the β-catenin/GSK-3β axis, enhances mitochondrial dynamics and mitophagy through ERO1α-mediated modulation of mitochondria-associated membranes (MAMs), thus alleviating cardiac hypertrophy and fibrosis [89].

Wnt/β-catenin pathway inhibition also contributes to improved metabolic remodeling. Overexpression of secreted frizzled-related protein 5 (sFRP5) in MI models inhibits Wnt/β-catenin signaling, activates AMPK by enhancing GSK-3β phosphorylation, promotes mitochondrial fusion (upregulating MFN1, MFN2) while reducing fission markers (p-Drp1, Mid49, MFF), ultimately improving mitochondrial integrity, decreasing oxidative stress, and mitigating left ventricular remodeling [90].

4.2 Targeting Wnt/β-catenin Signaling in Arrhythmias

Pharmacological modulation of the Wnt/β-catenin signaling pathway shows therapeutic potential in mitigating oxidative stress, fibrosis, and cardiomyocyte apoptosis, as well as improving cardiac dysfunction linked to arrhythmias. Treating healthy individuals deprived of sleep for 48 hours with statins can inhibit the Wnt/β-catenin signaling pathway by suppressing endoplasmic reticulum stress in myocardial cells, reduce the expression of MDA, inhibit oxidative stress, and lower the incidence of arrhythmia [91,92]. Additionally, in a sunitinib-induced myocardial fibrosis rat model, sacubitril/valsartan regulates the antioxidant system thioredoxin-interacting protein (TXNIP)/thioredoxin (TRX) and inhibits the Wnt/β-catenin/SOX9 signaling axis, thereby alleviating oxidative stress and reducing the incidence of AF [16,93].

Targeting Wnt signaling pathways or their associated proteins has been shown to reduce atrial fibrosis in arrhythmic conditions. For instance, miR-27b-3p overexpression in AF rats inhibits the Wnt/β-catenin pathway, downregulates fibrosis markers Col I, Col III, and CX43, and reduces atrial fibrosis [65]. Angiotensin receptor blockers (ARBs) also mitigate atrial fibrosis in AF rats, prolong the effective atrial refractory period, and alleviate AF by blocking the activation of FZD8 and the Wnt5a signaling pathway [94]. However, a study reports contradictory findings, such as Wnt1 upregulation in 24-month-old rat LV fibroblasts treated with relaxin, which inhibits the TGF-β pathway, reduces fibrosis markers, and decreases arrhythmia susceptibility [95].

Targeting Wnt/β-catenin signaling pathways or associated proteins through metabolic reprogramming can also help alleviate arrhythmias. Empagliflozin, an SGLT2 inhibitor, inhibits adipogenesis in preadipocytes by modulating the Wnt/β-catenin pathway which can be regarded as a new therapeutic strategy for AF patients [69,96]. In HFD-induced mouse cardiomyocytes, L-carnitine (LCA) promotes AMPK phosphorylation, suppresses Wnt/β-catenin signaling, increases the expression of fatty acid-related transmembrane protein CD36 and PGC-1α, reduces fat accumulation, and diminishes inflammatory markers (e.g., IL-1β, IL-6, and TNF-α). Additionally, CX43 and CX40 expression is enhanced, which reduces susceptibility to AF [97,98].

Therapeutic strategies targeting the Wnt/β-catenin signaling pathway, including GSK-3β inhibitors, Wnt antagonists (such as sFRP2, sFRP4, and sFRP5), pioglitazone, and small molecules like cardiomogen, have shown promise in the treatment of LVH and arrhythmias. These interventions have demonstrated potential in improving mitochondrial function, promoting cardiomyocyte regeneration, and reducing LV remodeling, as supported by various preclinical studies [69,97,99]. Additionally, agents such as flavonoids, angiotensin inhibitors, and empagliflozin modulate the Wnt/β-catenin pathway, mitigating AF and reduc-

Table 1. The therapeutic strategy targeting Wnt/β-catenin for LVH and arrhythmia.

Treatment	Target	Model	Conclusion	Reference
long non-coding RNA TUG1	Inhibit Wnt/β-catenin pathway	TAC and deoxyadrenaline-induced LVH mouse	Inhibition of miR-34a expression and an increase in DKK protein levels significantly reduced the expression of cardiac hypertrophy-related genes and alleviated cardiac hypertrophy	[82,83]
sFRP2		hypertension induced LVH mouse	Improvement in cardiomyocyte hypertrophy, interstitial fibrosis, and cardiomyocyte apoptosis	[84]
CGX1321		TAC-induced LVH mouse	Reduced expression of myocardial hypertrophy-related genes (*frizzled-2*, *cyclin-D1*, and *c-Myc*), inhibition of the non-classical Wnt signaling pathway, reduced levels of NFAT and phosphorylated c-Jun, and inhibition of the fibrosis process	[86]
Cardiomogen1		Zebrafish model	Cardiomyocyte proliferation and wound healing accelerated regeneration after heart injury. Simultaneously, it promoted the formation of cardiac progenitor cells and increased the number of cardiomyocytes, thus expanding the size of the embryonic heart	[10,87]
TP		ISO-induced myocardial fibrosis rat model	Reduced expression of fibrosis markers (e.g., COL-I and α-SMA), attenuation of myocardial hypertrophy and fibrosis, and improvement of left ventricular function	[40]
Upregulated notch signaling		Zebrafish heart damage model	Promoted the expression of Wnt antagonists Wif1 and Notum1b, enhanced cardiomyocyte proliferation, inhibited fibrosis, and improved ability of heart regeneration	[88]
NPLOC4		Ang II-induced LVH mouse and H9c2 cardiomyocytes	Upregulation of ERO1α expression, regulating MAMs, enhancing mitochondrial dynamics and mitophagy, and regulating fibrosis and myocardial hypertrophy	[89]
statins		48-Hour Sleep Deprivation induced Arrhythmia patients	Suppressing endoplasmic reticulum stress reduce the expression of MDA, inhibit oxidative stress in myocardial cells, and lower the incidence of arrhythmia	[91,92]
ARB		AF rats	Inhibition of FZD8 expression, inhibition of atrial fibrosis in AF rats, and prolonged effective atrial refractory period	[94]
miR-27b-3p		AF rats	Downregulation of fibrosis-related proteins Col I, Col III, and CX43 inhibited atrial fibrosis	[65]
LCA		HFD-induced AF mouse	Promoted AMPK phosphorylation, elevated the expression of CD36 and PGC-1α, alleviated fat accumulation, reduced the production of inflammatory factors (such as IL-1β, IL-6, and TNF-α), and increased CX43 and CX40 expression	[98,100]
Empagliflozin	Activate Wnt/β-catenin	Cardiac surgery patient	Inhibition of SGLT2 expression, suppression of adipogenesis in preepicardial adipocytes, and alleviation of oxidative stress in cardiomyocytes	[69,96,99]

Wnt/β-catenin, wingless-int1/β-catenin; TUG1, taurine up-regulated gene 1; sFRP2, secreted frizzled-related protein 2; NPLOC4, nuclear protein localization protein 4; ARBs, angiotensin receptor blockers; LCA, L-carnitine; TAC, transverse aortic constriction; LVH, left ventricular hypertrophy; AF, atrial fibrillation; ISO, isoproterenol; HFD, high-fat diet; Dkk-1, Dickkopf-related protein-1; α-SMA, alpha-smooth muscle actin; COL I/III, collagen I/III; MAMs, mitochondria-associated membranes; CX43, connexin43; PGC-1α, PPAR-gamma coactivator 1 alpha; TNF-α, tumor necrosis factor-α; SGLT2, sodium-glucose cotransporter 2.

ing fibrosis, further corroborating their therapeutic efficacy in heart disease management [94,98]. Collectively, these findings highlight the therapeutic potential of targeting Wnt/β-catenin signaling in LVH and arrhythmias. An overview of these strategies and their mechanisms of action is summarized in Table 1 (Ref. [10,40,65,69,82–84,86–89,91,92,94,96,98–100]).

5. Clinical Translations and Challenges

Therapeutic strategies targeting Wnt/β-catenin pathway—such as PPIs, sFRP2, Porcupine inhibitors, relaxin, and miRNA modulators—have demonstrated promising efficacy in ameliorating cardiac hypertrophy and fibrosis in preclinical models. Currently, Wnt-targeted interventions are in the early stages of clinical investigation. For instance, statins may indirectly inhibit the Wnt/β-catenin pathway by alleviating endoplasmic reticulum stress, thus reducing arrhythmia risk in sleep-deprived individuals [91,92]. Liensinine [101] and the LncRNA RNA GAS5 [102] have also been identified as potential therapeutic targets for arrhythmia. GSK-3 inhibitors, including tideglusib [103] and lithium [104], have shown promise in ameliorating arrhythmic phenotypes in arrhythmogenic cardiomyopathy (ACM) [105]; however, their clinical application remains limited due to potential carcinogenicity [106], pro-hypertrophic effects [107,108], risks of immunosuppression [109], and off-target activity. In CKD, downregulation of Klotho induced by TGF-β1 activates Wnt/β-catenin signaling, providing a novel therapeutic target [34]. The drug pyrvinium has been shown to prevent adverse cardiac remodeling and promote cardiomyocyte proliferation, thereby offering a potential therapeutic benefit for LVH [110]. Moreover, a variety of emerging Wnt pathway inhibitors—including small molecules (e.g., LGK-974 [111], CGX1321 [112], IWR-1 [113], and ICG-001 [114]) and traditional Chinese medicine formulas (e.g., Linggui Zhugan Decoction formula [115])—have demonstrated favorable safety profiles and translational potential in preclinical studies. Several of these agents have already advanced into early-phase clinical trials. The SIRT2 inhibitor AGK2 holds promise in improving conditions characterized by cardiac fibrosis [116]. However, most clinical evidence remains correlative, with a paucity of interventional studies targeting specific patient subgroups. The heterogeneity in Wnt-related protein expression across disease subtypes underscores the need for personalized treatment strategies based on molecular profiling [21].

Despite the clear mechanistic relevance of the Wnt/β-catenin pathway in cardiovascular disease, clinical translation faces substantial challenges. The structural complexity of the pathway and its involvement in multiple physiological systems pose risks of off-target effects [117]. Additionally, current animal and *in vitro* models fail to fully recapitulate human cardiac pathology, particularly regarding age-related changes, comorbidities, and molecular heterogeneity, limiting the extrapolation of preclinical findings [118]. Furthermore, while many current studies emphasize average therapeutic outcomes, others are limited to short-term observations, and patient responses to Wnt pathway inhibitors vary considerably across individuals. Nevertheless, Wnt-targeted therapeutic strategies remain promising.

Although emerging therapeutic strategies targeting the Wnt/β-catenin pathway have shown promise in basic and preclinical studies, translational barriers remain due to the pathway's inherent complexity, disease heterogeneity, and limitations of current experimental models. The clinical advancement of Wnt-targeted drugs for malignancies highlights their broader translational potential in cardiovascular medicine [119]. To realize this potential, future research should integrate systems biology, big data analytics, and single-cell technologies to comprehensively dissect the regulatory network of Wnt signaling and its crosstalk with other pathways [120]. This will enable the design of mechanism-driven, biomarker-based patient stratification strategies and help clarify patient-specific molecular signatures. Furthermore, optimizing dosing regimens to minimize off-target effects and developing companion diagnostics for precise patient selection will be essential. Robust long-term clinical trials and real-world studies are also needed to verify sustained therapeutic efficacy and monitor potential adverse effects, ultimately translating mechanistic insights into safe and effective personalized therapies for cardiovascular disease.

6. Conclusion

The Wnt/β-catenin signaling pathway is a pivotal regulator in the pathogenesis and progression of LVH and arrhythmias. By modulating cardiomyocyte hypertrophy, fibroblast-mediated fibrosis, oxidative stress, and metabolic reprogramming, it contributes to cardiac structural remodeling and electrophysiological dysfunction. Its extensive crosstalk with key signaling cascades such as TGF-β, NF-κB, and MAPK further complicates the disease landscape and presents additional therapeutic challenges. Mechanism-guided clinical trial designs and a better understanding of Wnt pathway interactions with other signaling networks may provide the foundation for multitargeted therapies. Such approaches could ultimately improve clinical outcomes and patient prognosis.

Abbreviations

α-SMA, alpha-smooth muscle actin; AMPK, AMP-activated protein kinase; Ang II, angiotensin II; AF, atrial fibrillation; ANP, atrial natriuretic peptide; β-MHC, beta-myosin heavy chain; CDMG1, cardiomogen 1; Col I, Collagen type I; Dvl, dishevelled; ERK, extracellular signal-regulated kinases; FA, fatty acid; FN, fibronectin; Fzd, Frizzled; GSK-3β, Glycogen synthase kinase-3; HF, heart failure; HFD, high-fat diet; IGF-R, insulin like-growth

factors receptor; ITGBL1, integrin beta-like 1; IL, interleukin; ISO, isoproterenol; LVH, left ventricular hypertrophic; MDA, malondialdehyde; MFN, mitochondrial fusion protein; MMP, mitochondrial membrane potential; MAPK, mitogen-activated protein kinase; MF, myocardial fibrosis; MI, myocardial infarction; NF-κB, nuclear factor-kappa B; PGC-1α, PPAR-gamma coactivator 1 alpha; ROS, reactive oxygen species; sFRP2, secreted frizzled related protein 2; SGLT2, sodium-glucose cotransporter 2; TGF-β, transforming growth factor beta; TAC, transverse aortic constriction; Wnt/β-catenin, wingless-int1/β-catenin.

Author Contributions

ZG, JW, LX, XG, XZ, YX and YS collected the literatures and interpreted the data. YX, RT, ZG and JW wrote the original manuscript. LX and XG drew the figures. RT, GZ and JY designed manuscript conception and critically revised manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

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Conflict of Interest

The authors declare no conflict of interest.

Declaration of AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work, the authors used ChatGPT in order to check spelling and grammar. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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