Targeting wingless-integrated/β-catenin (Wnt/β-catenin) signaling pathway as a new therapeutic modality

Asmaa M. Abdelghafour, Nahla N. Younis, Sally K. Hammad,*Hoda E. Mohamed

Biochemistry Department, Faculty of Pharmacy, Zagazig University, Zagazig, 44519, Egypt

* **Corresponding author** E-mail: hmohammed@zu.edu.eg , Phone/ Fax: 002 055 2303266.

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Abstract

Wingless-integrated/β-catenin (Wnt/β-catenin) signaling pathway is an evolutionarily conserved signaling which is not only important for regulation of embryogenesis and organ development, but also for injury repair, homeostasis and tissue remodeling. Dysregulation of this pathway either by upregulation or even downregulation is highly implicated in various diseases such as; liver diseases, kidney diseases, lung fibrosis, heart failure, vascular calcification, osteoporosis, cellular senescence, neurodegeneration, Alzheimer's disease and cancers. Thus, targeting Wnt/β-catenin signaling has attracted scientific research as a good strategy ameliorating several diseases. In this review we discussed Wnt/β-catenin components, the Wnt-on state and the Wnt-off state. Furthermore, we summarized the effects of Wnt/β-catenin signaling in several distinct organs including brain, bone, liver, heart, lung and kidney. We also discussed various molecules that act as modulators of Wnt/β-catenin signaling pathway via targeting its components (Wnt, Frizzled, LRP5/6, Porcupine, Disheveled, β-catenin destruction complex and β-catenin activity) aiming to show their possible therapeutic potential in several diseases.

Keywords: Canonical Wnt signaling; klotho; casein kinase 1α; Frizzled; Disheveled

Introduction

The wingless integrated (Wnt) signaling pathways are a group of conserved evolutionarily pathways that play a critical role in regulating many cellular processes such as cell fate, migration, polarity, in addition to organogenesis and stem cell renewal. Dysregulation of those pathways has severe consequences not only for embryogenesis but also for the adult human causing many diseases such as cancer and other chronic diseases **(Komiya and Habas 2008).**

The word Wnt is a merge of the names of homologous genes; *Drosophila* gene wingless (Wg) and proto-oncogene integrated or (int-1) **(Nusse and Varmus 1992).**The Wnts are a group of secreted glycoproteins which are represented in human, mouse and rat by 19 ligands (Wnt1, Wnt2, Wnt2b, Wnt3, Wnt3a, Wnt4, Wnt5a, Wnt5b, Wnt6, Wnt7a, Wnt7b, Wnt8a, Wnt8b, Wnt9a, Wnt9b, Wnt10a, Wnt10b, wnt11 and Wnt16) **(Nelson, Von Toerne et al. 2011).**They consist of about 350-400 amino acids with a conserved domain rich in cysteine residues through which Wnt proteins bind to many different receptors. The Wnts proteins undergo post-translational modifications such as palmitoylation and glycosylation which are important for their function, secretion and binding to lipoprotein particles. These post-translational modifications accounts for its water insolubility and hydrophobic properties

(Ackers and Malgor 2018).

Once bound to their receptors, Wnts trigger two major signal transduction; the canonical (β-catenin dependent) pathway, and the non-canonical (β-catenin independent) pathway which includes Planar Cell Polarity and Wnt/Ca^{2+} pathways **(Komiya and Habas 2008)**. The Wnt proteins are therefore classified according to their downstream signaling effects into canonical Wnts which include (Wnt1, 2, 3, 8a, 8b, 10a and 10b) and non-canonical Wnts that include (Wnt4, 5a, 5b, 6, 7a, 7b and 11) **(Ackers and Malgor 2018)**.

Canonical Wnt/β-catenin pathway

The Wnt/β-catenin pathway, is an evolutionarily conserved signaling which is important for regulation of organ development, repair of injury, homeostasis and remodeling of tissues, in addition to inflammation **(Zhou and Liu 2016)**. When Wnt ligand is absent (**Wnt-off state**), β-catenin binds to its destruction complex which consists of axin, glycogen synthase kinase-3β (GSK-3β), adenomatous polyposis coli (APC) and casein kinase 1α (CK1α). This results in phosphorylation of β-catenin by GSK3 and CK1α, ubiquitination and subsequent proteolytic degradation by proteasomes **(Komiya and Habas 2008)** as shown in figure 1a.

In the presence of Wnt ligand (**Wnt-on state**), it binds to Frizzled (Fz) and low-density lipoprotein receptor-related proteins-5/6 (LRP-5/6) receptor complex. This disrupts β-catenin destruction complex, inhibits β-catenin degradation, resulting in cytoplasmic accumulation of β-catenin which undergoes nuclear translocation where it binds to T-cell specific transcription factor (TCF) and/or

lymphoid enhancer factor (LEF) complex resulting in transcription of Wnt downstream target genes. This β-catenin activation accounts for cell differentiation, proliferation and determination of cell fate **(Nelson, Von Toerne et al. 2011)** as shown in figure 1b.
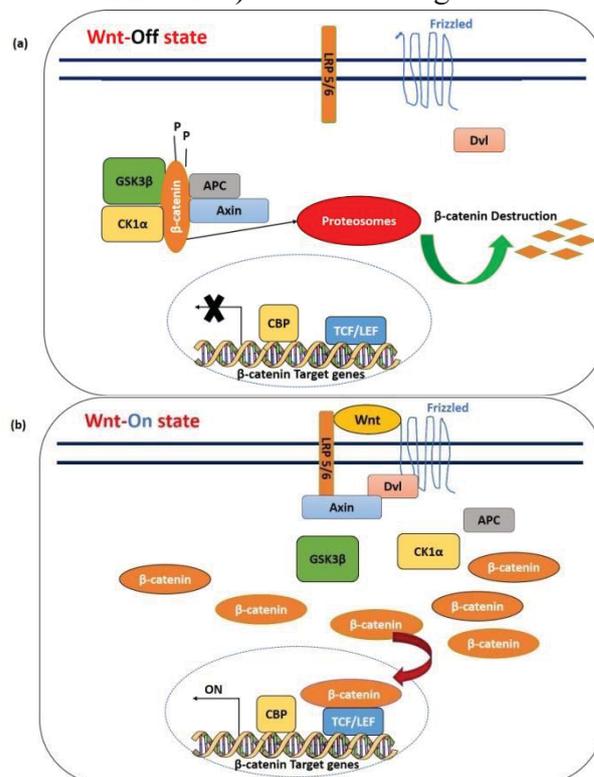
Figure 1: Overview of Wnt/β-catenin signaling pathway *(a) When Wnt ligand is absent (**Wnt-off state**), β-catenin binds to its destruction complex which consists of axin, glycogen synthase kinase-3β (GSK-3β), adenomatous polyposis coli (APC) and casein kinase 1α (CK1α). This results in β-catenin phosphorylation by GSK3 and CK1α, ubiquitination and subsequent proteolytic degradation by proteasomes,* (b) *In the presence of Wnt ligand (**Wnt-on state**), it binds to Frizzled and low-density lipoprotein receptor-related proteins-5/6 (LRP-5/6) receptor complex, consequently Disheveled (Dvl) binds to Frizzled c-terminus resulting in axin recruitment from β-catenin destruction complex. This disrupts β-catenin destruction complex, inhibits β-catenin degradation, resulting in cytoplasmic accumulation of β-catenin which undergoes nuclear translocation where it binds to T-cell specific transcription factor (TCF) and/or lymphoid enhancer factor (LEF) complex resulting in cyclic AMP response element binding protein (CBP) recruitment, and transcription of Wnt downstream target genes.*

Wnt/β-catenin pathway in different organs

1.Wnt/β-catenin pathway in the kidney

The Wnt/β-catenin signaling plays an important role in embryological kidney development via regulation of nephron formation. It is also responsible for injury repair, homeostasis of tissue, as well as kidney diseases pathogenesis **(Huang and He 2008)**. Although Wnt/β-catenin is relatively silent in normal adult kidneys, this signaling is robustly reactivated after a wide variety of kidney injuries. The early and transient up-regulation of Wnt/β-catenin after acute kidney injury facilitates tubular repair and kidney regeneration. However, its chronic activation promotes the progression to chronic kidney disease (CKD) **(Xiao, Zhou et al. 2016)**. Several models of CKD exhibited upregulation of Wnt/β-catenin signaling including unilateral ureteral obstruction, ischemia reperfusion injury (IRI), 5/6 nephrectomy and doxorubicin nephropathy **(Zhou, Li et al. 2013; Xiao, Xu et al. 2019; Younis, Mohamed et al. 2021)**. Also, upregulated Wnt ligands as well as β-catenin were found in human kidney biopsies taken from patients with diabetic nephropathy where oxidative stress, fibrosis and podocyte injury are common features **(Dai, Stolz et al. 2009)**.

Mechanism of CKD caused by Wnt/β-catenin activation

Sustained activation of Wnt/β-catenin signaling following kidney injury is detrimental leading to CKD progression. After nuclear translocation of β-catenin, it performs its actions via induction of its downstream target genes such as renin angiotensin system (RAS) components, fibronectin, matrix metalloproteinase-7(MMP-7), fibroblast-specific protein 1 (Fsp1), Snail1 and plasminogen activator inhibitor-1 (PAI-1) resulting in hypertension, fibrosis, renal inflammation, podocyte dysfunction and proteinuria **(Tan, Zhou et al. 2014)**. Several studies have reported that blockade of renal Wnt/β-catenin signaling ameliorates renal fibrosis, inflammation, podocytes dysfunction and proteinuria**(Zhao, Wang et al. 2019; Younis, Mohamed et al. 2021)**.

2.Wnt/β-catenin pathway in the heart and vascular system

The Wnt/β-catenin pathway has several distinct essential roles through mammalian heart development. ***Lickert et al*** found that β-catenin ablation in embryonic endoderm resulted in the generation of several ectopic hearts which demonstrated that the inhibition of this pathway is essential for mammalian heart specification **(Lickert, Kutsch et al. 2002)**. However, another study reported that Wnt/β-catenin signaling stimulated heart specification in the early stages of development, but suppresses it later **(Klaus, Saga et al. 2007)**.

Not only does Wnt/β-catenin pathway play an essential role in cardiac development, but it is also involved in cardiac remodeling upon injury. Although being quite silent in adult heart, Wnt/β-catenin pathway is reactivated following cardiac injuries which ranges from acute ischemia to chronic pressure overload **(Zheng, Chen et al. 2013)**. In a mouse model of transverse aortic constriction (TAC)-induced heart failure, **Zhao *et al*** repeted the upregulation of active β-catenin, several Wnt ligands along with several RAS components resulting in inflammation, fibrosis, hypertrophy and diminished cardiac function. β-catenin blockade was reported to ameliorate

these effects **(Zhao, Wang et al. 2019)**. Also ,**Zhao** *et al*. reported the crucial role played by Wnt/β-catenin signaling in the mediation of hypertension, cardiac hypertrophy and fibrosis suggesting that the suppression of this signaling is a good strategy in amelioration of several heart diseases **(Zhao, Wang et al. 2018)**.

In blood vessels, Wnt/β-catenin signaling plays vital roles, where it is implicated in the survival and proliferation of endothelial cells (EC), vascular smooth muscle cells (VSMC) and fibroblasts. It also contributes to EC permeability, VSMC migration and cholesterol efflux **(Albanese, Khan et al. 2018)**. Upregulated Wnt/β-catenin signaling was reported to induce vascular calcification (VC) via activating bone morphogenetic protein 2 which regulates osteogenic events resulting in VC**,** and also by abnormal differentiation of vascular pericytes **(Rajamannan 2011; Albanese, Khan et al. 2018)**.Rajamannan *et al.* reported less aortic valve calcification in LRP5/6 knockout hypercholesteremic mice which support the implication of Wnt/β-catenin signaling in VC and diseases of coronary artery **(Rajamannan 2011)**.

3.Wnt/β-catenin pathway in the bone

The Wnt/β-catenin signaling has an essential role in bone development and skeletal homeostasis. During early bone development, it controls skeletal pattern generation before skeletal elements establishment **(Kim, Liu et al. 2013).** It promotes the progression of mesenchymal stem cells into mature osteoblasts via the upregulation of several osteogenic regulators **(Bennett, Longo et al. 2005)**. Moreover, Wnt/β-catenin signaling is highly implicated

in tooth morphogenesis, where stabilized β-catenin promoted continuous dental development in embryos, but its ablation suppressed tooth development **(Liu, Chu et al. 2008)**.

Dysregulation of this pathway has been greatly associated with several human bone defects, where Wnt3a deficiency was reported to induce axial defects in embryos **(Takada, Stark et al. 1994)** and LRP5 mutations is associated with osteoporosis and reduced bone density **(Yousefi, Samadi et al. 2016)**. Furthermore, Wnt/β-catenin pathway plays an essential role during bone healing process. Liposomal Wnt3a delivery was able to induce bone progenitor cells proliferation and differientiation into osteoblasts resulting in accelerated bone regeneration **(Minear, Leucht et al. 2010),** decrease osteoclasts generation and promote its apoptosis, while β-catenin ablation counteracted this effect **(Martin-Millan, González-Martín et al. 2019).**

4.Wnt/β-catenin pathway in the liver

The Wnt/β-catenin pathway is highly implicated in hepatobiliary development, maturation as well as zonation during embryogenesis **(Thompson and Monga 2007)**. Although being silent in adult healthy liver, it is reactivated through cell renewal processes in addition to pathological diseases and cancer. Wnt/β-catenin pathway was reported to be hyperactive in cholangiocarcinoma and hepatocellular carcinoma resulting in increased tumor dissemination and growth **(Monga 2015).**

In a rat model of partial 2/3 hepatectomy (PHx), residual liver lobes were enlarged through hepatic hyperplasia and hypertrophy to compensate removed parts. The Wnt/β-

catenin pathway was reported to be involved in this hepatic regeneration observed in this model, where a significant increase in β-catenin was found within minutes of PHx resulting in hepatocytes proliferation **(Monga, Pediaditakis et al. 2001)**. However, β-catenin ablation resulted in a marked decrease in proliferating hepatocytes which causes a delay in liver regeneration **(Tan, Behari et al. 2006)**. Similarly, mice with LPR5/6 deficiency in their hepatocytes had delayed hepatic regeneration capability **(Yang, Mowry et al. 2014)**.

In hepatic IRI, hypoxia inducible factor1α (HIF1α) competes for binding to β-catenin resulting in increased its mediated transcription and cell survival **(Kaidi, Williams et al. 2007)**. Moreover, the deficiency of hepatic β-catenin diminished HIF1α signaling and increased the susceptibility to IRI, while hepatic Wnt1 overexpression offered a protection **(Lehwald, Tao et al. 2011)**. In hepatic steatosis and cholestatic liver disease, LPR6 mutation induced fatty liver development via AKT/mTOR signaling which increased hepatic lipogenesis. The Wnt3a treatment was reported to normalize these effects **(Go, Srivastava et al. 2014)**. Furthermore, Wnt/β-catenin pathway is involved in hepatic stellate cells activation and liver fibrosis **(Miao, Yang et al. 2013),** while its blockade ameliorated liver fibrosis **(Akcora, Storm et al. 2018)**.

5. Wnt/β-catenin pathway in the lung

In the lung Wnt/β-catenin signaling is involved in fetal lung development, differentiation and morphogenesis. It is also involved in lung repair and regeneration following injury **(Hussain, Xu et al. 2017)**. **Caprioli** *et al*. reported massive lung hypoplasia and tracheal abnormalities during embryogenesis following Wnt4 transgenic ablation **(Caprioli, Villasenor et al. 2015)**. Dysregulated Wnt/β-catenin signaling is also highly implicated in several pulmonary diseases pathogenesis such as chronic obstructive pulmonary disease (COPD) and idiopathic pulmonary fibrosis (IPF) **(Shi, Li et al. 2017)**.The Wnt/β-catenin signaling activation along with overexpression of its target genes were found in airways of IPF patients. However, in COPD patients, suppressed Wnt/β-catenin signaling was observed. Reactivation of this pathway promoted amelioration of experimentally induced emphysema **(Kneidinger, Yildirim et al. 2011; Chilosi, Poletti et al. 2012)**.

6. Wnt/β-catenin pathway in the brain

Unlike other organs, Wnt/β-catenin signaling pathway is essential in all life stages of brain **(Wisniewska 2013)**. Aberrant Wnt/β-catenin signaling during brain development resulted in birth defects. It has been reported that Wnt1 deficiency in mouse embryos caused massive malformation in brain along with a complete absence of midbrain and hindbrain which would form cerebellum **(Brault, Moore et al. 2001)**. Besides its role in initial brain development, Wnt/β-catenin signaling remains imperative in adult brain, where it regulates synaptic plasticity and the integrity and function of blood brain barrier. Thus, Wnt/β-catenin signaling dysregulation is greatly associated with several neurological disorders including Alzheimer's disease(AD), where suppressed Wnt/β-catenin signaling in AD brain was reported **(Noelanders and Vleminckx 2017)**.

Activation of this pathway diminishes β-amyloid production along with

hyperphosphorylation of tau protein. Thus, Wnt/β-catenin restoration is considered a good strategy for AD treatment **(Jia, Piña-Crespo et al. 2019)**. Moreover, it was reported that several neuroprotective compounds which enhance neurogenesis in AD perform their effects via Wnt/β-catenin activation **(Fu, Yang et al. 2010; Tiwari, Agarwal et al. 2016).**

7. Wnt/β-catenin pathway in aging

The Wnt/β-catenin signaling pathway is activated during aging in hair, muscle, skin and blood vessels causing hair graying, renal and cardiac disorders**(Naito, Shiojima et al. 2010; Zhang, Lei et al. 2017)**. **Zhang** *et al*. reported the link between upregulated Wnt/β-catenin signaling and hair graying in aged mice which is caused by extreme melanocytes differentiation resulting in their exhaustion and canities **(Zhang, Lei et al. 2017)**.

Cellular senescence is a decrease in cellular replication ability due to telomeres shortening present at chromosomes ends.

Ye *et al*. reported that inactivation of Wnt/β-catenin induced cellular senescence, but its activation encouraged cellular proliferation and provide protection against cellular senescence **(Ye, Zerlanko et al. 2007)**. However, other studies found contrary results, where upregulation of Wnt/β-catenin was responsible of aging and its related phenotypes. In a model of impaired klotho expression, upregylated Wnt/β-catenin, diminished stem cells number and increased senescent cells were observed **(Liu, Fergusson et al. 2007)**.

Modulators of Wnt/β-catenin pathway components

Since Wnt/β-catenin signaling has an aberrant role in several diseases/conditions, its targeting has attracted scientific research as a possible therapeutic approach for various diseases. The modulation of distinct components of this pathway is reviewed below and summarized in **table 1**.

Table 1: Targeting/Modulators of Wnt/β-catenin signaling

Wnt/β-catenin modulator	Target	Model	Effect on Wnt/β-catenin signaling	References
R-spondin Proteins	Wnt	Osteoblast-lineage cells, *in vitro* R-spondin-2 knockout mice	Wnt agonist, ↓Wnt receptor turnover and activate signaling	**(Knight, et al., (2018))**
Klotho	Wnt	UUO, DOX-induced nephrotoxicity, mice DOX-induced CKD, rats	Wnt antagonist, inhibits signaling	**(Zhou, et al., (2013)), (Younis, et al., (2021))**
IWP-L6 IWP-2 Wnt-C59	Porcupine	Zebrafish embryos Zebrafish embryos Murine UUO	Porcupine inhibitors, ↓Wnt	**(Wang, et al., (2013)) (Wang, et al.,**

LGK974		Mouse tumor xenograft	palmitoylation and secretion, inhibit signaling	(2013)) (Madan, et al., (2016)) (Liu, et al., (2013))
OMP-18R5 SFRPs	Fz	Patients with advanced solid tumors Transfected 293T cells, *in vitro,*	Binds to Fz, ↓Wnt binding to Fz, inhibit signaling	(Smith, et al., (2013)) (Bafico, et al., (1999))
DKK1 Sclerostin	LRP5/6	Transfected 293T cells, *in vitro* Xenopus embryos Osteoblastic cells, *in vitro*	Bind to LRP5/6, inhibit signaling	(Niida, et al., (2004)) (Winkler, et al., (2003); Semĕnov, et al., (2005))
Niclosamide Sulindac	Dvl	Bleomycin-induced pulmonary fibrosis, CCl4-induced liver fibrosis, rats Xenopus embryos	Inhibit Dvl, causes β-catenin destruction, inhibit signaling	(Boyapally, et al., (2019)), (El-Ashmawy, et al., (2020)) (Lee, et al., (2009))
Pyrvinium pamoate	CK1α	Myocardial infarction, mice Xenopus embryos	Activate CK1α, inhibit signaling	(Saraswati, et al., (2010); Thorne, et al., (2010))
LiCl	GSK3β	D-galactose induced neurodegeneration, rat Neural stem cells, *in vitro*	Inhibits GSK3β, activate signaling	(Xia, et al., (2017)) (Zhang, et al., (2019))
ICG-001	CBP	CCl4-induced liver fibrosis, mice Bleomycin-induced lung fibrosis, mice TAC-induced cardiorenal syndrome, mice	Inhibits β-catenin/CBP interaction, inhibits signaling	(Henderson, et al., (2010); Akcora, et al., (2018); Zhao, et al., (2019))

Abbreviations: CCl4: carbon tetrachloride; CK1α: casein kinase 1α;CKD: chronic kidney disease; CBP: cyclic AMP response element binding protein;DKK1: Dickkopf1; Dvl, Disheveled; DOX: doxorubicin; Fz: frizzled;GSK3β: glycogen synthase kinase-3β;IWP: Inhibitors of Wnt production; LiCl: lithium chloride;LRP5/6: low-density lipoprotein receptor-related proteins-5/6;SFRPs: Secreted frizzled-related proteins; TAC: transverse aortic constriction. UUO: unilateral ureteral obstruction

1. Wnt

The Wnt/β-catenin pathway can be modulated via endogenous or synthetic Wnt antagonists and agonists. Klotho is an example of the endogenous antagonists of Wnt. Klotho is a novel aging suppressing protein which is expressed in limited types of cells and tissues **(Zou, Wu et al. 2018)**. Renal distal convoluted tubules and brain choroid plexus represent the highest expression areas. One of the important functions of klotho its ability to sequester and bind many Wnt ligands preventing them from binding to their receptors **(Kuro-o 2009)**. *Zhou et al* reported that that *in vivo* expression of klotho via gene delivery system suppressed β-catenin activity as well as its target genes resulting in amelioration of kidney injury **(Zhou, Li et al. 2013)**. Furthermore, upregulated renal klotho content induced inactivation of Wnt/β-catenin signaling and amelioration of renal injury induced by doxorubicin, UUO and IRI **(Zhou, Li et al. 2013; Younis, Mohamed et al. 2021)**. In addition to its ability to inhibit Wnt/β-catenin signaling, it suppresses tumor growth in hepatocellular carcinoma patients **(Tang, Wang et al. 2016)**. **Kadoya** *et al*. demonstrated its capability to ameliorated peritoneal fibrosis through targeting Wnt/β-catenin signaling **(Kadoya, Satoh et al. 2020)**.

The Wnt can also be modulated by targeting porcupine, an essential enzyme for Wnt palmitoylation process which is crucial for Wnt secretion and activity. Inhibitors of Wnt production (IWP) are considered one of those compounds including IWP-L6 and IWP-2. IWP-L6 was reported to reduce or even block the morphogenesis of zebrafish tailfin **(Wang, Moon et al. 2013)**. Another porcupine inhibitor, Wnt-C59, was reported to ameliorate renal fibrosis via suppression of Wnt/β-catenin signaling **(Wang, Moon et al. 2013; Madan, Patel et al. 2016)**. Likewise, LGK974 is another porcupine inhibitor which showed great efficiency in cancer treatment **(Liu, Pan et al. 2013)**.

Moreover, Wnt/β-catenin signaling can be activated by Wnt agonists like R-spondin proteins, a group of matricellular proteins **(Knight, Karuppaiah et al. 2018)**. They induce Wnt/β-catenin activation via inhibiting turnover of Wnt receptor through binding to the G-protein coupled receptor containing leucine rich repeat followed by interacting with ZNRF3/RNF43 which are E3-Ubiquitin ligases **(Hao, Xie et al. 2012)**. **Knight** *et al*. found that RSPO2 , a R-spondin protein, induced mineralization, and osteoblastogenesis via β-catenin stabilization, but its deficiency caused reduced bone formation, mass and strength **(Knight, Karuppaiah et al. 2018)**.

2. Fz and its co-receptor LRP5/6

The Wnt/β-catenin signaling can also be modulated by targeting Wnt interaction with Fz receptor and LRP5/6. The monoclonal antibody directed to target Fz receptors, OMP-18R5, was reported to suppress Wnt/β-catenin signaling leading to inhibition of various human tumors growth possibly by binding to Fz cysteine rich domains (CRD), causing steric hinderance to Wnts **(Smith, Rosen et al. 2013)**. Secreted frizzled-related proteins (SFRPs), a group of proteins with CRD homologous to those of Fz receptors, were reported to inhibit Wnt signaling either by binding to Wnt ligands changing their ability to bind to CRD of Fz, or by forming

complexes with Fz receptors **(Bafico, Gazit et al. 1999)**.

The LRP5/6 also plays an important role in Wnt/β-catenin signaling modulation. Dickkopf1 (DKK1), *Kremen* and LRP5/6 form a ternary complex resulting in LRP5/6 endocytosis and removal from the cell surface. Thus, DKK1 is considered a potent Wnt signaling inhibitor **(Niida, Hiroko et al. 2004)**. Sclerostin, a glycoprotein mainly expressed in osteocytes, was reported to suppress Wnt/β-catenin pathway in osteoblasts via binding to LRP5/6 resulting in inhibition of new bone generation and growth **(Winkler, Sutherland et al. 2003; Semënov, Tamai et al. 2005)**.

3.Disheveled (Dvl)

Once Wnt binds to Fz and LRP5/6 co-receptor, Disheveled (Dvl) binds to Fz c-terminus resulting in axin recruitment from β-catenin destruction complex and β-catenin accumulation **(Gao and Chen 2010)**.Thus, blockade of Dvl can inhibit Wnt/β-catenin signaling. NSC668036, niclosamide and sulindac are examples of Dvl blockers. Niclosamide was reported to ameliorate pulmonary fibrosis and protect against liver fibrosis via targeting Wnt/β-catenin signaling **(Boyapally, Pulivendala et al. 2019; El-Ashmawy, Al-Ashmawy et al. 2020)**. Sulindac, a non-steroidal anti-inflammatory drug, was reported to block Wnt/β-catenin signaling via inhibiting Dvl-PDZ domain making it a desirable anticancer drug **(Lee, Wang et al. 2009)**.

4.β-catenin Destruction complex
CK1α

CK1α is a component of β-catenin destruction complex. Thus, its activation causes β-catenin destruction and suppression of further events **(Cruciat 2014)**. Pyrvinium pamoate, an approved anthelmintic drug, was reported to activate CK1α making it an effective blocker of Wnt signaling **(Saraswati, Alfaro et al. 2010; Thorne, Hanson et al. 2010)**.

GSK3β

Also, GSK3β is a part of the destruction complex of β-catenin which phosphorylates β-catenin resulting in its proteasomal degradation. The over-expression of GSK3β was reported to downregulate Wnt/β-catenin signaling resulting in various pathologic conditions such as AD **(Sirerol-Piquer, Gomez-Ramos et al. 2011)**. Thus,GSK3β blockers act as Wnt/β-catenin activators which can be used as treatment for the diseases caused by suppressed Wnt/β-catenin signaling **(Wan, Xia et al. 2014)**. Lithium chloride (LiCl) is a mood stabilizing drug widely used for bipolar disorder therapy **(Machado-Vieira, Manji et al. 2009)**. It was reported that LiCl performs its neuroprotective effect by inhibiting GSK3β. **Xia et al.** found that traetment with LiCl ameliorated D-galactose induced neurodegeneration in rats via Wnt/β-catenin signaling activation **(Xia, Zhao et al. 2017)**. Moreover, **Zhang et al.** reported that LiCl promoted neural stem cells proliferation by the same mechanism **(Zhang, He et al. 2019)**.

5.Nuclear β-catenin activity

Once nuclear β-catenin binds TCF, cyclic AMP response element binding protein (CBP) is recruited to induce the transcription of various β-catenin target genes. Thus, blocking the interaction among β-catenin and CBP is a good way to suppress Wnt/β-catenin signaling

(Ono, Lai et al. 2018). ICG-001 is a β-catenin/CBP blocker that was reported to ameliorate various diseases in which Wnt/β-catenin signaling is upregulated such as liver and pulmonary fibrosis and cardiorenal syndrome **(Henderson, Chi et al. 2010; Akcora, Storm et al. 2018; Zhao, Wang et al. 2019)**.

Conclusion

Aberrant Wnt/β-catenin signaling has been highly associated with several conditions. Therefore, targeting this pathway is considered a possible therapeutic approach for various diseases. This can be achieved by the modulation of distinct components of Wnt/β-catenin signaling pathway.

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استهداف مسار إشارات المتكاملة غير المجنحة / بيتا كاتينين (ونت/بيتا كاتينين) كطريقة علاجية جديدة

أسماء محمد عبد الغفور، نهله نبيل يونس، سالي كامل حماد، هدي السيد محمد

قسم الكيمياء الحيوية – كلية الصيدلة – جامعة الزقازيق – الزقازيق – ص.ب: 44519 – مصر

تعتبر اشارة ونت/بيتا كاتينين إشارة محفوظة تطوريًا والمهمة ليس فقط لتنظيم التطور الجنيني وتطور الأعضاء، ولكن أيضًا لإصلاح الإصابات والتوازن وإعادة تشكيل الأنسجة. إن أي خلل بهذا المسار يعد متورطا بشكل كبير في أمراض مختلفة مثل؛ أمراض الكبد، أمراض الكلي، تليف الرئة، قصور القلب، تكلس الأوعية الدموية، هشاشة العظام، الشيخوخة الخلوية، التنكس العصبي، مرض الزهايمر، والسرطان. وبالتالي، فان استهداف اشارة ونت/بيتا كاتينين قد اجتذب البحث العلمي كاستيراتيجية جيدة لتخفيف العديد من الأمراض. لقد ناقشنا في هذه الدراسة مكونات اشارة ونت/بيتا كاتينين وحالتيه النشطة والخاملة. علاوة علي ذلك، لقد قمنا بتلخيص تأثيرات اشارة ونت/بيتا كاتينين في العديد من الأعضاء المختلفة بما في ذلك المخ، والعظام، والكبد، والقلب، والرئة، والكلي. لقد ناقشنا أيضا العديد من الجزيئات التي تعمل كمعدلات لمسار اشارة ونت/بيتا كاتينين من خلال استهداف مكوناتها المختلفة بهدف اظهار قدرتها العلاجية المحتملة في العديد من الأمراض.