Role of Wnt/β-catenin and Dickkopf-1 protein in Systemic Lupus Erythematosus and lupus nephritis

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Abstract

Background: o the wingless-related integration site (WNT) signaling pathways are group of conserved signal transduction pathways made of proteins that regulate a wide range of biological processes including cellular proliferation, embryogenesis, tissue homeostasis, and other systemic effects. It has been recently discovered that any aberration or dysregulation of the Wnt/β-catenin cascade could contribute to the development and progression of variety of disorders and cancers due to its involvement in many physiological processes such as cell proliferation, differentiation, migration, apoptosis, and tissue homeostasis. The canonical Wnt pathway is hyperactivated in SLE and plays a significant role in lupus nephritis pathogenesis and induction of renal fibrosis. Over activation or dysregulation of Wnt signaling may result in an imbalance of bone remodeling in the form of stimulation of bone formation by inducing ostoblastic differentiation, increasing osteoblast proliferation, and inhibiting osteoblast apoptosis. o When Wnt/β-catenin pathway is activated, β-catenin is accumulated and translocated to the nucleus where it forms a transcription activation complex with TCF/LEF that activates the expression of a set of target genes such as fibronectin, fibroblast-specific protein1 (Fsp1), matrix metalloproteinase-7 (MMP7), plasminogeng activator inhibitor-1, Snail-1, and Twist. o It has been suggested that blocking the WNT/β-catenin signaling attenuated renal fibrotic lesions as the overexpression of Dkk-1 inhibited the activation of β-catenin, fibroblast-specific protein 1 and αSMA protein, which inhibited the transformation of myofibroblasts and the synthesis of type I collagen, as well as fibronectin, thus reducing collagen deposition.

Keywords: Wnt/β-catenin, Dickkopf-1 protein, Systemic Lupus Erythematosus, lupus nephritis

Introduction

Lupus nephritis is a form of glomerulonephritis and one of the most severe complications of systemic lupus erythematosus. Lupus nephritis occurs in about 50-60 % of patients with SLE and is the most common cause of kidney injury in SLE Lupus nephritis is commonly presented in male sex and young age. It typically develops early in the disease course, generally within the first 6 to 36 months, and may be present at initial diagnosis. **(1).**

The wingless-related integration site (WNT) signaling pathways are group of conserved signal transduction pathways made of proteins that regulate a wide range of biological processes including cellular proliferation, embryogenesis, tissue homeostasis, and other systemic effects **(2).**

The Wnt signaling was first identified for its role in carcinogenesis, then for its function in embryonic development when genetic mutations in Wnt pathway proteins produced abnormal fruit fly embryos. Abnormal regulation of Wnt signaling has been associated with a variety of disorders such as embryonic deformities, degenerative diseases, diabetes and cancer. It also has been suggested to be involved in the pathogenesis of many types of autoimmune diseases, such as rheumatoid arthritis RA, SLE, and ankylosing spondylitis (AS) because it has a crucial role in the development of T cells and the

immune system **(3)**

The first Wnt gene was discovered in 1982 and it was derived from integrase-1 (Int1) gene in mouse breast tumors and the wingless (wg) gene of the Drosophila. The term of Wnt comes from a combination of the wingless gene and the *Int1* gene, because it was found that the two genes are homologous in the structure **(3)**

Classification of Wnt pathway

The Wnt signaling is classified into two major categories:

The Wnt/β-catenin dependent pathway:

The canonical WNT pathway includes canonical Wnt proteins such as (Wnt1, 2, 3, 8b, 10a, and 10b) **(4).**

The WNT/β- catenin independent pathway:

The non-canonical WNT/planer cell polarity pathway

Th non-canonical WNT/ calcium pathway **(4).**

The non-canonical WNT pathway includes non-canonical proteins such as (Wnt4, 5a, 5b, 6, 7a, 7b, and 11) **(4)**.

The Wnt/β- catenin dependent signaling is primarily involved in regulation of cell fate, proliferation and survival, while differentiation, polarity and migration of the cell are regulated by Wnt/β- catenin independent pathway. The two pathways form an intersecting signaling network that coordinately regulates complex processes **(5).**

Wnt proteins

Wnt proteins are a diverse family of 19 secreted, hydrophobic, and cysteine-rich glycoproteins in mammals and they consist of about 350 to 400 amino acids. Wnt proteins in human include Wnt1, Wnt2, Wnt2B, Wnt3, Wnt3A, Wnt4, Wnt5A, Wnt5B, Wnt6, Wnt7A, Wnt7B, Wnt8A, Wnt8B, Wnt9A, Wnt9B, Wnt10A, Wnt10B, Wnt11, and Wnt16 **(6).**

In Wnt signaling, these proteins act as ligands to activate the different Wnt pathways **(7).**

β-catenin

It is a multifunctional protein that belongs to a group of cell-cell adhesion catenin proteins and their main role is to sustain epithelial integrity. It is normally present in the cytoplasm and its level is mostly regulated via phosphorylation by the destruction complex and proteasomal degradation. When Wnt protein is active, the cytosolic β-catenin is stabilized and accumulated with subsequent translocation of β-catenin to the nucleus where it binds to TCF/LEF transcription factors. Therefore, it is an essential component of Wnt signaling pathway and it could provide an explanation about how extracellular Wnt signals are transduced to the cell nucleus **(8).**

The Wnt/β- catenin pathway

Components of Wnt/β- catenin pathway

The Wnt/β-catenin pathway comprises four parts as following:

Extracellular signals: are mainly mediated by Wnt proteins, including Wnt3a, Wnt1, and Wnt5a

The cell membrane segment: contains the Wnt receptors Frizzled (Fz) and co-receptors such as low-denisty lipoprotein receptor-related protein 5/6 (LRP5/6), receptor tyrosine kinase (RTK) and receptor

tyrosine kinase-like orphan receptor (ROR) **(9).**

The cytoplasmic segment: mainly includes β-catenin, disheveled protein (DVL), glycogen synthase kinase-3β (GSK-3β), AXIN protein, adenomatous polyposis coli (APC), and casein kinase I (CK1)

The nuclear segment: mainly includes β-catenin, which translocates to the nucleus, TCF/LEF family members, and β-catenin target genes, such as MMPs and c-Myc **(10).**

Mechanism of Wnt/β-catenin signaling pathway

In the absence of Wnt ligands (Wnt signal off):
The destruction complex is constitutively active when Wnt is not bound to its receptors. The destruction complex is composed of Axin, adenomatous polyposis coli (APC), glycogen synthase kinase 3 beta (GSK3β), casein kinase -1 (CK1), and β- transducing repeat- containing E3 ubiquitin- protein ligase (β- TrCP)

The cytoplasmic β-catenin binds to active destruction complex and phosphorylated by the kinases of the complex. The phosphorylated form of β-catenin is recognized by an E3 ubiquitin ligase (β-TrCP) and then targeted to proteasomal degradation, resulting in low cytosolic levels of β-catenin and decreased its translocation into the nucleus. In the absence or decrease of nuclear β-catenin, TCF/LEF proteins repress Wnt target genes expression through a direct association with transcriptional inhibitors of the Groucho family or histone deacetylases (HDACs) **(10).**

In the presence of Wnt ligands (Wnt signal on):
Wnt signaling is activated when Wnt proteins bind to their receptor complex, consisting of Frizzled family receptor (G-protein coupled receptors GPCRs) and LRP5/6 coreceptor. This binding inhibits the destruction complex function. The disruption of the destruction complex prevents phosphorylation and degradation of β-catenin with subsequent accumulation of β-catenin in the cytoplasm. The unphosphorylated active β-catenin translocates to the nucleus, where it binds to TCF/LEF to induce Wnt target genes expression. Extracellular Wnt signaling can be inhibited by binding of members of the secreted frizzled related protein (sFRP) and Wnt inhibitory factor (WIF) families to Wnt ligands, or by the interaction of soluble Dickkopf (DKK) with LRP **(11).**

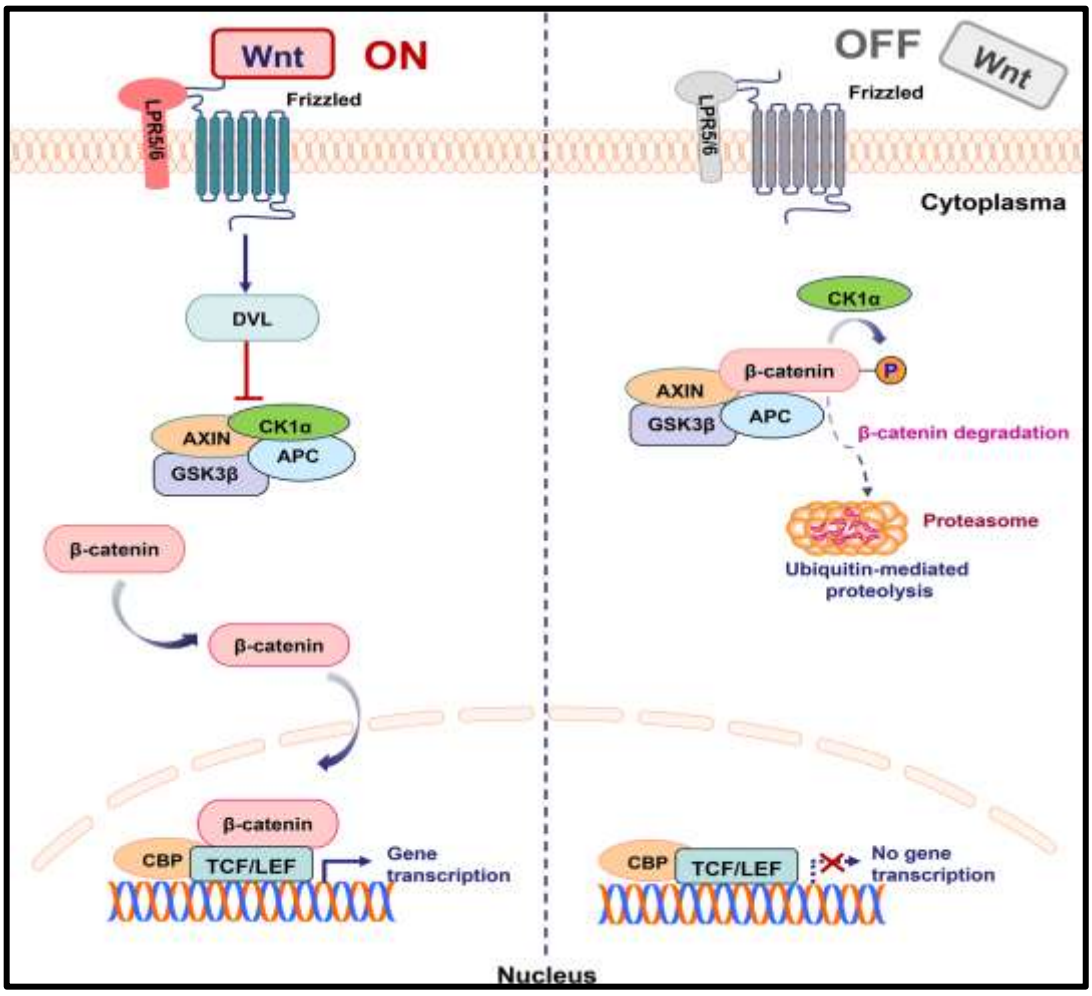

Figure (1): overview of the Wnt/β-catenin signaling **(12).**

The products of Wnt signaling pathway (Wnt target genes)

Multiple Wnt target genes have been identified and they are specific to each tissue type. The most common studied Wnt target genes include the following:

AXIN2, RNF43 and ZNRF3: genes encode proteins that function in negative feedback mechanisms to control the Wnt pathway

LGR5: positively regulates the pathway by binding to R-spondin ligands and facilitating downregulation of RNF43 and ZRNF3 **(13).**

Cyclin D1 and c-Myc: Proto-oncogenes that are involved in various types of cancers

Regulation of Wnt/β-catenin pathway

Wnt signaling is constantly regulated at several points along it signaling pathway to ensure its proper function by the following mechanisms:

Post-translational modification (PTMs)

Until now, more than 200 different types of PTM have been identified including the following:

Phosphorylation

It is mediated by addition of phosphate group to amino acid residues of protein.

Many components of Wnt/β-catenin pathway is regulated by phosphorylation such as Frizzled receptor, Wnt co-receptors, β-catenin, destruction complex members, and disheveled protein **(14).**

Ubiquitination
It is a process where ubiquitin protein is attached to a target protein and it is mediated by three types of enzymes: ubiquitin-activating enzyme (E1), ubiquitin-conjugating enzyme (E2), and ubiquitin ligases (E3)**.** It is involved in regulation and inactivation of β-catenin level in the absence of Wnt ligands through ubiquitination of phosphorylated β-catenin **(15).**
Deubiquitination
It is an opposite process of ubiquitination where ubiquitins are removed from target proteins by deubiquitinating enzymes (DUBs), so it modulates the stability of signaling factors **(15).**

Palmitoleic acid modification (Palmitoleation)
It is a post-translational lipid modification of all Wnts which regulates Wnt proteins localization, accumulation, secretion, and fuction by altering protein affinity to the cell membrane. This process is mediated by porcupine (PORCN) which is an O-acyltransferase enzyme that located on the endoplasmic reticulum and provides Wnt proteins with a palmitoleate group **(16).**

Wnt inhibitors
Dickkopf protein family: they inhibit the interaction of Wnt, Fz, and LRP5/6 by competitive binding to LRP5/6 co-receptors **(17).**
Sclerostin (Scler.): it has the same mechanism of DKK1

Secreted Frizzled-related proteins (SFRPs): they have high similarity with Frizzled receptors so they bind to Wnt proteins and prevent Wnt ligands binding to Frizzled receptor **(17).**
Wnt inhibitory factor-1 (WIF1): it inhibits Wnt signaling by direct binding to Wnt protein**s (18).**

Notum: an enzyme which removes palmitoleate group from Wnt proteins, so it blocks their extracellular secretion **(19)**

Figure (2): different types of Wnt inhibitors

Wnt activators
R-spondin family proteins (RSPO): they promote binding of Wnt proteins to LRP5/6 receptor and inhibit DKK1 binding to LRP5/6 **(20).**

Norrin (Norrie Disease Protein): it is suggested to have similar structure and function as Wnt ligands so it can activate Wnt signaling by binding to Frizzled and LRP5/6 **(21).**

Roles of the Wnt/β-catenin pathway in normal health state

The Wnt/β-catenin pathway participates in the physical processes and the development of different organs as the following:

Skeletal formation and development

It plays an important role in bone homeostasis by stimulating chondrogenesis, the differentiation and proliferation of osteoblasts as well as the differentiation and function of osteoclasts **(21).**

Gastrointestinal system

It plays a crucial role in regulating proliferation and homeostasis in normal gastric mucosa. Therefore, the dysregulation of the Wnt pathway in the form of overexpression and loss of Wnt inhibitors could be involved in the development of gastric carcinogenesis **(11).**

Liver development

The Wnt/β-catenin pathway is an important regulator that controls liver growth and regeneration in liver injury. So, its aberration or dysregulation could be associated with several common liver diseases such as cholestasis, liver fibrosis, fatty liver, and polycystic liver disease **(22).**

Cardiovascular system

It plays an important role during heart development and regulation of cardiomyocytes proliferation. It is also activated to stimulate cardiac remodeling in response to cardiac injury **(22).**

Respiratory tract

It plays an important role in the development and differentiation of the lung and promotes the differentiation of the airway epithelial cells and the regeneration of alveoli. Therefore, the imbalance of the Wnt/β-catenin signaling could be related to many lung diseases, including chronic obstructive pulmonary disease (COPD), pulmonary inflammation, idiopathic pulmonary fibrosis (IPF), and lung cancer **(23).**

Central nervous system development

The Wnt signaling regulates the formation and function of neuronal circuits by controlling neuronal differentiation, migration and polarization, axon outgrowth, dendrite development, synapse formation, and synaptic function **(24).**

Renal system

It has been revealed that Wnt signaling is crucial in normal nephrogenesis through the regulation of pronephric and nephrons development, mesenchymal-to-epithelial trans-differentiation (MET), tubulogenic, and morphogenesis**.** It is also found to be involved in kidney repair and regeneration after acute kidney injury. Dysregulation of Wnt signaling pathway is implicated in a wide variety of kidney disorders ranging from fibrosis, cystic formation and proteinuria to carcinogenesis **(25).**

Roles of the Wnt/β-catenin pathway in the immune system

Recent studies suggest that Wnt signaling performs an essential function in immune cell modulation, development, activation, regeneration, and downregulation as the following:

It plays a key role in the maintenance, proliferation, differentiation, and self-renewal of hematopoietic stem cells, which can further differentiate into immune cells, such as T cells, B cells, natural killer (NK) cells, and macrophages.

It regulates differentiation, maturation and activation of dendritic cells DCs **(25).**

It was thought to have role in the activation of natural killer T (NKT) cell development and function

It has been reported to perform a significant function in thymopoiesis and in T cell development and regulation **(26).**

It is found to be involved in the regulation of B-cell growth and B-cell proliferation through LEF1 **(27).**

Consequently, the dysregulation of the Wnt/β-catenin signaling can lead to development of various autoimmune diseases and cancer **(26).**

The role of Wnt/β-catenin pathway in diseases

It has been recently discovered that any aberration or dysregulation of the Wnt/β-catenin cascade could contribute to the development and progression of variety of disorders and cancers due to its involvement in many physiological processes such as cell proliferation, differentiation, migration, apoptosis, and tissue homeostasis **(12).**

Role in tumor

Aberrant activation of Wnt/β-catenin pathway can promote the transcription of many oncogenes such as c-Myc and CyclinD-1 **(9).**

The Wnt/β-catenin signaling pathway is associated with regulating the pluripotency, self-renewal and differentiation ability of stem cells, therefore any abnormal activation of the Wnt/β-catenin can promote cancer stem cells (CSC) progression and thus leads to deterioration and metastasis of cancer **(12).**

Colorectal, breast, lung, oral, cervical, and hematopoietic malignancies are the most prominent cancers that are associated with Wnt signaling abnormalities. As Wnt signaling has crucial roles in carcinogenesis, metastasis, cancer recurrence, and chemotherapy resistance, therefore, many components of the Wnt pathway represent interesting therapeutic targets for cancer treatment **(28).**

Metabolic diseases

Many studies have demonstrated that components of the WNT pathway are involved in pancreatic β-cell proliferation, lipid metabolism and glucose-induced insulin secretion. Therefore, it plays an important role in the pathophysiology of diabetes and WNT signaling components could be potential therapeutic targets **(29).**

Autoimmune diseases

The activation of Wnt signaling during an inflammation could repress regulatory T-cell (Treg) function, which can trigger an autoimmune response and predispose to pathogenesis of autoimmune diseases such as rheumatoid arthritis (RA), SLE, and ankylosing spondylitis (AS) **(3)**

Wnt signaling is a master regulatory pathway that keeps the balance between T helper 17 and regulatory T cells; thereby it can affect the outcome of immune response**.** Recently, the evolving roles of some microRNAs (miRNAs) (class of small and noncoding RNAs) have been recognized and implicated in the pathogenesis of autoimmune diseases due to their crucial role in the regulation of Wnt signaling activity **(29).**

Role of Wnt/β-catenin in SLE and lupus nephritis

The canonical Wnt pathway is hyperactivated in SLE and plays a significant role in lupus nephritis pathogenesis and induction of renal fibrosis.

The most important Systemic effects of increased Wnt signaling activity in SLE patients

Imbalance of bone remodeling

Over activation or dysregulation of Wnt signaling may result in an imbalance of bone remodeling in the form of stimulation of bone formation by inducing ostoblastic differentiation, increasing osteoblast proliferation, and inhibiting osteoblast apoptosis **(30).**

Induction of renal fibrosis

Many evidences suggest that sustained activation of Wnt/β-catenin pathway might play a significant role in the development and progression of lupus nephritis and renal fibrotic lesions with subsequent end stage renal disease **(31).**

Mechanism of renal fibrosis in lupus nephritis

When Wnt/β-catenin pathway is activated, β-catenin is accumulated and translocated to the nucleus where it forms a transcription activation complex with TCF/LEF that activates the expression of a set of target genes such as fibronectin, fibroblast-specific protein1 (Fsp1), matrix metalloproteinase-7 (MMP7), plasminogeng activator inhibitor-1, Snail-1, and Twist **(31).**

These genes are implicated in renal fibrosis by different ways such as the following**:**

Increasing in the synthesis and deposition of collagen and extracellular matrix metalloproteinases with consequent defective remodeling and loss of renal glomerular membrane integrity **(31).**
Interstitial myofibroblast activation. Podocytes injury and dysfunction with consequent proteinuria **(32).**

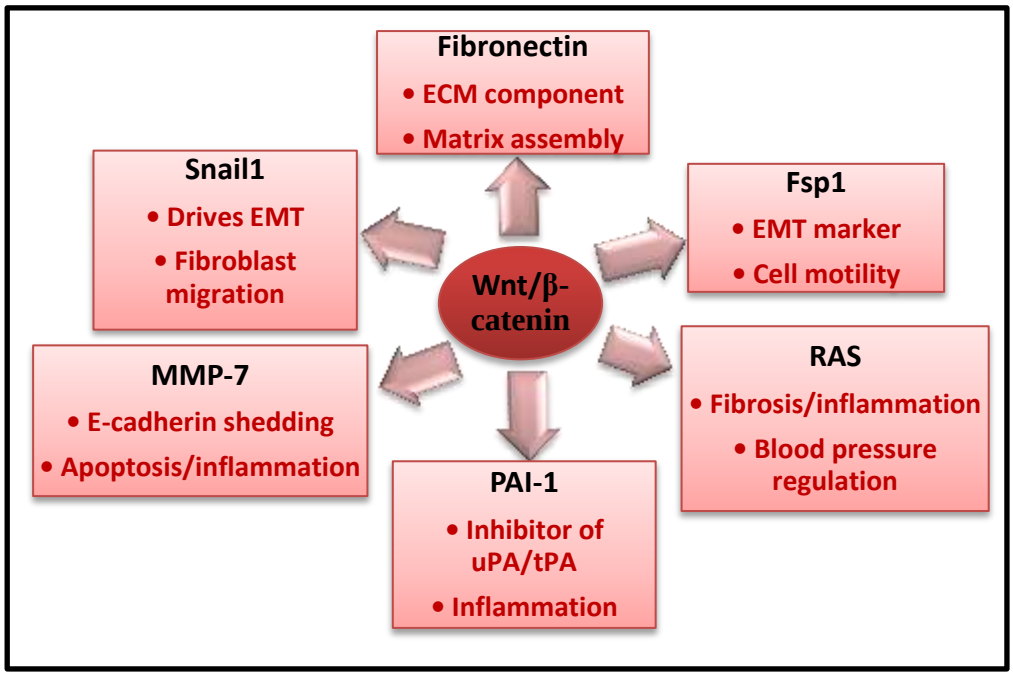

Figure (3): schematic representation shows several target genes that are relevant to kidney injury and fibrosis **(33)**

It has been suggested that blocking the WNT/β-catenin signaling attenuated renal fibrotic lesions as the overexpression of Dkk-1 inhibited the activation of β-catenin, fibroblast-specific protein 1 and αSMA

protein, which inhibited the transformation of myofibroblasts and the synthesis of type I collagen, as well as fibronectin, thus reducing collagen deposition **(25).**

Therefore, the continuous studies and researches that concerned about the Wnt/β-catenin pathway made it a promising and crucial pathway to understand the pathogenesis of lupus nephritis and to develop new therapeutic targets **(25).**

Induction of cellular senescence and osteoarthritis

Senescence is an irreversible cell cycle arrest that limits the proliferative potential of cells**.** Hyperactivated or dysregulated Wnt/β-catenin could produce stem cell aging by promoting senescence of mesenchymal stem cells of the bone marrow; therefore, the Wnt signaling may be associated with many aging-related diseases **(12).**

It was found that activation of Wnt/β-catenin signaling could promote chondrocyte senescence which plays a role in the development and progression of osteoarthritis **(34).**

Dickkopf-1 protein

Dickkopf-1 (DKK1) is a secreted glycoprotein which is a component of Wnt/β-catenin signaling pathway. It is a potent and specific antagonist of canonical Wnt /β-catenin signaling pathway and it was discovered in 1998 **(23).**

Structure and source of dickkopf protein

The dickkopf family in human consists of four main secreted and soluble glycoproteins of about 255 to 350 amino acids. These four members are DKK1, DKK2, DKK3 and DKK4 **(17).**

DKK1, DKK2 and DKK4 show some similarity in the primary sequence structure, but DKK3 differs from them, so it cannot regulate the Wnt signaling pathway by binding to the same receptors **(34).**

Among the DKK family members, DKK1 is the most commonly studied protein **(17).**

DKK1 protein is composed of 266 amino acids and its relative molecular weight is about 29 KDa **(35).**

DKK1 consisted of five domains as the following:

Signal sequence
Linker 1 (L1)
The amino-terminal cysteine-rich domains (N-terminal)
Linker 2 (L2)
The carboxyl terminal domain (C-terminal) **(17).**

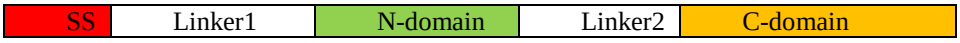

Figure (4): schematic diagram of the primary structures of full length DKK1 **(17).**

The amino-terminal cysteine-rich domain may be associated with an anti-apoptotic signaling pathway. The carboxyl terminal cysteine-rich domain is important for Wnt pathway inhibition and binding to LRP5/6 coreceptor to prevent formation of the FZ-LRP6 complex **(16).**

DKK1 gene:

DKK1 protein is encoded by DKK1 gene which located in the long arm of chromosome 10 **(35).**

DKK1 expression occurs mainly in bone, placenta, kidney, prostate and colon **(36).**

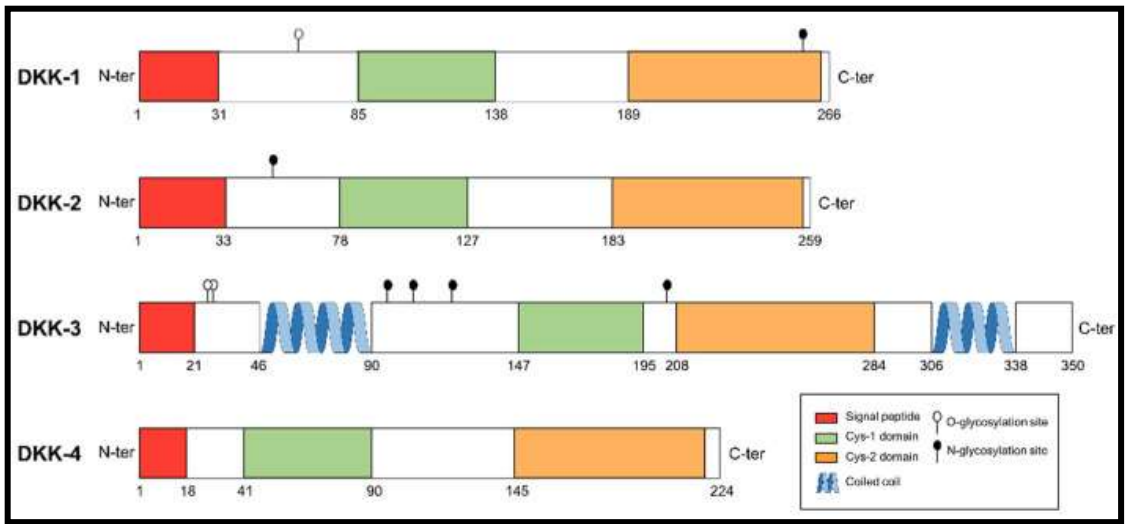

Figure (5): structure of human DKK protein family **(37).**

Function of DKK1

DKK1 is mainly involved in the embryonic development and bone formation and homeostasis in adults through inhibition of Wnt/β-catenin signaling pathway **(34).**

It can induce head formation during embryogenesis, so it was named Dickkopf that means big head in German. It also plays a key role in heart and forearm development during morphogenesis of embryo **(17).**

It acts as down-regulator or inhibitor of Wnt/β-catenin pathway **(35).**

Mechanism of inhibition of the Wnt/β-catenin pathway by DKK1

DKK1 regulates the canonical pathway mainly through inhibition of the typical Wnt signal pathway by the following mechanisms:

Competing with the LRP5/6 receptor for Wnt ligand **(35).**

Binding to kremen proteins (family of two transmembrane receptors for DKK1 characterized by their kringle domain**)** to form kremen-LRP6-DKK1 complex that is endocytosed to cells and degraded with subsequent decrease in LRP receptors in the cell membrane **(35).**

DKK1 forms a complex with LRP5/6 and frizzled which leads to phosphorylation of β-catenin **(35).**

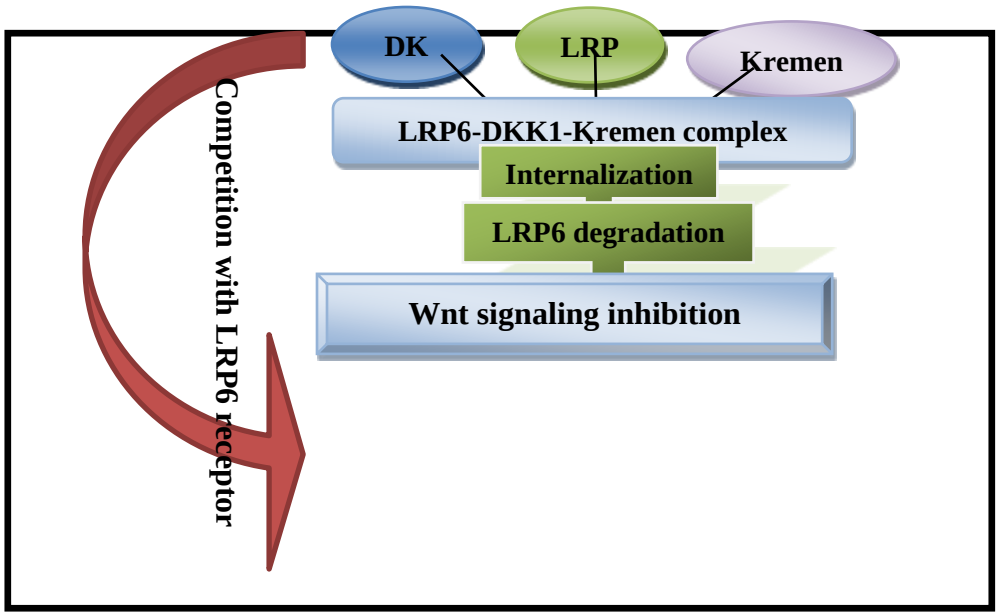

Figure (8): Schematic diagram of mechanism of Wnt pathway inhibition by DKK1

DKK1 role in other signaling pathways

It participates in activation of the c-Jun N-terminal kinase (JNK) pathway. This pathway is involved in many neurological disorders, heart diseases and cancers **(38).**

It is involved in activation of the Dickkopf1 - cytoskeleton - associated protein 4 (DKK1- CKAP4) signaling axis pathway that has a role in cancer cell proliferation **(38).**

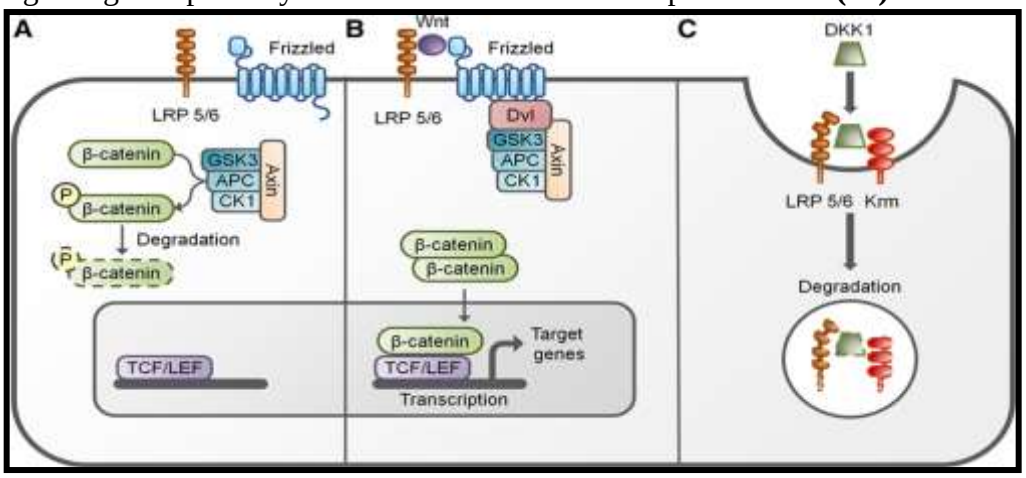

Figure (6): Wnt/β-catenin signaling pathway inhibition by DKK1. A, Inactive Wnt/β-catenin signaling. B, active Wnt/β-catenin signaling. C, Binding of DKK1 to LRP5/6 leads to a complex formation with the Kremen receptor (Kre), followed by degradation of the LRP5/6 receptor **(39)**

Clinical significance of DKK1 in different diseases

Dysregulation of DKK1, in the form of increased expression, can be associated with many health problems such as osteoporosis, lupus nephritis, Alzheimer's disease, diabetes, autoimmune diseases, and various cancers **(34).**

Therefore, DKK-1 may be used as a biomarker for the occurrence and development of cancer and autoimmune diseases such as lupus nephritis, and can be a possible target in the management of autoimmune diseases **(40).**

Role of DKK1 in cancer

Many evidences show that *DKK1* plays a complex and different role in tumor occurrence, development and metastasis in different tumor environments

DKK1 is expressed differently in different types of tumors as the following:

It is elevated in a wide variety of cancers such as lung cancer, bladder cancer, hepatocellular carcinoma, cervical carcinoma, multiple myeloma, breast cancer, and ovarian cancer, indicating that it may have a potential oncogenic function and it is associated with poor prognosis **(12).**

On the other hand, it is down-regulated in some tumors, such as prostate cancer and colorectal cancer **(34).**

DKK1 has different effects on the progression of different tumors as the following:

In most tumors, high expression of DKK1 could contribute to tumor progression by promoting migration, invasion, and proliferation of cancer cells, preventing their apoptosis and enhancing cancer stem cell-like properties **(17).**

However, in other tumor studies, highly expressed DKK1 can inhibit tumor invasion, metastasis and biological effect of tumor through inhibition of the classical Wnt pathway in tumors **(36).**

Collectively, DKK1 has lately become a focus of attention in cancer research, both as a biomarker and a potential therapeutic target.

Role of DKK1 in nephropathies

It was found that gene therapy using DKK1 significantly suppresses fibroblast-specific protein 1(Fsp1), type I collagen, and fibronectin in cases of obstructive nephropathy, thereby it could repress the activation of myofibroblast and improve renal fibrosis **(34).**

In vivo, DKK1 can effectively inhibit the renal inflammation and fibrosis associated with ureteral obstruction. As a Wnt antagonist, DKK1 blocks Wnt-mediated fibrosis and also down-regulates Wnt signaling pathway under fibrotic conditions. **(23).**

Role of DKK1 in the renal involvement in SLE

DKK1 has a protective role against renal deterioration by the following mechanisms:

Regulation of excess fibrosis by dissolving the excess matrix deposits
Maintaining of renal glomerular membrane integrity
Limitation of podocytes lesions and reduction of proteinuria **(33)**
inhibiting myofibroblast activation and ultimately fibrosis **(33)**

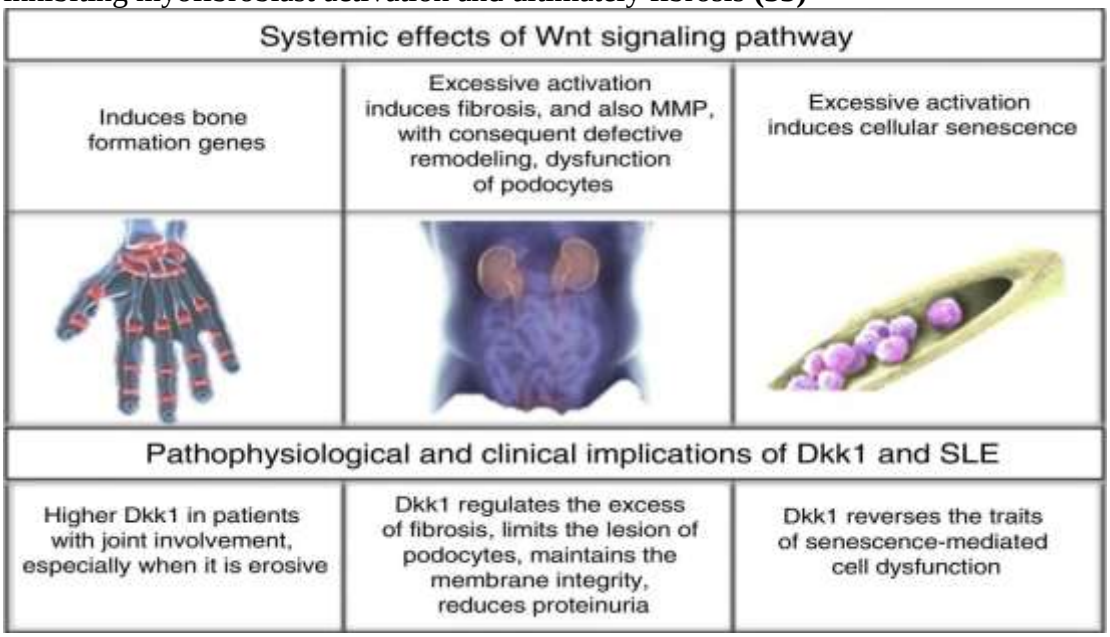

Figure (7): Systemic effects of Wnt signaling pathway and its inhibitor Dkk1 **(12).**

Role of DKK1 in bone diseases

Both preclinical and clinical data were suggestive that DKK1 overexpression can impair osteoblast activity and cause bone loss as in patients of multiple myeloma and ankylosing spondylitis **(12).**

In plasma myeloma cells, it has been well established that DKK1 blocks osteoblast differentiation and thereby it causes impaired bone formation, pathological fractures, and fracture repair inhibition. Therefore, treatment with DKK1 antibody could be an effective way of increasing bone formation in bone loss diseases. In addition, DKK1 blockade prevented bone erosion in the sacroiliac joints and enhanced sacroiliac ankylosis in ankylosing spondylitis patients **(13).**

Role of DKK1 in Alzheimer's disease

The Wnt signaling pathway is fundamental to the development of the central nervous system and it is involved in synaptic stability, development of neuronal circuits and cognition, so the dysregulation of Wnt signaling could be involved in the pathophysiology of Alzheimer's disease **(41).**

As a negative regulator of Wnt signaling, the excess DKK1 in the brain has been demonstrated to trigger synaptic loss mediated by amyloid-β and neuronal apoptosis and it has been linked to predisposition of Alzheimer's disease **(42).**

Role of DKK1 in atherosclerosis

DKK1 has been identified as one of the platelet-derived molecules participating in the atherosclerotic process**.** It is also involved in endothelial dysfunction and the inflammatory interaction between platelets and endothelial cells (ECs). These evidences suggest that Dkk-1 can contribute to the earlier stages of atherosclerosis and it could be a promising biomarker in patients at high cardiovascular risk and a new target of statins, which considered an important medication for prevention and treatment of cardiovascular diseases **(43).**

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