Wnt Signaling Pathway in Cardiovascular and Other Clinical Diseases: Review

Kardiyovasküler ve Diğer Klinik Hastalıklarda Wnt Sinyal Yolu

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ABSTRACT The Wnt signaling pathway (WntSP) plays important roles during embriyonic development and in homeostatic mechanisms. Abnormal Wnt/beta-catenin signaling is associated with many diseases including cardiovascular diseases, cancer, obesity and degenerative disorders. Mutations in the components and the activators or inhibitors of WntSP cause a wide spectrum of diseases. Since each one of them is involved in some regulatory processes, mutations may lead to aberrant regulations as well as severe clinical consequences. Since activation of WntSP is closely associated with the development of many cancer types, several Wnt pathway specific inhibitors are currently under development. Inhibition of WntSP gains importance for the new therapeutic approaches in cancer treatment, during which, the aim is to reduce beta-catenin and thus T-cell factor-dependent transcription. Inactivation or silencing of tumor suppressors, which serve as Wnt antagonists, causes various human cancers and tumor formation. In this review article, WntSP as a therapeutic target in cancer therapy, its significance in obesity treatment, its involvement in the pathogenesis of bone-related diseases, aortic valve calcification, degenerative muscle diseases as well as some neurodegenerative diseases were discussed. WntSP along with its components and contributors appears to be a new pathway due to its close association with diseases gaining importance throughout the world in recent years. Investigations performed on each one of these parameters and on this complicated pathway as a whole will be helpful in the prevention and during the treatment of the cardiovascular diseases and some other closely associated diseases.

Key Words: Wnt proteins; signal transduction; beta catenin; diseases; obesity; Alzheimer disease

ÖZET Wnt sinyal yolu (WntSY) embriyonik gelişim sırasında ve homeostatik mekanizmalarda önemli görevler üstlenmektedir. Anormal Wnt/beta-katenin sinyali, kardiyovasküler hastalıklar, kanser, obezite ve dejeneratif bozuklukları da içerecek tarzda birçok hastalık ile beraberlik göstermektedir. WntSY aktivatörleri ve inhibitörleri ile bileşenlerindeki mutasyonlar çok çeşitli hastalıklara neden olmaktadır. Bunların her birinin bir takım düzenleyici olaylarda yer almaları nedeniyle, mutasyonlar ciddi klinik sonuçlara ve kusurlu düzenlemelere yol açabilmektedir. WntSY nun aktivasyonu birçok kanser tipinin gelişimi ile yakından ilişkili olduğu için, günümüzde Wnt yoluna özgü birtakım inhibitörler ile ilgili çalışmalar sürdürülmektedir. WntSY nun inhibisyonu, beta-katenin ve ardı sıra T hücre faktörü-bağımlı transkripsiyonun azaltılmasının amaçlandığı kanser tedavisi sürecinde tedaviye ilişkin yeni yaklaşımlar açısından önem kazanmaktadır. Wnt antagonistleri olarak görev yapan tümör baskılayıcılarının inaktivasyonu ya da sessizleştirilmesi insanlardaki çeşitli kanser ve tümör oluşumlarına neden olmaktadır. Bu inceleme makalesinde, kanser tedavisinde tedaviye yönelik bir hedef olarak WntSY, bu yolun obezite tedavisindeki önemi ile kemiğe ilişkin hastalıkların, aort kapağı kalsifikasyonunun, dejeneratif kas hastalıklarının ve bazı nörodejeneratif hastalıkların patogenezindeki rolü tartışılmıştır. Bileşenleri ve katkıda bulunan parametreleri ile birlikte WntSY, son yıllarda tüm dünyada önem kazanan hastalıklar ile olan yakın beraberliği nedeniyle yeni bir yol olarak ilgi çekmektedir. Bir bütün olarak bu karmaşık yol üzerine ve bu parametrelerin her biri üzerine gerçekleştirilecek araştırmalar, kardiyovasküler ve ilgili hastalıkların tedavileri sırasında ve önlenmeleri konularında yardımcı olacaktır.

Anahtar Kelimeler: Wnt proteinleri; sinyal iletimi; beta katenin; hastalıkları; şişmanlık; Alzheimer hastalığı

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The Wnt signaling pathway (WntSP) plays important roles during embriyonic development and in homeostatic mechanisms. They are involved in cell polarity, differentiation, proliferation, survival, motility, maturation, activity and function. Wnt ligands can be classified into two distinct groups based on the subcellular signaling elements. The first group, which includes Wnt1, Wnt3a, Wnt7a and Wnt 8, uses the "canonical" pathway for intracellular signaling. The second group includes Wnt4, Wnt5a, Wnt6 and Wnt 11 and uses a very different subcellular signaling network, the "noncanonical" pathway. Of the currently known pathways of Wnt signaling (Figure 1), the best studied is the canonical Wnt/β-catenin pathway. Wnt pathway regulates the stability of β-catenin and therefore β-catenin dependent gene expression by preventing β-catenin phosphorylation-dependent degradation. In the absence of the Wnt ligand, the cytosolic β-catenin protein level is low because it undergoes ubiquitination and proteosomal degradation due to its phosphorylation. Abnormal Wnt/β-catenin signaling is associated with many diseases, including diabetes, hyperlipidemia, early coronary diseases, obesity, cancer, osteoporosis, lung diseases and degenerative disorders.[1-13]

Wnt/β-CATENIN SP, β-CATENIN DEGRADATION COMPLEX, CLINICAL CONSEQUENCES OF MUTATIONS IN THE COMPONENTS, ACTIVATORS AND INHIBITORS OF THE Wnt/β-CATENIN SP

The Wnt family comprises around 20 secreted glycoproteins exhibiting diverse functions and expression patterns. They regulate the Wnt/β-catenin SP. The Wnt pathway becomes activated upon binding of Wnt proteins to a receptor complex consisting of the Frizzled (Frz) receptor and low density lipoprotein receptor-related protein 5 or 6 (LRP 5/6). β-catenin is a multifunctional protein and essential for the cell-cell adhesion of the normal polarized epithelia. It links E-cadherin to α-catenin and mediates anchorage of this complex to actin. The other function of β-catenin is related to its participation into WntSP. β-catenin interacts with the Wnt ligands directly, or it acts through the specific cell surface receptors functioning as co-receptors for the Wnt ligands.[1-3,14]

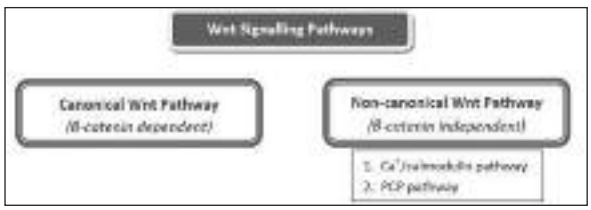

FIGURE 1: Wnt Signaling Pathways *(PCP; Planar Cell Polarity).*

The interaction of Wnt proteins with their receptors on the cell surface is the first step in transducing an extracellular signal into intracellular responses. Ten Frz proteins, which are members of the family of seven-pass transmembrane receptors, have been identified as Wnt receptors. In addition to Frz proteins, the Wnt/β-catenin SP requires single-pass transmembrane proteins that belong to a subfamily of LRPs; LRP5 and LRP6.[12,15-17]

When Wnt binds to Frz-LRP5/6 receptor complex, axin is directed to the plasma membrane, Disheveled (Dsh) is activated. These events altogether cause the inhibition of β-catenin phosphorylation and prevent its degradation. This causes β-catenin stabilization and accumulation in the cytoplasm. β-catenin, then, enters the nucleus, forms transcriptional complexes with TCF(T cell factor)/LEF (lymphoid enhancer factor)-transcription factor family nuclear proteins, acts as a transcriptional coactivator and enhances the expression of target genes in this compartment of the cell (Figure 2).[1-3,14]

β-catenin degradation multiprotein complex is composed of axis inhibitor (axin), β-catenin, adenomatous polyposis coli gene product (APC), casein kinase 1 (CK1) and glycogen synthase kinase 3β (GSK3β). In the absence of Wnts, β-catenin is phosphorylated. Phosphorylation of β-catenin is a key event, which determines the fate of Wnt/β-cateninSP. APC gene product, CK1 and GSK3β are essential for β-catenin phosphorylation. Phosphorylated β-catenin, recognized by an ubiquitin ligase subunit; β-Trcp, undergoes ubiquitination and then, degradation in proteosomes.[1-3,14]

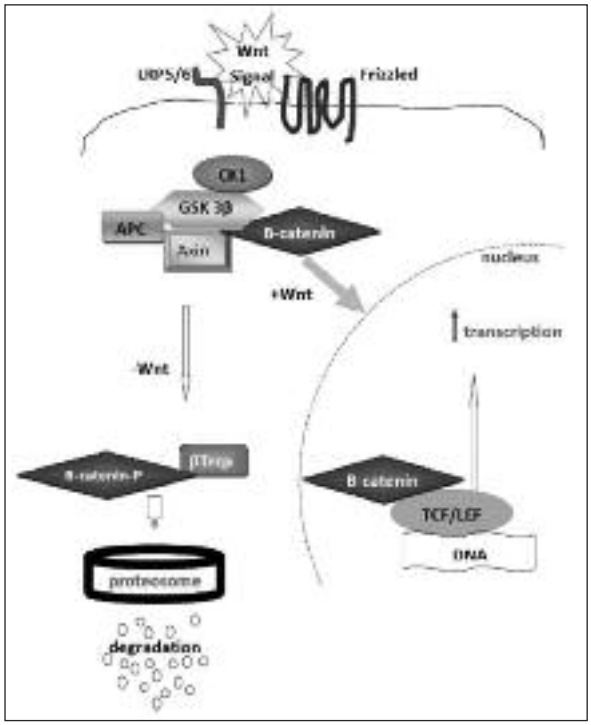

FIGURE 2: Fate of Canonical Wnt/β-catenin pathway in the presence and in the absence of Wnt signaling. *(APC; adenomatous polyposis coli gene product, axin; axis inhibitor, CK1; casein kinase 1, GSK3β; glycogen synthase kinase 3β, LRP 5/6;* low density lipoprotein receptor-related protein 5 or 6, *LEF; lymphoid enhancer factor, TCF; T cell factor.)*

Mutations in the components and the activators or inhibitors of WntSP cause a wide spectrum of diseases. Since each one of them is involved in some regulatory processes and/or is related to the target genes of some clinically important proteins, mutations may lead to aberrant regulations as well as severe clinical consequences.[2,18-20] Some selected examples related to the mutations are shown in Figure 3.

LRPs are a family of cell-surface receptors involved in diverse biologic processes, including lipid metabolism, retinoid uptake and neuronal migration. LRP5 regulates two different functions; bone formation and vision.[21]

Mutations in the LRP5 gene affect bone mass in humans. These mutations may cause high bone mass or osteoporosis.[22-27]

LRP5 is also important during eye development. It is essential for the development of retinal vasculature. LRP5 mutant mice have been proposed as a useful model to explore the clinical manifestations of familial exudative vitreoretinopathy in humans.[25,28,29]

The LRP5 receptor and WntSP may also play a critical role in the calcification of aortic valves. Vascular calcification is a process very similar to bone mineralization and many of the key regulators of bone formation and bone mass regulation are active during cardiovascular calcification. The mineralization process in aortic valves is a consequence of abnormal activation of WntSP.[2,25,27,30-33]

Identification of a missense mutation in LRP6 gene in a family with autosomal dominant early coronary artery disease (CAD) links to a single gene defect in Wnt signaling to CAD and multiple cardiovascular risk factors.[9]

A significant association between single-nucleotide polymorphisms (SNPs) and haplotypes in the LRP5 gene with obesity suggests the importance of LRP5 in the pathogenesis of human obesity.[34]

Soluble/secreted Frizzled-related proteins (sFRPs) directly bind to Wnts and make them unavailable for LRP5 activation. Therefore, mutations on this and the other components of this pathway or allelic variants may be related to the pathophysiology of several bone diseases including osteoporosis. There are some associations between Wnt inhibitors and bone metastasis. Wnt antagonists e.g. sFRPs appear to promote the development of osteolytic lesions and contribute to the formation of osteolytic disease. sFRP1 acts as a negative regulator of trabecular bone formation in adult mice. sFRP1 deficiency may cause cellular alterations. It may influence bone remodeling through some mechanisms, including the regulation of osteoclastic activity.[23,35-37]

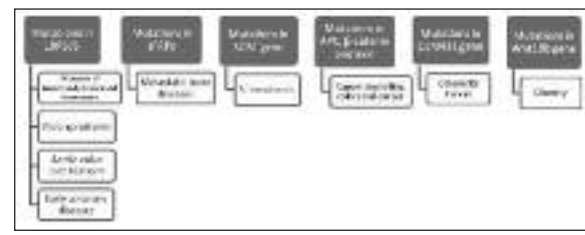

FIGURE 3: Mutations in the components of WntSP and the associated diseases.*(LRP 5/6; low density lipoprotein receptor-related protein 5 or 6, sFRP; soluble/secreted Frizzled related protein)*

Mutations in modulators of Wnt signaling such as the SOST gene, which produces sclerostin, give rise to the increased bone mass disease, sclerosteosis.[2]

Mutations in APC gene, CTNNB1 gene, β-catenin and Axin lead to a number of different types of cancer. The majority of colorectal cancers are caused by the alterations in the molecules, which participate in WntSP, particularly the mutations in the APC gene and to a lesser extent, in the CTNNB1 gene. Mutations in the APC gene result in defective APC protein, which cannot form β-catenin degradation complex. Mutation in the CTNNB1 gene is often detected in CK1 and GSK3β phosphorylation sites of the complex. Mutations in both genes lead to the activation of WntSP stimulated by the accumulation of β-catenin. Transactivation of a set of TCF-4 target genes by accumulated β-catenin is crucial in colorectal cancers.[1-3,18-20] Overexpression of Wnt-1 or a β-catenin mutant activates Wnt/β-cateninSP, which inhibits adipogenesis.[2,38,39]

One proband with early-onset obesity was found to be heterozygous for a C256Y mutation. It abolished the ability of Wnt 10b to activate WntSP and block adipogenesis. This mutation and the other rare missense variants represent the first naturally occurring missense variants of Wnt 10b. All relatives of the proband who carried this allele were either overweight or obese. The finding of a non-functioning Wnt 10b allele in a human family affected by obesity suggests that Wnt 10b might be a potential monogenic/oligogenic factor in severe familial obesity.[40]

These are just a few examples emphasizing the clinical significance of the members of WntSP and the related mechanisms confined to a variety of diseases.

WntSP is controlled by Wnt ligands, Wnt receptors and Wnt inhibitors. Dickkopf 1 (Dkk1), a Wnt inhibitor, inhibits Wnt/β-catenin signaling by binding to and antagonizing LRP5/6. On the other hand, sFRPs block Wnts by preventing their binding to Frz receptors.[41-46]

Recently, two compounds (CGP049090 and PFK 115-584) have been identified, which specifically inhibit complex formation of β-catenin and LEF1 leading to its transcriptional inactivation in colon carcinoma cell lines.[47]

Considering that the WntSP is involved in various developmental stages and that misregulation of Wnt signals at cell surface levels is involved in many diseases, a good understanding of Wnts, their receptors, or antagonists is highly required because of the potential use of them as molecular targets for therapeutic usage.[12]

SIGNIFICANCE OF WNTSP IN CLINICAL DISEASES

In this article, WntSP in cardiovascular diseases (CVDs) and some other closely associated diseases will be reviewed.

WntSP AND DISORDERS OF CARDIOVASCULAR SYSTEM

Wnt proteins are implicated in a wide variety of developmental and physiological processes. WntSP plays an important regulatory role in the vasculature and is required for cardiac and vascular development, including myocardial specification, cardiac morphogenesis and cardiac valve formation as well as endothelial and vascular smooth muscle cell proliferation. Defective Wnt signaling can result in different cardiac and vascular abnormalities. Wnt signaling activity is quite low under normal circumstances. However, this pathway is reactivated during the pathological cardiac remodeling induced by increased pressure, in injured arteries and after myocardial infarction.

Inhibition of WntSP results in increased angiogenesis, better infarct healing and an attenuated hypertrophic response of the heart. Therefore, pharmacological inhibition of WntSP may be suggested as a therapeutic strategy to prevent excessive cardiac and vascular remodeling.[48,49]

In spite of the existence of strongly emphasized relations between WntSP and some diseases e.g. cancers, obesity, the role of this pathway in CVDs has not been clearly described yet. Vascular calcification is a major cause of CVDs in the dialysis patients. Probable mechanisms, which reveal the association between osteoporosis and vascular calcification, are also suggested.[50]

Valvular heart disease is still an important cause of cardiovascular morbidity and mortality.[51] WntSP is also involved in regulation of cardiac valve formation and in the mineralization process in aortic valves. It is active in cardiovascular calcification.[33,52]

Vascular calcification is also quite important from the point of view of chronic renal failure (CRF). Vascular calcification is associated not only with passive calcium phosphate deposition, but also with an active, cell-mediated process.[53] Cardiovascular events are the leading causes of mortality in CRF. The risk of CVDs in patients with CRF appears to be much greater than in the general population. Dialysis patients constitute a high-risk subset of patients for developing CVD. Vascular calcifications are very frequent extraosseous calcifications in patients with chronic renal diseases. In end stage renal disease patients, extensive vascular calcification in coronary arteries can be observed. Cardiovascular calcification may affect the arterial media, atherosclerotic plaques, myocardium, and heart valves. Medial calcification causes arterial stiffness and consequently increased pulse pressure. Valvular calcification mostly affects the aortic but also affects the mitral valves in dialysis patients and contributes to progressive stenosis and associated morbidity.[54,55]

Dkk1, a major modulator of Wnt signaling, is identified as a novel mediator in platelet-mediated endothelial cell activation. It enhances inflammatory interaction between these cells and shows increased expression in atherosclerosis.[56]

Folate binding protein one (Folbp1) is recently introduced as an important candidate mediator, which promotes embryonic myocardial cell proliferation, apoptosis and differentiation through the WntSP.[57]

Further studies, which will be performed in this field will enlighten these associations, which have not been clearly defined yet.

WntSP AND CANCER

The relationships between obesity and CVDs are fairly defined. Growing evidence also points out the association of obesity with malignant diseases. Excess body weight is found to be associated with increased risk of various cancers.[58]

Activation of WntSP is closely associated with the development of many cancer types e.g. gastric, colorectal, prostate cancers.[59-63] Therefore, inhibition of WntSP gains importance for the new therapeutic approaches in cancer treatment, during which, the aim is to reduce β-catenin and thus TCF-dependent transcription.[64-66]

Cadherin-17 (CDH17) adhesion molecule has been shown to be up-regulated in human liver cancers and identified as a novel oncogene in hepatocellular carcinoma. The antitumor mechanisms underlying CDH17 inhibition involve inactivation of Wnt signaling, because growth inhibition and cell death are accompanied by relocalization of β-catenin to the cytoplasm. This suggests that CDH17 is an attractive therapeutic target for this malignancy.[67]

Tumor suppressor molecules e.g. Sox7 protein suppress β-catenin mediated transcriptional activity and down-regulate Wnt signaling.[68,69] Inactivation or silencing of tumor suppressors e.g. the adenomatous polyposis coli (APC), Sox7, sFRPs, Wnt inhibitory factor-1 (WIF-1), which serve as Wnt antagonists, cause various human cancers and tumor formation.[69,70] Progesteron induction of Dkk1 results in inhibition of Wnt signaling in the human endometrium. This Wnt inhibitory effect of progesterone is likely to play a rate-limiting role in the maintenance of endometrial homeostasis and, on its loss, in tumor onset and progression toward malignancy.[71] WntSP is also inhibited by the inhibition of cyclooxygenase-2, which exerts an anticarcinogenic potential.[72]

Colorectal carcinoma is one of the major malignancies worldwide. sFRPs play important roles in tumor progress through antagonizing Wnt signaling. sFRP-1 and sFRP-4 appear to be candidate markers for colorectal lesions.[73] Cancer cells stop growing and undergo differentiation upon inhibition of WntSP. A nonsteroidal antiinflammatory drug, sulindac, decreases β-catenin levels and inhibits the growth of tumors activated by β-catenin in

colorectal cancers.[8,74,75] Cardiovascular effects of anticancer drugs, cardiovascular effects of radiation therapy and direct effects of oncologic diseases on cardiovascular system are major problems to be considered.[76] Considering the association between some cancers and Wnt signaling, the benefits of therapeutics targeting this pathway are clear. Therefore, several Wnt pathway specific inhibitors are currently under development.

WntSP AND METABOLIC DISEASES

From a clinical point of view, it is well established that obesity is associated with metabolic co-morbidities such as arterial hypertension and pancreatic β-cell dysfunction.[77] Obesity is an important risk factor for coronary heart disease, ventricular dysfunction, congestive heart failure, stroke, and cardiac arrhythmias.[78] Central obesity is one of the major cardiovascular risks among Turks, which leads tightly to atherogenic dyslipidemia.[79]

WntSP, an extracellular signaling pathway, affects adipogenesis.[10,80] Inhibition of Wnt-signaling is a prerequisite for the differentiation of adipocytes.[39] Adipocytes target endocrine cells because they secrete Wnt signaling molecules to regulate metabolic functions.[77] WntSP is regulated by some proteins including β-catenin. As activated β-catenin prevents adipogenesis it induces myogenesis and osteoblast differentiation.[38,81] Inflammation promotes adipogenesis. Low-grade chronic inflammation associated with maternal obesity may alter fetal skeletal muscle development through several mechanisms including down-regulation of Wnt signaling, which attenuates myogenesis. In summary, inflammation down-regulates myogenesis and enhances adipogenesis in fetal skeletal muscle.[82-84] Components as well as the inhibitors of the pathway should be considered because of the association between WntSP antagonists and many diseases including obesity. Mutations in the Wnt-10b gene are described in obesity. Polymorphisms of LRP5 are also associated with obesity phenotypes.[9,34,40,85] Abnormal recruitment of adipose precursor cells is involved in hyperplasia of adipose tissue in severe obesity.[86] Therefore, pharmacological molecules that control adipose stem cell pool gain importance.

Activation of WntSP inhibits adipogenesis.[85,87,88] WntSP modulators may be useful in treating disease. Lithium (Li) activates WntSP by inhibiting GSK3β and thus, inhibits adipogenesis.[39,89] Wnt genes; Wnt10b and Wnt1, are capable of inhibiting adipogenesis through activation of the WntSP.[39] Wnt5b promotes adipogenesis by antagonizing WntSP. WntSP is the regulator of adipocyte differentiation.[90] Inhibiting negative regulators of WntSP, e.g. Cby, Wnt-5b or axin, provides new therapeutic options for obesity and its associated disorders.[85,90]

Dact1, a preadipocyte gene that decreases during adipogenesis, regulates adipogenesis through coordinated effects on gene expression that selectively alter the components of the Wnt/β-catenin SP. A functional network formed by Dact1, sFRP, and Wnt ligands facilitates cross talk in adipose tissue between preadipocytes and mature adipocytes. Dysregulation of this network may ultimately lead to a spectrum of adipose tissue cellularity ranging from hyperthrophy to hyperplasia. Similarly, modulation of this network by targeting Dact1 may be of therapeutic value to prevent obesity-associated metabolic complications.[91]

Inhibitors of WntSP are of great concern because of their possible involvement in therapeutic protocols of many diseases. GSK3β involved in differentiation of preadipose cells may be a therapeutic target. Considering the fact that abnormal WntSP is associated with obesity as well as cancer, exploration of the further details of WntSP may be helpful in enlightening the link between cancer and obesity from the molecular point of view.

WntSP AND NEURODEGENERATIVE DISEASES

Aside from the processes related to carcinogenesis and obesity,[7,79] WntSP is suggested to play also in neurodegenerative diseases such as Alzheimer's disease (AD).[11,92-95] Atherosclerosis is one of the risk factors for AD. Individuals with cardiovascular risk factors have an increased risk of both vascular dementia and AD.[96]

The abnormal accumulation of amyloid-beta protein (Aβ) in the form of amyloid plaques is the major biomarker of AD. The alternative processing

of amyloid -precursor protein (APP) in the brain of AD patients leads to the production of the insoluble aggregates of neurotoxic Aβ. Aβ fibrils induce neurotoxicity caused by neuronal cell death. Aβ-dependent neurotoxicity leads to the inactivation of WntSP by the activation of β-catenin degradation complex. β-catenin-mediated transcription plays an important role in neuronal viability and prevents Aβ-induced toxicity.[97-102] Interaction between neurons and Aβ fibrils, and its effect on the parameters of β-catenin degradation complex as well as the performance of WntSP are summarized in Figure 4.

Li acts as a neuroprotective agent against Aβ-induced toxicity through WntSP. Li therapy reversibly inactivates GSK3β and prevents Aβ-induced β-catenin destabilization. This activates WntSP.[89,95,103,104]

Li or other compounds, which are capable of activating WntSP set a stage for the new era on the therapeutic interventions in AD.

Increased evidence suggests a role for altered Wnt/β-catenin signaling in the etiology of AD, neuropathologically characterized by amyloid plaques and hyperphosphorylated tau accumulation. Genetic varations in LRP 6 in AD have been associated with reduced Wnt signaling. Tau phosphorylation is mediated by GSK3β, a key antagonist of the Wnt pathway. Participation of this pathway in AD pathogenesis makes the components of WntSP possible therapeutic targets in the future.[105]

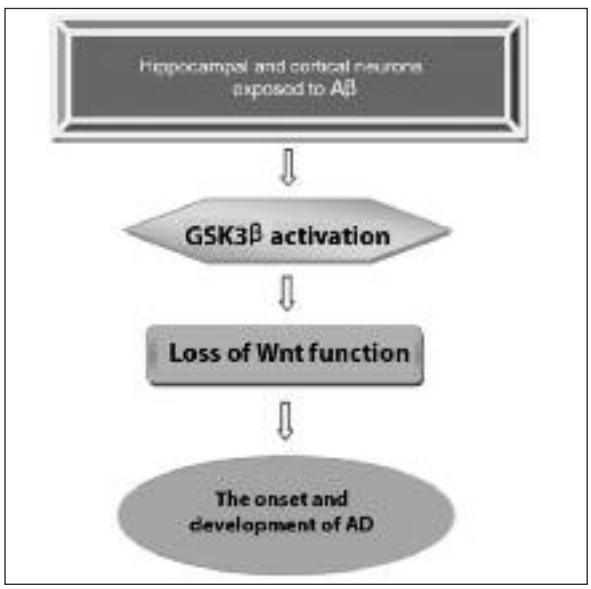

FIGURE 4: Participation of WntSP in the development of AD. *(Aβ; amyloid-beta protein, AD; Alzheimer's disease, GSK3β; glycogen synthase kinase 3β).*

WntSP AND DISORDERS OF BONE AND MUSCLE

Mutations in genes encoding the components of WntSP cause aberrant regulation of the pathway and contribute also to the pathophysiology of a wide spectrum of diseases other than disorders of cardiovascular system, various types of cancer (hepatocellular carcinoma, pancreatic cancer, ovarian cancer, prostate cancer, breast cancer), obesity and neurodegenerative diseases.[2,7,10,11,61,106,107] The most striking examples in this group are bone-related diseases and some muscle diseases.[38,108-110]

Recent reports suggest the role of WntSP in the regulation of osteoblastogenesis. Canonical Wnt signaling encourages mesenchymal progenitor cells to differentiate into osteoblasts. In osteoblasts, Wnt SP also promotes proliferation and mineralization, while blocks apoptosis and osteoclastogenesis by increasing the osteoprotegerin (OPG)/ receptor activator of NF-kappa β ligand (RANKL) ratio.[22] BMP-2 may regulate osteoblast function, differentiation and bone formation in part through modulation of the Wnt/β-catenin signaling.[111] Sclerostin, a SOST gene product, inhibits BMP-stimulated bone formation. It antagonizes Wnt signalling in osteoblastic cells. Increased WntSP may cause high bone mass in sclerosteosis and van Buchem disease.[109,110,112-117]

Wnt/β-catenin signaling is an important pathway for bone development and homeostasis. Wnt modulators such as sFRPs; sFRP-1 and sFRP-2, are expressed in osteoblasts and differentially regulate hematopoietic stem cells.[118] Overexpression of sFRP-1, an antagonist of Wnt signaling, inhibits bone formation and attenuates the anabolic action of parathyroid hormones on bone.[119]

Dkk1 has a direct inhibitory effect on osteoblasts, disrupts the Wnt 3a-regulated OPG and RANKL expression in osteoblasts. Since it indirectly enhances osteoclast function in multiple

myeloma, Dkk1 with its pivotal role in bone health and disease, may be suggested as a promising target for the management of myeloma patients with lytic bone disease.[120]

Currently, there are no efficient treatments for degenerative muscle diseases e.g. Duchenne muscular dystrophy, the most common and lethal genetic muscle disorder in children. Stem cell therapy may be a promising strategy for the treatment of this disease; however, some ethical and immunological problems have not been overcome yet. On the other hand, mesenchymal stromal cells (MSC) are capable of differentiating into skeletal muscle cells, osteoblasts, chondrocytes and adipocytes. WntSP plays a potentially important role in the control of the stem cell properties of MSC. Therefore, WntSP is associated with myogenesis in embryogenesis and postnatal muscle regeneration. Activation of the pathway by overexpression of a stabilized β-catenin promotes myogenesis and induces myogenic differentiation in MSC. This may allow for its therapeutic application in degenerative muscle diseases.[38,108]

CONCLUSION

Cardiovascular diseases aside from cancers, obesity, neurodegenerative diseases are severe clinical problems awaiting for the therapeutic solutions. There are many attempts to detect some targets and the pharmacological aids to affect them as the potential treatment options. WntSP along with its components and contributors appears to be a new pathway due to its close association with the diseases gaining importance throughout the world in recent years. Investigations performed on each one of these parameters and on this complicated pathway as a whole will be helpful in the prevention and during the treatment of the related diseases.

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