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An overview of the effect of the Wnt signaling pathway in lung cancer

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ABSTRACT

Wnt signal is known to play a significant role in many cellular processes such as cell proliferation, survival, self-renewal, and differentiation. This pathway has been linked to various types of cancer after the definition of mutations and various dysfunctions after the discovery of this pathway. Lung cancer is a type of maligned cancer caused by the deterioration of cellular homeostasis due to various reasons, such as the unbalanced proliferation of cells in the lung, gene expression change, epigenetic factors, and mutation accumulation. It is the most common type of cancer among all types of cancer. There are also various intracellular signal transmission pathways known to be active or inactive in cancer. Although the role of the Wnt signaling pathway in lung cancer development has not yet been clearly clarified, its role in the development and treatment of cancer is seen as very important. Active Wnt signaling or *Wnt-1* is overexpressed in lung cancer. Therefore, targeting the Wnt signal pathway is important in cancer treatment, especially lung cancer. Because by creating a minimal effect on somatic cells, inhibiting tumor growth, and preventing resistance to classic treatment methods such as chemotherapy, radiotherapy is necessary for the treatment of disease. New treatment methods developed to target these changes will find a cure for lung cancer. In fact, its incidence may be reduced.

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Introduction

Lung cancer is a type of maligned cancer caused by the deterioration of cellular homeostasis due to various reasons, such as the unbalanced proliferation of cells in the lung, gene expression change, epigenetic factors, and mutation accumulation (1). Out-of-control proliferating cells tumor and metastasize to surrounding tissues. It is the most common type of cancer among all types of cancer. Lung cancer ranks first in men and second in women among cancer-related deaths in the world. Geographical variability in the country/region between men and women and smoking are examples that influence the difference (2). Lung cancer is divided into two main groups according to microscopic classification. These include small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). NSCLC is divided into four subgroups: adenocarcinoma, squamous cell carcinoma, large cell, and mixed histotypes (3). NSCLC accounts for 80-85% and SCLC accounts for 15-20% of lung cancer (4).

Although bronchoscopy, biopsy and bronchial lavage, tumor markers, computerized tomography (CT), magnetic resonance imaging (MRI), ultrasound, mediastinoscopy, and positron emission tomography scan (PET) are used in the diagnosis of lung cancer, surgery cannot be performed because the disease is at an advanced stage when diagnosed. Therefore, chemotherapeutic drugs, targeted therapy, and immunotherapy are used in the treatment of lung cancer (5). Despite cancer diagnosis and treatment studies, five-year-old rates of lung cancer increased by 5% in the last two decades. The 5-year relative survival rate for all lung cancers is 22% (6).

The mortality rate increases due to the diagnosis of the disease in advanced stages and due to inadequacy in treatment. Besides, recently, the determination of molecular abnormalities in most lung cancer patients has caused the emergence of personalized, targeted therapies. Identifying tumors responsive to targeted therapies for the use of predictive biomarkers means a change in lung cancer diagnosis (7).

There are more than 100 types of cancer known to affect the human body and cancer is the second leading cause of death after cardiovascular disease (8, 9). Based on rate changes and demographic changes observed between 2006 and 2010, the study found that lung cancer would be the most lethal cancer in the ranking of cancer death rates in 2020 and 2030 (10). Moreover, it is estimated that there will be 1,918,030 new cancer cases and 609,360 cancer deaths in the United States of America in 2022. About 350 cases of lung cancer are reported daily and the number of lung cancer patients is projected to be 236,740 (11). For these reasons, the discovery of different molecules thought to be effective in cancer, the molecular mechanism of the effect of these molecules in the related type of cancer, and the prognosis of the disease is important to change the survival rate.

Signal pathway in cancer

Although each cancer treatment varies according to the patient, there are also differences between the treatment of cancer types. Each organ is affected by each cancer at different levels and in different ways. In this context, specific molecular studies are carried out specific to the type of cancer to treat each type of cancer. One of them is the

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identification of signal pathways that act actively or passively in the cancer process and the attempt to change the mechanism of action according to the function of these signal pathways in the aforementioned cancer (12).

There are numerous signal transmission pathways in our cells. Some of these signal transmission pathways are involved in the pathogenesis of various diseases, especially cancer. There are also various intracellular signal transmission pathways known to be active or inactive in cancer. The function status of proteins/genes found in these pathways has been associated with diseases and has been a beacon of hope for treatment by acting on the formation of the disease mentioned in the studies to provide amplification of the gene mentioned or to silence the gene. From there, the researchers determined which signaling pathways affected the disease process and conducted studies on which signal message pathways were effective in that disease and therefore how they could prevent the formation or development of the disease with an intervention. One of the diseases that is being carried out for this purpose is cancer. There are many signaling pathways thought to affect cancer development (13, 14).

Wnt signal pathway in cancer

This review will discuss the effect of the Wnt signaling pathway on lung cancer. *WNT*-1 is a gene called *INT*-1 that is defined in breast tumor development in mice. The homolog of this gene is called Wingless in Drosophila, and this gene is called *WNT*. Humans have 19 *WNT* proteins (15). The Wnt signal pathway is known to play an important role in many cellular processes, such as cell proliferation, survival, self-renewal, and differentiation (16). Wnt is paracrine glycoproteins that regulate cell growth, motility, and differentiation during embryonic development (17). This pathway is effective both in the embryonic development process and in the provision of tissue homeostasis in adulthood (18). This pathway has been associated with various types of cancer after the definition of mutations and various dysfunctions in the discovery of this pathway (19). Three types of Wnt signaling pathways have been defined: Wnt/β-catenin (Canonical/Classical), Wnt/Ca^{+2} (Non-Canonical), and Wnt/Planar Cell Polarity (PCP) (Non-Canonical) (20).

Wnt /β catenin signaling pathway

The activation of the signal pathway begins with connecting the Wnt protein to the cell membrane receptor. After the receptor is connected to the ligament Wnt protein, various phosphorylation occurs in the cell, and the signal is transferred from the cell membrane to the cytosol. The Wnt protein creates a triple complex by connecting with frizzled (FZ) and low-density lipoprotein receptor-related protein 5/6 (LRP5/6) receptors in the cell membrane (21). β-catenin accumulates and is carried to the core in the cytosol with the transferred signal. Activates transcription factors of β-catenin accumulated in the nucleus (22). The deterioration of the homeostasis of this signal pathway causes many diseases, especially cancer. This signal pathway regulates the level of β-catenin in the cell. It is involved in both the provision of intercellular adhesion and the transcription of many genes (Figure 1) (23).

PCP signaling pathway

This pathway is involved in the regulation of cell migration and cell skeleton elements (24). This pathway contains Rho GTPases and their associated proteins, RhoA, Act1 (RAC), and Cdc42 (25).

Wnt /calcium signaling pathway

The signal pathway is activated by connecting the Wnt protein to the receptor in the cell membrane (26). The amount of calcium within the cell is increased by connecting the Wnt to the receptor. Increased calcium causes the activation of various enzymes in the cytosol, such as Ca^{+2}/Calmodulin-dependent protein kinase II (CamKII) and Protein kinase C (PKC). Activated enzymes are involved in regulating cell migration and cell proliferation of this signal pathway (18, 27, 28).

Activation of the Wnt signaling pathway

Wnt protein binds to the Fz receptor in the cell membrane (29). Then the LRP5/6 receptors also participate in this structure and the "FZ-Wnt-LRP5/6" triple complex occurs. By binding the Wnt protein to its receptors, the signal that starts in the cell membrane is transferred to the cytosol. The transmission of the signal takes place in two stages. The first of these steps is the phosphorylation of the Dvl protein (30). By binding the Wnt protein to the Fz receptor located in the cell membrane, a conformational change occurs in this receptor (29). With the effect of this change, the Dvl protein, which is free in cytosol, heads towards the cell membrane. The resulting complex stimulates the phosphorylation of the Dishevelled (Dvl) protein by the enzyme CK1 found in the cytoplasm (30).

In the second step, the intracellular part of the LRP5/6 receptor is phosphorylated. This phosphorylation pulls Axin protein into the cell membrane from the cytosol (31). In this way, the Axin protein that combines the destructive complex is separated from the destructive complex. This complex, which is responsible for the breakdown of the protein of the β-catenin, becomes inactive with the onset of the Wnt signal. There are two reasons for this inactivation: The Axin protein that keeps the destructive complex with the structure of the Axin protein, connecting to the LRP5/6 protein in the cell membrane and inhibiting the glycogen synthase kinase-3 beta (GSK-3β) enzyme, which is in the structure of the destructive complex and is responsible for the phosphorylation of the β-catenin. When the signal is transferred to cytosis, the destructive complex is disintegrated. Therefore, the β-catenin protein is not phosphorylated. Some β-catenin protein goes to the cell membrane and serves in cell connections. The other part of the β-catenin protein accumulates in the cytoplasm. The accumulated β-catenin protein in the core delivers the signal from the cytoplasm to the core (32). Before reaching the signal core, the T cell factor/lymphoid enhancer factor family (TCF/LEF-1) transcription factor in the core is connected with various inhibitory proteins and inactive conditions. The task of the β-catenin protein entering the core is to ensure that inhibitory proteins are separated from the TCF/LEF1 transcription factors (Figure 2) (16).

For this purpose, β-catenin interacts with numerous auxiliary biomolecules in the nucleus, forming a "multiprotein complex". This multiprotein complex of β-catenin and auxiliary molecules binds to TCF/LEF-1 transcription factors (33). The task of this connection is to ensure that the inhibitory proteins are separated from TCF/LEF-1 transcription factors (34). The formed "TCF/LEF-1-β-

catenin" transcription complex starts transcription by connecting to the appropriate area of DNA. In this way, the signal passing the core activates the expression of many genes such as *c-MYC*, *Cyclin*-D1, and *Survivin*, ensuring important biological processes such as cell proliferation, differentiation, and cell migration to realize (35).

The Wnt/β-catenin signal path is inhibited and controlled by the inhibitory molecules in the ECM. When the signal mechanism is inactive, the Wnt proteins cannot connect to FZ and LRP5/6 receptors in the cell membrane. Therefore, the triple complex required for the start of the signal mechanism cannot be established (36). Conformational changes do not occur in receptors because Wnt proteins cannot connect to their cell membrane receptors. Therefore, the DVL protein in the cytoplasm and the intracellular part of the LRP5/6 in the cell membrane cannot be phosphorylated by kinases. Thus, the destructive complex dispersed by the action of phosphorylation reactions remains in an active state (18). The β-catenin protein connected to the destructive complex is primarily phosphorylated by the CKI enzyme, then by the GSK-3β enzyme (37). β-catenin protein cannot get into the nucleus without cytoplasm because it is broken down. Since the signal does not reach the nucleus, the TCF/LEF-1 transcription factors in the nucleus are found to be suppressed by various inhibitors. In this way, the transcription of the genes targeted by the signal path of Wnt/β-catenin does not occur, and the signal pathway is inhibited.

Uncontrolled Wnt signaling pathway activation

The state of activation of intracellular signal pathways without any warning and the expression of target genes are called "uncontrolled activation". This activation of the Wnt signal pathway causes various diseases, especially cancer (38).

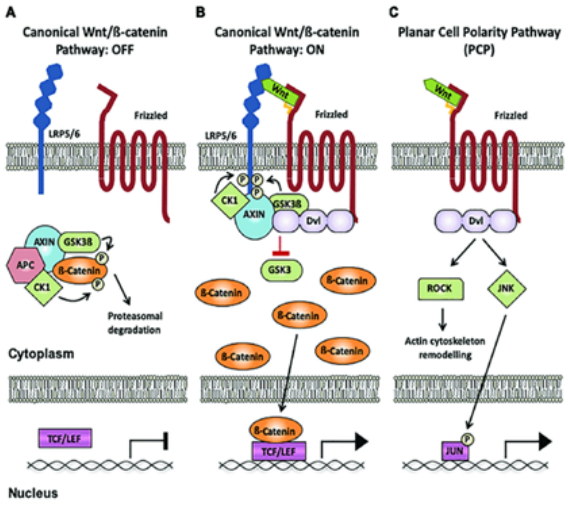

Figure 1. Wnt signaling pathway; (A) Canonical Wnt /β catenin pathway: when there is no Wnt protein, the destruction complex (CK1, GSK3-β, Axin, and APC) and β-catenin interact and are phosphorile by Gsk3-β and CK1. In this way, degradation occurs by the proteasome. (B) When the canonical Wnt /β-catenin pathway is open: Wnt binds to LRP5/6 and Fz receptors. Dvl impairs the degradation complex by recruiting Axin1, CK1, and GSK3-β to the membrane and impairs β-catenin phosphorylation and degradation. (C) In the Planar Cell Polarity (PCP) path: LRP5/6 is not required. When Wnt combines with Fz, Dvl becomes active. Therefore, ROCK and JNK activation is increased. Gene transcription via Jun phosphorylation (39).

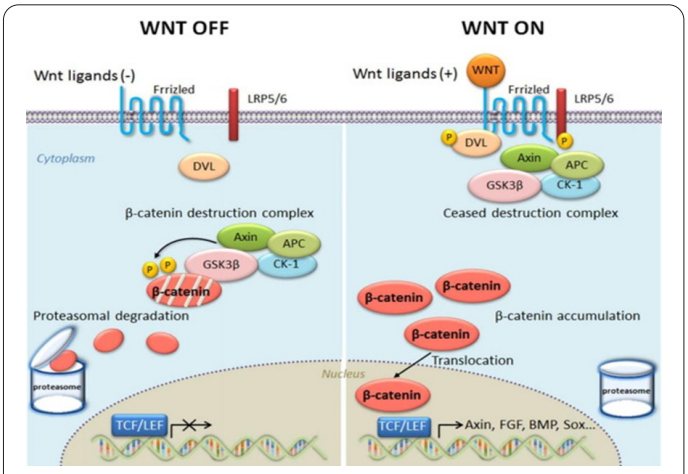

Figure 2. Wnt signaling pathway off and on; In the absence of Wnt ligands, β-catenin is phosphorylated. When Wnt binds to its receptor, non-phosphorylated β-catenin begins to accumulate in the cytoplasm and nucleus. The target genes are then transcribed (40).

The Wnt signaling pathway plays a role in the pathogenesis of many diseases, especially lung cancer (41–44). Many types of cancer, such as lung cancer, breast cancer, and colorectal cancer, are known to be caused by mutations that cause the accumulation of β-catenin, which plays a major role in the Wnt signaling pathway (45). Mutations in APC, Axin, Axin2/Conductin, and β-catenin affect the progression of various tumors such as lung cancer, colorectal cancer, hepatocellular carcinoma, melanoma, medulloblastoma, ovary, endometrial adenocarcinoma, esophageal squamous cell carcinoma (18, 46–48).

Targeting the Wnt signal pathway is important in cancer treatment. Because by creating a minimal effect on somatic cells, inhibiting tumor growth, and preventing resistance to classic treatment methods such as chemotherapy, radiotherapy is necessary for the treatment of disease. For this reason, Wnt signaling pathway inhibitors attract the attention of many researchers and work continues to develop different inhibitors.

Wnt in lung cancer

Most research on Wnt signaling pathway and cancer has been performed in colon tumors, but recent studies highlight a potentially important role for Wnt pathway components in lung cancer (49).

Wnt pathway genes also are upregulated within the lung of Kras transgenic mice, and activation of Wnt signaling in Kras mutant mice noticeably increases tumorigenesis (50). In NSCLC cell lines and xenografts, inhibition of *WNT2* by protein induced programmed cell death decreased expression of Wnt target genes, downregulated cytosolic expression of β-catenin and *Survivin*, and decreased TCF-dependent transcriptional activity (51, 52). As a result, the Wnt pathway is very important biologically in NSCLC.

Active Wnt signaling or *WNT*-1 is overexpressed *in vitro* studies carried out with small cell lung cancer cell lines (53–56). Although there has been recent progress in the diagnosis and treatment of cancer, the treatment of lung adenocarcinoma is inadequate (57). During the resection of the tumor, seen as the most precise treatment method, systemic inflammation may occur and the cancer cells can spread to the blood. In this case, cancer prepares the ground for metastasis (58). In addition, the resected

lung adenocarcinoma prognosis, poor response rates, severe toxicities, and high relapse rates and the desired result cannot be reached. Therefore, new approaches are needed in treatment.

Rhizoma Curcumae (CUR) is a medicinal plant known to have strong anti-tumor activity (59). In the studies using this plant, the formation and metastasis of gastric cancer, duodenal cancer, colon cancer, and breast cancer was effectively inhibited and the tumor size was reduced to smaller (60, 61). In the first *in vitro* study that has clarified the effect and mechanism of this plant in lung cancer, A549 and H460 cell lines were treated with 24 hours CUR. It has been observed that phosphorylation of LRP5/6 is inhibited, increases the expression of Axin, APC, and GSK3-β proteins, without any change on Frizzled8, and therefore the PI3K/ECT and Wnt /β-catenin pathways are inhibited, and as a result of this inhibition, the proliferation and metastasis of pulmonary adenocarcinoma is inhibited (62).

Thyroid hormone receptor interactionist 13 (TRIP13) is an ATPase. It was associated with various proteins belonging to various cellular activities (63). Although overexpression of TRIP13 has been observed in many tumors, the role of TRIP13 and its underlying mechanism in lung cancer progression remain unclear. In a study conducted to eliminate this uncertainty; Different types of lung cancer cell lines were studied to examine the expression level of TRIP13 and its relationship with clinicopathological factors in lung cancers (64–66). The role of the Wnt signal in cancers and its effects on cell motility have been shown before in studies (67–69). This study examined whether TRIP13 affects the activation of the Wnt signal pathway and the epithelial-mesenchymal transition. The results showed that active β-catenin levels of TRIP13 overexpression and the expression of the upstream activator LRP6 regulated GSK3-β down and up-regulated Wnt signaling target genes such as *MMP7, Cyclin D1*, and *c-Myc*. In addition, TRIP13 promoted the epithelial-mesenchymal transition in lung cancer cells in line with the study shown to support the epithelial-mesenchymal transition in colorectal cancer (70). The destruction of TRIP13 has led to the reversal of the above-mentioned results. Therefore, this study is proof that TRIP13 supports the proliferation and invasion of NSCLCs through the activation of the Wnt signal pathway and supports the epithelial-mesenchymal transition. TRIP13 is highly expressed in NSCLCs, which explains the progress of the disease and the poor patient prognosis. Overexpression of TRIP13 supports the proliferative and invasive ability of lung cancer cells by activating the Wnt signaling pathway and epithelial-mesenchymal transition process (71). In the studies, *WNT-7A* expression decreased in lung cancer, increased DVL expression, and decreased the expression of Axin (72, 73).

A study to determine the relationship between β-catenin and infiltration of $CD8^+$ T cells in non-small cell lung cancer patients has shown that a change in β-catenin expression can suppress anti-tumor activity by down-regulating CD8+ T cells. Inhibition of β-catenin expression can be used as a treatment for immunotherapy (74).

Conclusion

Active Wnt signaling or *WNT1* is overexpressed in lung cancer. Changes in the activity of the WNT signaling pathway have been detected in lung cancer. Since these changes play a role in the pathogenesis of lung cancer, the researchers target these changes, leading to success in treatment. For this reason, Wnt signaling pathway inhibitors attract the attention of many researchers and work continues to develop different inhibitors. Although the role of the Wnt signaling pathway in lung cancer development has not yet been clearly clarified, its role in the development and treatment of cancer is seen as very important. Once the importance of the Wnt pathway in lung cancer is more clearly understood, studies can be carried out to use this pathway as a therapeutic option in clinical treatment.

Interest conflict

The authors declare that they have no conflict of interest.

Consent for publications

The authors read and proved the final manuscript for publication.

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