

Three Effects of B-Catenin Factors in Liver Cancer and Its Treatment

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Abstract. Liver cancer is a typical malignant tumor and the fourth most typical cancer in the Earth. Clinically, more than 90% of patients with primary liver cancer are caused by hepatocellular carcinoma. Epidemiological and experimental data show that human infection with HBV and HCV hepatitis virus is firmly connected with the occurrence of liver cancer. In the past 20 years, the level of diagnosis and cure of liver cancer in China has been greatly improved, but little progress has been made in the study of liver cancer markers. For then, with the understanding of Wnt signal transduction pathway, it is found that β -catenin, as a key molecule in Wnt signal transduction pathway, is closely associated to the incidence of HCC. Recently, more and more studies have shown that the abnormal activation of classical Wnt signal pathway plays a compelling part in the occurrence and advancement of hepatocellular carcinoma. Hepatocytes because of hidden onset, early rise can be no clinical symptoms, so the clinical discovery is mostly late, the mortality rate is high. At present, the clinical methods for the treatment of hepatocellular carcinoma are liver transplantation, radiotherapy and chemotherapy. However, hepatocellular carcinoma is easy to metastasize and has a high recurrence rate, so the mortality rate of hepatocellular carcinoma is still high. Wnt/ β -catenin signal pathway has become major topic of debate in cancer research. In this paper, we begin with the classification of liver cancer and some pathogenic mechanisms. The effects of β -catenin protein on the occurrence, metastasis and immune regulation of hepatocellular carcinoma were also discussed. Under the background of the popular "signal transduction therapy" in recent years, to explore the therapeutic effect of targeted drugs targeting Wnt/ β -catenin signal pathway in hepatocellular carcinoma. Because of the high degree of malignancy and limited treatment of hepatocellular carcinoma, we will mainly discuss the effect of Wnt signal pathway on the metastasis of hepatocellular carcinoma and its effect on the differentiation of immune cells. Abnormal activation of Wnt signaling pathway in hepatocellular carcinoma.

Keywords: β -catenin; liver cancer; immunity; treatment; activation.

1. Introduction

The current data released by the International Agency for Research on Cancer shows that Primary liver cancer has become the third largest cancer with a high mortality rate worldwide. China is a country with a high incidence of hepatocellular carcinoma, with about 110000 deaths every year, accounting for 45% of the annual deaths of hepatocellular carcinoma in the world, which is a serious threat to people's lives and health. At present, there are many treatments for liver cancer, including surgery, radiotherapy and chemotherapy. However, the effect of these treatments is poor. Wnt signaling pathway is a complex and strictly controlled molecular mechanism, which mainly regulates the key physiological and pathological processes of multicellular organisms. In the liver, excessive accumulation of β -catenin in the nucleus is an important mechanism for hepatocarcinogenesis. Therefore, in-depth understanding of the molecular activation mechanism of β -catenin is of great connotation to the occurrence and advancement of hepatocellular carcinoma. As a key protein in Wnt/ β -catenin signal transduction pathway, β -catenin plays an important role in promoting cell

proliferation and migration, on the other hand, it plays an important role in the occurrence, development and metastasis of hepatocellular carcinoma. Its expression was positively correlated with tumor metastasis and intrahepatic metastasis. Additional, changes in this pathway are involving the pathogenesis of the liver and can lead to benign and malignant hepatobiliary diseases. Based on the classification and pathogenic mechanism of hepatocellular carcinoma, this paper deeply discusses the activation and metastasis mechanism of β -catenin on hepatocellular carcinoma and how it affects the differentiation of T cells. To find new therapeutic targets for the treatment of hepatocellular carcinoma and to deepen and improve the basic theoretical research on metastasis and invasion of hepatocellular carcinoma.

2. Classification and pathogenic mechanisms of liver cancer

2.1. Classification of liver cancer

Primary liver cancer and secondary liver cancer are two major categories of liver cancer. Among them, dominant liver cancers include hepatocellular carcinoma (HCC), intrahepatic cholangiocarcinoma (ICCA) and other rare tumors, especially fibroplate lamellar carcinoma (FLC) and hepatoblastoma (HB). It is difficult to distinguish HCC from ICCA clinically. HCC refers to primary hepatocellular carcinoma and ICCA refers to dominant intrahepatic cholangiocarcinoma. HCC is more common in clinic, accounting for about 80% of primary liver cancer. AFP (alpha-fetoprotein) will increase significantly at a previous phase of the disease, and most transaminases will increase. ICCA is rarely seen clinically, accounting for about 20%. In the early stage of the liver cancer, most of the AFP is normal or slightly elevated, and the jaundice index will increase, and most of the intrahepatic bile ducts are dilated. But the malignant degree of the two is basically the same. HCC is different from almost all other human malignant tumors in pathological examination. Its diagnosis does not depend on pathological examination. At present, computed tomography or magnetic resonance imaging shows high sensitivity and specificity in the detection of specific features of HCC patients, so that clinicians can avoid the use of invasive biopsies [1]. The malignant degree of FLC is lower than that of primary hepatocellular carcinoma. ALT (glutamic pyruvic transaminase), AKP (alkaline phosphatase) and serum bilirubin may increase slightly to moderately during the onset of HCC. HB is a malignant embryonal tumor with multiple differentiation patterns. The levels of AFP, serum cholesterol, bilirubin, alkaline phosphatase and aspartate transferase are increased during the onset. Secondary liver cancer, also referred to as metastatic liver cancer, which means the spread or metastasis of malignant tumors from other body organs to the liver. Compared with primary HCC, secondary HCC is more common. The ratio of both 2:1 to 4:1 in China and more than 20:1 in western countries. In this article, we focus on the related pathways and their treatment in HCC.

2.2. Pathogenic mechanism of liver cancer

2.2.1 Macroscopic aspect pathogenic mechanism of liver cancer

Some pathogenic factors in primary liver cancer include dietary and drinking water contamination, poisoning, schistosomiasis, and familial genetic predisposition. In general, these elements have an influence on the DNA of hepatocytes, leading to abnormal cell growth and cancer. It was found that as a detoxification organ, the liver is easier to accumulate and store toxic substances than other parts, and the concentration and content of pollutants are much higher than those in other parts in a past study. In the process of low concentration pollution and chronic drug production, DNA damage in fish hepatocytes was detected to be more sensitive than that in other parts, which could lead to canceration in severe cases. In patients with hepatitis, viral DNA can be inserted directly into the DNA of hepatocytes, resulting in hepatocyte carcinogenesis. Secondary liver cancer is mainly due to the release of cancer cells into the circulatory system. After malignant tumors in other parts of the liver grow to a certain extent, they finally enter the liver. Among them, the cancer cells will release

growth factors, promote the proliferation of tumor cells, and finally form independent tumor cell clusters

Clinical statistics show that most of the patients with HCC are caused by liver cirrhosis. In the background of clinic, the occurrence of hepatocellular carcinoma is referred as a multi-step process. The preneoplastic lesions of tumors are truly characterized by a continuous accretion of molecular and morphological anomaly. The central histological expressions are affiliated with the previous transformation of malignant tumors are the increase of cell density and nuclear and cytoplasmic ratio, unmatched arteries and the arrangement of pseudoglands. The order of carcinogenesis has been identified and previous lesions consist of low-grade large nodules, high-grade large nodules, previous HCC and small and progressive HCC. The well-developed HCC is further characterized by structural anomaly (loss of sinus lining, pseudoglandular formation, interstitial infiltration) and cytological variations (higher cell density and atypia). The occurrence of HCC is caused by internal and external risk factors of genetic or acquired genetic mutations, for instance the ethyl alcohol, smoking and hepatotropic viruses B, C and D. It is generally believed that the two elements participate in the occurrence and development of liver cancer. Hepatocytes undergo pernicious transformation by preventing tumor destruction, avoiding apoptosis, and promoting tumor proliferation and angiogenesis in the tumor environment. Liver cirrhosis can cause carcinogenic changes, which are found in 90% of HCC patients. In the remaining 10% of patients, the carcinogenic mechanism of non-cirrhosis is the cause of malignant disease.

2.2.2 The pathogenesis of hepatocellular carcinoma by tumor microenvironment

The tumor microenvironment (TME) is a highly sophisticated ecosystem. It comprises the surrounding blood vessels, immune cells, fibroblasts, bone marrow-derived inflammatory cells, various signaling molecules, and the extracellular matrix. TME has many kinds of tumor-promoting effects, such as releasing various growth factors, removing growth barrier and forming immunosuppressive microenvironment to avoid immune destruction. Altered Wnt signaling pathway in the TME makes hepatocytes cancerous [2]. Fibrosis in the liver can lead to deposition of the extracellular matrix (ECM), inhibiting oxygen molecule exchange. In addition, angiogenic cytokines secreted by stromal cells and hypoxia-inducible factor-1 α (HIF-1 α) induced by stromal cells act on TME to further hypoxic TME [2]. Hypoxic environment can promote angiogenesis, increase of HIF-1 α and other angiogenic factors. Thus, the hypoxic environment will play a role in resisting apoptosis and promoting cell proliferation [2]. Deposition of ECM and reduced remodeling and renewal in vivo leads to environmental fibrosis. Increased integrin signaling, which mediates cell adhesion to ECM, stimulates tumor growth [2]. Not all the immune cells in TME constrain the growth of cancer cells, but some promote the growth of cancer cells. For example, tumor-associated fibroblasts (TAF) are one of the dominant factors of the tumor microenvironment. It can secrete factors that promote cancer cell growth, invasion, metastasis and angiogenesis. In addition to TAF, there are tumor-associated macrophages (TAM) and regulatory T cells. The former belongs to the M2 macrophage, which can secrete EGF, IL10, and other factors to increase the proliferation of tumor cells and inhibit the body's immunity. Overactivation of the latter to maintain high tolerance and ever suppress the immune response [2, 3].

Angiogenesis plays a crucial part in developing and multiplication of hepatocellular carcinoma (HCC). Tumor cells, vascular endothelial cells, and other cells produce excessive angiogenic factors, which accumulate in TME to form an abnormal vascular network. Capillary endothelial growth factor (VEGF) is a crucial ingredient produced by hepatocellular carcinoma cells, which is regulated by oncogene mutation, hormones, and cytokines. Its overexpression leads to vascular leakage and abnormal vascular structure and function. This abnormal vascular structure provides an anoxic and acidic environment, which in turn promoting overexpression of vascular endothelial growth factor [4]. VEGF and angiogenin act synergistically to resist apoptosis and promote cell proliferation. Hypoxia induces autophagy, which allows catabolism of some substances in cells to generate energy for tumor cells and their surroundings, helping to boost cancer survival [2]. Ang-2 can enhance the angiogenic effect of VEGF on new vessels and allow vascular endothelial cells to secrete

substances that destroy the basement membrane. The disrupted basement membrane can enhance the hypoxic condition of the TME. Basic fibroblast growth factor (BFGF) and VEGF can jointly induce neoangiogenesis. Platelet-derived endothelial permeability factor promotes vascular endothelial cell proliferation and neovascularization. In addition, hepatocyte growth factor (HGF) and many other factors are increased in patients with hepatocellular carcinoma. In summary, the angiogenic pathway is activated in endothelial cells, whereas the antiangiogenic way is down-regulated in HCC.

3. Mechanism of Wnt/ β -catenin pathway activation in HCC

In hepatocellular carcinoma (HCC), Wnt catenin signaling is often over-activated and promotes tumor growth and spread. In the process of HCC, the genes encoding proteins and enzymes related to Wnt/ β -catenin signaling pathway are mutated.

β -catenin is involved in intercellular adhesion. In normal somatic cells, as a cytoskeletal protein, catenin designs a complex with E-cadherin at the cell membrane to maintain the adhesion of homotypic cells and prevent cell movement. β -catenin was the first to be identified as a member of the Wnt pathway. β -catenin is located in the cytoplasm, and β -catenin makes a molecular effector of the Wnt signal. In cytoplasm β -catenin is strictly managed by the annihilation complex, which amount to scaffold protein Axin, APC, casein kinase I isoform- α (CK1 α), and glycogen synthase kinase 3 β (GSK3 β). β -catenin can also be located in the cytoplasm. The gene is located in 3p21 and consists of 16 exons. The coding region of codons 37, 33, 41, and 45 of exon 3 constitutes the NH2 end of the β -catenin protein, which is the binding site of GSK3 and the site of carcinogenic activation. If directed mutation or deletion occurs in this region, it can lead to too high activity of catenin, so that the degeneration of β -catenin by GSK3 is blocked, and β -catenin accumulates in the cytoplasm. APC gene mutation can occur in any exon. The coding region of the 1020-1169 codon and 1323-2075 codon is the binding site between β -catenin and APC. The mutation in this region leads to the inability of β -catenin to bind to APC and then cannot be phosphorylated by GSK3, which hinders the degradation of β -catenin. Axin has multiple protein-protein domains. Like APC, Axin plays the role of scaffold protein and is the framework basis of the scaffold protein complex. Axin gene mutation was detected in hepatocellular carcinoma. Axin is considered a tumor suppressor, and its gene mutation promotes the occurrence of tumors. GSK phosphorylates β -catenin. GSK3 is a negative regulator of the Wnt pathway and a candidate tumor suppressor.

In the absence of an extracellular Wnt ligand, The Wnt/ β -catenin pathway is dormant (Wnt off). In this complex, β -catenin is phosphorylated successively in the N-terminal domain. The first is CK1 α Phosphorylation at ser45, followed by GSK3 β It is phosphorylated at ser33, ser37, and thr41[5]. CK1 α is recognized by β -TrCP by phosphorylating ser45 labeled protein, which mediates the degeneration of β -catenin, and the proteasome of 26S is also degraded. TCF is a downstream component of the Wnt pathway and belongs to DNA binding protein. It includes a HighMobility group and a β -catenin scope. Although TCF transcription factor families have different characteristics, they can bind DNA. TCF and β -catenin act and recruit coactivators (BCL9, CBP / 300, pygo, etc.) to activate the transcriptional process.

In the state of β -catenin pathway activation (Wnt on), β -catenin is in a basic position in the Wnt pathway. Wnt protein acts as a messenger by connecting with the cell surface and extracellular matrix. There are two kinds of Wnt receptors: one is a member of frizzled (Fzd) receptor family, which is a receptor with 7 transmembrane fragments. At present, 11 kinds have been found. The other is low-density lipoprotein receptor-associated proteins LRP5 and LRP6. The classical Wnt signaling pathway is a reaction process in which Wnt protein binds to LRP5 / 6 helper receptor through Frizzled (Fzd) specific receptor to trigger intracellular signal transduction and make β -catenin aggregate. Wnt protein forms Fzd – LRP receptor complex after binding with Fzd binding domain. LRP6 is phosphorylated by several kinases and Axin is recruited to the cytoplasmic tail of LRP6. Disheveled (DVL) is a positive regulator of the Wnt pathway. Its N-terminal Dix domain can bind to Axin and lead to the phosphorylation of LRP5 / 6, while its C-terminal dep domain can regulate cell polarity

and cell movement. Unphosphorylated β -catenin accrues in the cytoplasm so that it is no longer ubiquitinated and loses the ability of protein hydrolysis. This makes the activity β -catenin is transferred to the nucleus [6].

About 26-37% of HCC is caused by CTNNB1 mutation [7]. These mutations are located in exon 3 of the β -catenin coding gene CTNNB1 and inhibit the degradation of β -catenin by affecting the phosphorylation and ubiquitination sites in the catenin promoter. Coding was detected in 15 - 25% of HCC activation mutation of CTNNB1 exon 3 of β -catenin. 10.4% of HCC had AXIN1, 3.3% had AXIN2 and 1.4% had AXIN1 mutation [7]. These mutations weaken the biological behavior of the destruction complex, which is conducive to the accretion of β -catenin. These mutations weaken the biological activity of the destruction complex and are conducive to the accretion of more β -catenin.

4. Mechanism of the transfer of the Wnt/ β -catenin pathway in HCC

The most important biological feature of cancer cells is the ability of infection and metastasis, which is the main reason for the poor prognosis of cancer patients. The infection and metastasis of cancer cells include the following processes: the change of cell adhesion, falling off from the primary focus, breaking through the basement membrane, interacting with the extracellular matrix, invading adjacent tissues, then invading lymphatic vessels and blood vessels, and establishing new cancer cell colonies in organs and tissues. At the front of tumor aggression, the expression of E-cadherin on the cell membrane disappeared, and β -catenin is expressed in the nucleus. In the cancer matrix, myofibroblasts represent the major subpopulation of cancer-related cells [8]. Myofibroblasts, epithelial cells, and connective tissue cells are firmly appropriate to tumor invasion. The loss of epithelial characteristics and transformation into epithelial-mesenchymal characteristics (EMT) affect the progression of hepatocellular carcinoma [9]. Among them, Wnt signal transduction plays a crucial role. Cancer cells destroy the extracellular matrix, invade blood vessels and enter other organs with blood flow. Matrix metalloproteinases can degrade the extracellular matrix. MMP-7 is a proteolytic enzyme that is associated with β -catenin co-expression. The growth and diffusion of tumors are closely related to angiogenesis. VEGF, EGF, TGF, FGF, and angiopoietin are growth factors that promote tumor angiogenesis. In Wnt / Ca2 + pathway, GSK3 is inactivated by activating PKC, and then the phosphorylation of β -catenin is inhibited. In the progression of liver cancer, some cells acquire metastatic characteristics by activating EMT signals, such as the loss of intercellular adhesion and the acquisition of migration, invasion, and angiogenesis. EMT can up-regulate migration proteins (such as MMP, vimentin, and fibronectin) and down-regulate cell adhesion proteins (such as cadherin). It is mainly composed of Wnt/ β -catenin, Hedgehog, Notch, and TGF- β . Activation of signal transduction. Wnt/ β -catenin pathway is a crucial step in the process of EMT. Through this process, immobile epithelial cells are transformed into fibroblasts and moving mesenchymal types [10]. For example, MTDH promotes the metastasis of liver cancer cells in three signal pathways related to the Wnt/ β -catenin pathway. MTDH up-regulates the expression of lymph enhancer-binding factor 1 (LEF-1), activates the EMT signal, and obtains the characteristics of metastasis. MTDH up-regulates the expression of lymphatic enhancer-binding factor-1 (LEF-1), activates the EMT signal, and obtains the characteristics of metastasis. Alternatively, MTDH downregulates E-cadherin in Wnt/ β -catenin signal pathway, and the accumulation of β -Catenin activates EMT signals. MTDH can also activate the p38 mitogen-activated protein kinase (MAPK) signaling pathway [11]. Activation of p38 MAPK makes GSK3 β phosphorylation, which in turn drives the nuclear translocation of β -catenin, through activating Wnt signaling [11] (Fig.1).

Now, some drugs have been found to have anti-migration activity. In Wnt/ β -catenin pathway, the addition of trimethylene glycol dimethacrylate (TD-10) and tetramethylene glycol dimethacrylate (TD-11) resulted in β -catenin decreases, inhibits EMT signal, and promotes liver cancer cell metastasis. Some experiments inhibit cell proliferation, invasion, and metastasis by knocking out genes related to EMT expression. For example, there is a compelling positive correlation between the expression of KIAA1199 in hepatocellular carcinoma and EMT [12]. KIAA1199 induced the EMT.

Enhance the phosphorylation of EGFR, STAT3, and ERK1 / 2 in the Wnt/ β -catenin pathway to transfer hepatoma cells [13].

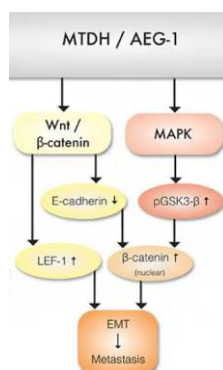


Figure 1. Molecular interactions between MTDH/AEG-1 and EMT pathways

5. Effect of Wnt/ β -catenin pathway on T cell differentiation in hepatocellular carcinoma

Wnt signal is a conservative signal pathway, which involves various processes of cell proliferation. The processes of these cell proliferation include carcinogenic effects and embryogenesis. It was recently found that it can also be an oncogenic signaling pathway associated with the evasion of immune clearance by cancer cells, hindering the anti-cancer immune response. This paper introduces the effect of the Wnt/ β -catenin pathway on T cells differentiation.

5.1. Effects of β -catenin on DIFFERENTIATION of CD8+ T cell

CD8+T cells play a crucial part in eliminating malignant cells in the body's immune response to cancer. And memory CD8+T cells serve long-term protective immunity to the body[14]. When T cells infiltrate the tumor site, the survival rate of patients is improved, and the prognosis of patients is better. Antigen-presenting cells recognize and bind to specific tumor antigens on the surface of cancerous cells. Major histocompatibility complex (MHC) class I molecules bind to co-receptor CD8 to activate Naïve CD8+ T cells. Activated CD8+ T cells migrate and infiltrate into the cancer site and recognize tumor antigen peptide-MHCI-like molecular complexes expressed on the tumor cell surface by their T cell receptor (TCR). Specific killing of cancer cells by perforin - granulation enzyme pathway. Cancer cells evade immune elimination by reducing the infiltration of CD8+T cells or inactivating CD8+T cells[15]. The behavior of tumor-infiltrating CD8+T cells is gradually lost due to the prolonged exposure to tumor antigen and the inhibition of TME. In the process of immune clearance, Naïve CD8+ T cells differentiate into effector T cells that can kill cancer cells. Memory T cells are activated by cancer cell surface antigens and differentiate into effector T cells to kill cancer cells. High transcription and translation of Wnt/ β -catenin signals in Naïve CD8 + T cells and memory CD8+ T cells. When Naïve CD8+ T cells differentiated effectively to CD8+T cells, the expression of the effector transcription factor T cytokine-1(TCF-1) of the Wnt signaling pathway decreased. The binding of TCF-1 and β -catenin in the nucleus can inhibit the differentiation of immature CD8+ T cells into CD8+ T effector cells and promote the discernment into memory precursors CD8 + T cells and central memory CD8+ T cells.

5.2. Effects of β -catenin on CD4 + T cell differentiation

Because Th cell expresses CD4, CD4+ T cells refer to Th cell. Initial CD4+T cells that have not received antigenic stimulation are called Th0. Th0 can differentiate into many subtypes of Th. For example, TH1 and TH17 effector T cells that coordinate pathogen clearance produce T follicle-assisted (Tfh) cells that make the discernment of B cells into plasma cell IL-21 and Th2 cells that assist B cell activation. Wnt pathway can regulate the differentiation of Th. The β -catenin supports Th2 polarization by activating the expression of the Th2 cell transcription factor conjugated protein

3 (GATA3) through a specific AT-sequence rich conjugated proteins 1 (SATB1)[16,17].The continuous activation of β -catenin in CD4⁺T cells causes up-regulation of the intracellular transcription factor RAR-associated orphan receptor C (RARC) and polarization of Th17 cells[18].After β -catenin activation, TCF-1 increased retinoic acid-associated orphan receptor γ T (ROR γ T) transcription. TCF-1 enhances the expression of B cell lymphoma 6 (Bcl-6) to promote Tfh differentiation. All in all, β -catenin face enhanced polarization of all TYPES of CD4⁺T cells.

5.3. Effects of β -catenin on FoxP3 + T cell (Treg) differentiation

Regulatory T cells can be devoted into natural regulatory T cells (nTreg) and inducible regulatory T cells (iTreg). The nTreg inhibits the pathological response mediated by autoreactive T cells. The iTreg inhibits autotraumatic inflammation and transplant rejection, which is beneficial to tumor growth. Poor anti-tumor immunity is related to the presence of Treg. Treg can inhibit target cells activation through direct contact and also secrete cytokines such as IL-10 to suppress the immune response. Treg enters the TME through chemokines secreted by innate immune cells to avoid killing immune cells and cancer cells[19, 20].The Wnt pathway constrains the transcription factor FoxP3 by regulating the expression of TCF-1 and inhibits the immune activity of cells[21].The blockage of Wnt signaling pathway in Treg cells reduced the construction of negative immunomodulators such as Foxp3 and IL-10.Treg mainly inhibits the immune activity of CD8⁺T cells, thus inhibiting the immune clearance of tumors[22].The key step in the development and advancement of regulatory T cells is the destruction of Foxp3 transcriptional activity by active WNT signals.Foxp3 deficiency reduces the number of Treg, which leads to serious autoimmune disease. In conclusion, β -catenin can inhibit the proliferation and function of effector T cells mediated by Treg cells.

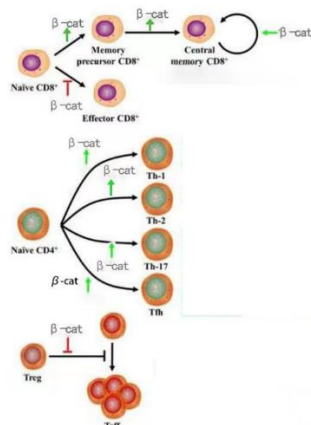


Figure 2. Effects of β -catenin on T cell differentiation

6. About the treatment of WNT pathway inhibitors in cancer immunity

Aberrant activation of β -catenin in hepatocellular carcinoma prevents spontaneous invasion of T cells into TME, allowing tumor cells to evade immune system surveillance. Intervention of the Wnt pathway in hepatocellular carcinoma can enhance the therapeutic efficacy of hepatocellular carcinoma by re-infiltrating T cells into the cancer site. Currently, several specific inhibitors targeting the Wnt/ β -catenin pathway have entered preclinical trials. These drugs mainly inhibit abnormally activated Wnt pathways to rebuild the body's anti-cancer immunity and eliminate cancer cells with the body's immune function (As shown in the table). Wnt inhibitors enhance the efficacy of immune checkpoint inhibitors (ICI) in combination with chemotherapy and immunotherapy. In animal studies of melanoma and lymphoma, β -catenin inhibitors IWP-L6 consume Treg cells from TME to establish immune-beneficial TME to limit tumor growth. [23] Alternatively, in the presence of β -catenin inhibitors, CD8⁺ T cells and CD4⁺ TH17 cells are differentiated into immune cells with more favorable anti-cancer

functions. [24] Thus, inhibition of the Wnt/ β -catenin pathway in hepatocellular carcinoma may constitute an anticancer therapeutic target (Table 1).

Table 1 An introduction of WNT inhibitors for cancer therapy

Mechanism of action of the drug	Medicament	Drugs are currently in the development stage	Treatment of tumors
PORCN inhibitor(Blocking the secretion of Wnt ligands)	C59	Preclinical	Patients treated for melanoma;Synergize with the CTLA4-targeted antibodies
PORCN inhibitor	ETC1922159	Stage 1a/1b	Treat patients with locally advanced or metastatic solid tumors
PORCN inhibitor	RXC004	Stage 1	Advanced malignancy not considered appropriate for further conventional treatment
PORCN inhibitor	WNT974; LGK974	Stage 1	Treat patients with mutations in the BRAF-mut mCRC and WNT pathway
		Stage 2	Treatment of patients with metastatic HNSCC
		Stage 1	Treatment of tumors with genetic alterations upstream of Wnt signaling
Competitive antagonism of the Wnt signaling pathway	OMP-54F28	Stage 1	Treatment of patients with locally advanced or metastatic hepatocellular carcinoma
WNT inhibitor	CGX1321	Stage 1	Treat patients with locally advanced or metastatic solid tumors
		Stage 1	Treatment of advanced GI tumors, such as hepatocellular carcinoma, colorectal adenocarcinoma, gastric adenocarcinoma, cholangiocarcinoma, etc
WNT5A inhibitor	WNT5A trap	Preclinical	Regulate the tumor environment and enhance immunity
β -Catenin inhibitor	PKF115-584	Preclinical	Recovery CTL activation in vivo
Monoclonal antibodies directed against coiled-coil receptors	OMP-18R5	Stage 1	Combination with paclitaxel in patients with metastatic breast cancer
WNT-5a mimetic	Foxy-5 Wnt Research AB	Stage 1	Metastatic breast cancer, mCRC, or prostate cancer with absent or decreased Wnt5a protein expression included in the IHC analysis
β -Catenin inhibitor	PRI724	Stage 1b	For the treatment of advanced or metastatic pancreatic cancer
		Stage 1/2	For treating patients with advanced myeloid malignancies
		Stage 2	Treatment of the Advanced mCRC
		Stage 1a/1b	Stage 1a: treat any advanced tumor; stage 1b: treat mCRC patients only

mCRC, metastatic colorectal cancer; CTL, Cytotoxic T lymphocytes; *CTLA-4*, *Cytotoxic T-lymphocyte-associated protein 4*

7. Conclusion

The β -catenin protein is a multifunctional protein that assists the cell in response to extracellular signals and effects through its interaction with the cytoskeleton, and is also involved in cell signaling and cell adhesion. Thus β -catenin plays an essential part in the development, metastasis, growth and development of HCC cells. Wnt signaling is extremely crucial in the normalization of liver function, which is dysregulated in HCC. Therefore, analysing the early phenotypic and molecular events of β -catenin sensitization is extremely essential for a even better comprehension of HCC pathogenesis. Here we mention three liver-catenin factors and immune cells and their efficacy: CD8 + T cells (immune clearance of cancer cells); CD4 + T cells assist cell differentiation, and FoxP3 + T cells inhibit anti-tumor immune response. Meanwhile, Wnt/ β -catenin signaling is abnormally stimulated during HCC progression. Potential mechanisms include the complex regulation of etiological factors in early-stage precancerous lesions and acquired the changes on genomics, epigenetics and transcriptional of components which were involving Wnt/ β -catenin signal transduction in later stage tumor foci. Accordingly, targeting Wnt/ β -catenin signaling pathway therapy, immunotherapy becomes a new approach for HCC. However, molecular inhibitors targeting Wnt/ β -catenin signaling are clinically effective in the treatment of HCC. Further investigation of these sensitive subgroups of inhibitors carrying specific molecular features will facilitate the design of more effective therapeutic strategies.

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