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Review Article

A Review of the Mechanisms of Wnt7b in the Process of Malignant Tumor Invasion and Metastasis

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Abstract

Wnt ligands play a crucial role in development, tissue turnover and human diseases. The extracellular matrix protein Wnt7b, a critical regulator of hundreds of genes is involved in the development, invasion and metastasis of tumor. Universally, high expression of Wnt7b occurs in tumor lesion compared with normal tissue and is related to clinicopathological characteristics and poor prognosis. Recently, the new mechanism of "canonical or non-canonical" Wnt7b signal pathway has been revealed at cellular and molecular level. The molecular function of new receptors of Wnt7b in the membrane has been characterized and the relationship between Wnt7b/β-catenin classical pathway and transcription factor including TGF-β, VEGF, MicroRNAs and related factors of EMT has been increasingly clear. Moreover, "non-canonical" pathway of Wnt7b rather than activating β-catenin plays a critical part in invasion and metastasis of tumor through PKC and stat3. Here, the available research for the role of Wnt7b on invasion and metastasis tumor was reviewed.

Key words: Wnt ligands, classical pathways, clinicopathological characteristics, cancer invasion and metastasis

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INTRODUCTION

In 2012, approximately 14 million people were diagnosed with cancer worldwide. It is expected that by 2030, the global cancer diagnosis will increase by 50% per year to 21.6 million people[1]. The five-year survival rate of lung cancer, liver cancer and pancreatic cancer in China is less than 20% and the survival rate of esophageal cancer, gastrointestinal cancer is far lower than that in Korea, Japan and other countries. This condition is closely related to types of cancer, affected area, medical resources, treatment methods and early diagnosis. The above cancers, including leukemia and breast cancer can be transferred through invasion, which is a major cause of the high mortality rate in cancer patients[2]. So far, the effective therapy of the above cancers has not been found and carried out. Therefore, it is imperative to explore new targets that are closely related to the occurrence and invasion of cancers.

The Wnt was derived from the wingless gene associated with visual mutations in Drosophila and the Int1 gene associated with mouse breast cancer. The Wnt signaling pathway is highly conserved throughout the vertebrate species and plays a key role in physical development, tissue self-renewal and human disease including cancer[3]. The classical Wnt signaling pathway drives the development and maintenance of gastrointestinal tumors, leukemia and breast cancer. Mutations of factors such as; adenomatous polyposis coli (APC), leucine-rich repeat-containing g-protein coupled receptor 5 (Lgr5), Frizzled 5 (FZD5) and B-cell CLL/lymphoma 9 protein (BCL9) in the canonical Wnt signaling pathway cause the development of tumor[4-7]. In addition, Wnt5a-mediated classical and non-canonical pathways can cause melanoma invasion and metastasis through synergy with receptors such as; LDL receptor related protein 6 (LRP6) and induction of interleukin-6 (IL-6) secretion[8,9]. This suggests that both β-Catenin-dependent and independent Wnt signaling pathways play an important role in tumor development. At present, more than 20 species of Wnt family proteins, 10 receptors and surrogate receptors have been discovered and their major functions have been characterized. However, Wnt signaling is highly complex in the context of tumor biology, functional characterization between unconcerned protein and new pathway groups is extremely important. According to literature surveys, it was found that Wnt7b is an extracellular matrix protein of Wnt family proteins[10], which may be related to the pathogenesis of the cancer in lung, kidney, nervous system, pancreas, prostate and bladder. The expression of Wnt7b was up-regulated in 52 of 53 patients with breast cancer and immunolabeling of human breast cancer showed that Wnt7b immunoreactivity is associated with tumor cells and tumor-associated macrophages[11]. Autocrine Wnt7b activates Wnt signaling pathways in pancreatic cell lines and breast cancer cells and promotes the growth of non-adherent cells[5,12]. This phenomenon indicates that Wnt7b plays an essential role in the development, invasion and metastasis of tumor cells. In this review, the expression of Wnt7b in different malignancies was focused on and the relationship and direct evidence between Wnt7b and tumor stem, invasion and metastasis were collected.

EXPRESSION OF WNT7B IN DIFFERENT MALIGNANT TUMORS

The Wnt proteins, which were first isolated from mouse breast cancer have a variety of biological functions. There is a difference in the expression of Wnt7b in different malignancies. According to the Oncomine database, the expression of Wnt7b is most differentially expressed in breast cancer and it also have significance in colorectal cancer, kidney cancer, leukemia, lung cancer and myeloma. Analysis of the expression of Wnt7b in 593 cases with TCGA breast revealed that Wnt7b highly expressed in breast cancer. Accordingly, the expression of Wnt7b in Invasive Breast Carcinoma (76), Invasive Ductal Breast Carcinoma (392) and Invasive Lobular Breast Carcinoma (36) were evaluated, respectively. Compared with normal breast tissue, Wnt7b was up-regulated in the three groups of breast cancer and the difference was significant (P = 1.91E-13, 2.01E-24, 1.44E-12). Interestingly, human breast cancer cells showed morphological changes and down-regulation of Wnt7b mRNA in the presence of anti-CA I positive human serum[13].

Compared with other normal tumor tissues, Wnt7b presented high expression in the malignant tumors such as; Rectal Mucinous Adenocarcinoma (6) (P = 1.53E-4), T-Cell Prolymphocytic Leukemia (6) (p = 0.001) and Lung Adenocarcinoma (226). Note worthily, it has been reported that the expression of Wnt7b may be related to the degree of tumor differentiation. In the poorly differentiated HCC cells, Wnt7b is highly expressed. Furthermore, poorly differentiated cells do not exhibit markers of epithelial cells and cell lineage and over express mesenchymal markers with active metastatic invasiveness[14]. This suggested that Wnt7b may be involved in tumor invasion and metastasis. According to the cBioPortal databases, Wnt7b gene has a very low mutation rate in different malignant tumors and is only higher than 1% in 12 types of malignant tumors such as; ovarian cancer, cutaneous melanoma, cervical cancer, colorectal cancer and esophageal gastric cancer. The mutation rate only accounted for 1.3% indicating that Wnt7b gene is highly conserved. Transcriptome sequencing confirmed that Wnt7b rarely has point mutations such as; Missense, Nonsense, Splice and Frameshift mutations in different tumors.

CORRELATION OF WNT7B WITH CLINICOPATHOLOGICAL CHARACTERISTICS AND POOR PROGNOSIS

Compared to normal breast tissue, Wnt7b is over expressed in some breast cancers[15]. Analysis of patient data from the International Classification of Breast Cancer (METABRIC) and published data on the prognosis of breast cancer found that high expression of Wnt7b is associated with poor overall breast cancer survival. Particularly, it is closely related to poor prognosis in estrogen receptor+(ER+) breast cancer ($p<0.001$), but not relevant with basal-like breast cancer and triple-negative breast cancers[16,17]. This might be due to the fact that transforming growth factor-β (TGFβ) associated with Wnt7b acts as a tumor suppressor in ER+breast cancer, while it acts as a tumor agonist in ER-breast cancer[18]. The Wnt7b plays a crucial role in the activation of Wnt7b/β-catenin in pancreatic cancer. Therefore, the expression of nuclear β-catenin in tumor tissues detected by immunohistochemistry could be a substitute for Wnt/β-catenin signaling pathway activation and Wnt7b expression levels[11]. Increased activation levels of Wnt7b were associated with lymphatic infiltration of pancreatic cancer and disease-specific survival (Fig. 1). The survival rates of patients with high-activated Wnt/β-catenin and low-activated Wnt/β-catenin in 41 patients with early pancreatic cancer were 20.3 and 43.9 months ($p = 0.03$), respectively[11]. Similarly, Wnt7B-mediated β-catenin expression and its abnormal localization in the nucleus was associated with poor prognosis in thyroid tumors, oral and laryngeal squamous cell carcinoma[19,20]. The correlation of Wnt7b expression with clinicopathological characteristics and poor prognosis indicated that Wnt7b as a Wnt/β-catenin signaling pathway ligand, may be the decisive factor for differential expression of Wnt/β-catenin signaling pathway and poor prognosis in different tumors. It suggested that, in the treatment of Wnt/β-catenin highly activated tumors, Wnt7b can be used as an observational clinical marker for malignant tumors, with a focus on Wnt7b for targeted therapy rather than APC, β-catenin or AXIN gene mutation-driven Wnt/β-catenin activation[11].

Note: Schematic of the mechanisms of Wnt7b involving in the development, invasion and metastasis of cancer by canonical or non-canonical signal pathway. The Wnt7b binding to the receptor FZD/LRP/GPR leads β-catenin to dissociating, accumulating and transferring to the nucleus and finally regulates transcription of the target genes by TCF/LEF or AR. Furthermore, Wnt7b is able to regulate MARCKs by phosphorylating PKCα and PKCδ. Wnt7b is also regulated by TCF-β signaling, miRNA and other transcription factors. However, the mechanism of Wnt7b and stat3/PKCθ is still unclear.

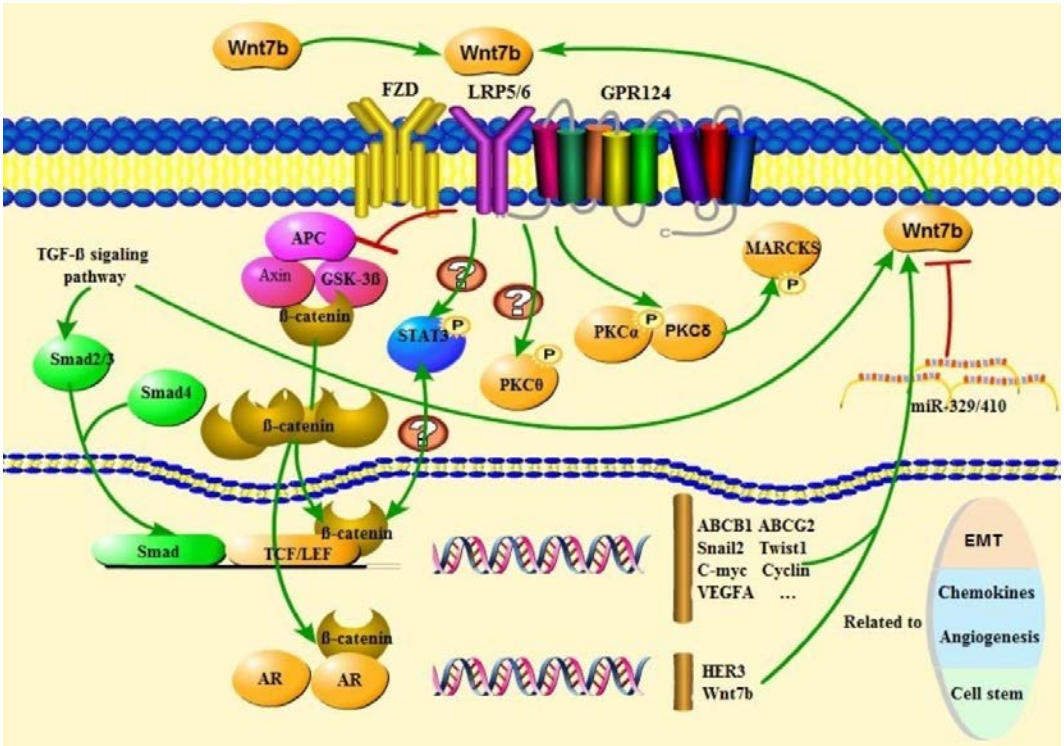

Fig. 1: Wnt7b signaling pathway in cancer (drawn by pathway builder tool 2.0.)

TCF/LEF-DEPENDENT WNT7B/β-CATENIN CLASSICAL SIGNALING PATHWAY

The Wnt family, an essential autocrine glycoprotein in the development of species, regulates cell life activities and is associated with vertebrate limb development and musculoskeletal formation[21,22]. In addition, Wnt signaling pathway may have an influence in the development of diseases such as cancer, diabetes, osteoporosis and coronary arteriosclerosis[3,23-28].

EXTRANUCLEAR TRANSDUCTION IN THE WNT7B/β-CATENIN CLASSICAL PATHWAY

In normal cells, Wnt receptor Frizzled bind to secreted frizzled-associated proteins (SFRPs) resulting in inactivation of the Wnt signal[29]. Intracellular, β-catenin coaxial protein (axin), APC and glycogen synthase kinase 3β (GSK3β) form a β-catenin destruction complex which promote GSK3β-mediated phosphorylation and degradation of β-catenin. This lead to intracellular enrichment of β-catenin, which suppressed nuclear activation of transcription factors[30,31].

When the Wnt7b ligand presents, it binds to the receptor Fzd on the cell membrane and the co-receptor LRP5/6. The intracellular region of the receptor acts on the disordered protein 1(Dvl), dissociating β-catenin from the complex and then accumulates in the cell. Later, it transfers to the nucleus and regulates transcription of a range of target genes[32,33]. This process is similar to other classical Wnt ligand activation pathways. Nevertheless, researchers found that the Wnt7 family-mediated Wnt signaling pathway is also dependent on the G-protein coupled receptor 124(GPR124). As a co-receptor of Wnt7, the last amino acids of GPR124 forms the typical PDZ conjugate with disks large homolog 1(DLG1) and participates in the classical β-catenin signal transduction. The activity is also regulated by the N-terminal leucine-rich repeat (LRR)[34,35]. The GPR124 is a specific G protein-coupled receptor required for angiogenesis. It is also a marker of tumor endothelium 5 (TEM5), which is highly expressed in colorectal cancer and murine tumors[34]. Meanwhile, it can be up-regulated by TGF-β and Rac signals[5], thus showing that Wnt7b may be closely related to angiogenesis and tumor cell metastasis. Furthermore, it highlighted that GPR124 may be a potential target for the invasion and metastasis of malignant tumors.

NUCLEAR TRANSCRIPTION IN THE WNT7B/β-CATENIN CLASSICAL PATHWAY

The Wnt7b is highly expressed in many malignant tumors and the expression of Wnt7b signaling is associated with GPR124 receptors on the membrane. This fact suggested that Wnt7b is involved in tumor invasion and metastasis and angiogenesis. In the presence of the Wnt7b signal, β-catenin is rapidly enriched into the nucleus and acts as a transcriptional coactivator that binds to the T-cell factor (TCF)/lymphocyte enhancer binding factor (LEF)[36]. This interaction occurred primarily in conserved sequences at the amino terminus of TCF/LEF. The TCF/LEF is the most relevant nuclear medium in the Wnt/β-catenin signal and the most important endpoint of this signal. It is DNA binding protein with high mobility that possesses multiple protein interactions and regulatory regions. It has been reported that TCF/LEF is heterogeneous and the relationship between Wnt/β-catenin and TCF/LEF heterogeneity mediated by different Wnt ligands has not been clarified[37].

WNT7B AS A BIOMARKER FOR TGF-β IN TUMOR THERAPY

The TGF-β is an oncogene closely related to tumor growth. Under different tumor microenvironments, it can act as a tumor suppressor gene, while it also plays a role as a tumor-promoting gene[38]. It promoted cancer mainly by inducing epithelial-mesenchymal transition, producing drug resistance and maintaining cell dryness[39,40]. Long-term stimulation of TGF-β can alter the genome-wide pattern of drosophila mothers against decapentaplegic protein 2/3 (SMAD2/3) and promote the interaction of SMAD and activated protein AP-1 (JUNB) to facilitate oncogene events[41,42]. The ChIP sequencing analysis showed that Wnt7b was enriched in advanced TGFβ/SMAD and coordinated with TGFβ, which activated the mammary gland gene to obtain a mesenchymal phenotype[43]. It constructed MCF10A MII cells expressing Wnt7b stably and zebrafish embryo transfer model and found that TGFβ-induced SMAD2/3 and ERK1/2 phosphorylation levels were significantly increased, while enhancing TGFβ/SMAD-induced invasion genes FN1, SERPINE1 and expression[44] of LAMA3. This indicated that Wnt7b is not only a downstream mediator of TGFβ/SMAD, but also promotes TGFβ-induced invasion and metastasis.

Gore *et al.*[45] reported that TGF-β also promoted SAMD2/3/4 phosphorylation and activation of Src, ERK and PI3K in KRC cells. It increased the expression of Wnt7b, promotes epithelial-mesenchymal transition and proliferation and metastasis of pancreatic cancer cells. The EMT process mainly reduces E-cadherin expression by TGF-β treatment and increases N-cadherin, ZEB1 and SNAIL expression. Also, this process is positively correlated with Wnt7b expression.

IMPORTANT FACTORS OF DRUG RESISTANCE BY WNT7B CISPLATIN TREATMENT

Lung cancer, breast cancer and colon cancer metastasize rapidly. Clinically, the resistance of cisplatin is often fatal. The main mechanism leading to cisplatin resistance is still not fully understood. It is suspected that Wnt7b may be an important factor in the development of drug resistance. As ABCB1 and ABCG2 drug transporters are involved in drug resistance and are substrates for non-small cell lung cancer (NSCLCs) drugs of erlotinib, irinotecan[46,47], they are given the ability to assess the effectiveness of drugs in the treatment of NSCLCs. In addition, association studies have shown that ABC is associated with poor clinical outcomes in advanced NSCLCs [48]. Studies showed that cisplatin treatment can significantly increase the mRNA expression of Wnt7b and ABCB1HE ABCG2 in lung D-trimer[49]. Perhaps the cause is that Wnt7b/β-catenin can enrich β-catenin and transfer it to nucleus. Subsequently, it acted as a transcriptional coactivator and bind to the TCF/LEF transcription factor to activate the ABCB1 promoter, which eventually make patients resistant to chemotherapy[36]. In addition to lung cancer, breast cancer and colon cancer also exist β-catenin-induced ABCB1 expression, resulting in drug resistance in patients[50,51].

WNT7B INDUCES EPITHELIAL-MESENCHYMAL TRANSITION TO PROMOTE CANCER INVASION AND METASTASIS

Epithelial-mesenchymal transition (EMT) is a reversible biological process in which epithelial cells are transformed into mesenchymal phenotype cells by specific procedures. During EMT, epithelial cells changed their mental state and cellular structure, thereby losing their characteristics and obtaining invasive and migratory mesenchymal phenotypes. Meanwhile, it accompanied by an increase in the abundance of mesenchymal markers such as vimentin, fibronectin, α-smooth muscle actin and N-cadherin[52]. To date EMT is known to involve its downstream transcription factors Snail, Twist and cytokines MMP2, MMP9 during inducing process[53]. Several growth factors such as TGF-β, Wnt and fibroblast growth factor (FGF) have been shown to induce EMT. This process leads to the production of metastatic tumor stem cells in primary tumors and the infiltration and metastasis of benign tumor cells into surrounding tissues[54]. In the classic pathway of Wnt7b-mediated Wnt/β-catenin/TCF/LEF, unphosphorylated β-catenin transfers into the nucleus and can bind to LEF-1 and form a complex. Afterwards, it induced EMT which is an important phenomenon. The transcription factors targeted by Wnt may be Snail2, Twist1 and the like. Wnt-targeted transcription factors may be Snail2, Twist1, etc: Snail2 in the Snail family of Wnt-targeted transcriptional repressor in basal-like breast cancer, binding to the CDH1 promoter of encoding E-cadherin to inhibit transcription[55], Wnt targets Twist1 of the bHLH transcript family in epithelial cells to induce EMT[56].

WNT7B PARTICIPATES IN TUMOR INVASION AND METASTASIS BY PROMOTING ANGIOGENESIS

In breast cancer research, there is evidence that hematopoietic cells, including tumor-associated macrophages (TAM), contribute to tumor development and metastasis. The TAM expresses Wnt2 and tyrosine kinase with immunoglobulin and epidermal growth factor homology domains (TIE2) that stimulate angiogenesis, promote increased vascular density and stimulate immune cells to synthesize interleukin-4(IL-4) or interleukin-7(IL-7), all of which promote the conversion of benign tumor to invasive cancer[57,58]. In contrast, Wnt7b regulates blood vessels promotes upregulation of TAMs during the development of prostate cancer. Yeo *et al.*[10] constructed a Csf1r-icre mouse model with a Wnt7b deletion, which also demonstrated that TAM-derived Wnt7b is an angiogenesis switch[10]. The Wnt7b deletion down-regulates the expression of β-catenin downstream target genes such as; Axin2, c-cmyc and Cyclin and inhibits the proliferation of NSCLC cells[59]. It affected the mRNA expression of a vascular endothelial cells (VECs) stimulating factor vascular endothelial growth factor A (VEGFA), which was a necessary mediator of tumor angiogenesis. These events lead to a reduction in tumor weight and size and a decreased rate of invasion and metastasis, but the relationship between Wnt7b and TIE2 is not yet clear[60]. In addition to breast cancer, Wnt7b is also observed to be involved in angiogenesis and remodeling in the eyes, lung and arteries[10,61].

WNT7B SIGNALING REGULATES TUMOR INVASION AND METASTASIS THROUGH OTHER WAYS

The Wnt7b not only mediates tumor invasion and metastasis through angiogenesis, but also related to chemokines with tumor-inducing effects and microRNAs. Finak *et al.*[61] showed that Wnt7b was significantly associated with bone marrow signal transduction factor CSF1, vascular marker factor CD31, tumor chemokines CCL3, CCL13 and CCR2 in breast cancer[61]. The MicroRNAs (miRNA or miR) are endogenous small non-coding RNAs (18-25 nucleotides) that bind to the target mRNA by base pairing with the 3' untranslated region (3'-UTR). It regulated gene expression

negatively at the post-transcriptional level. Gene expression[62,63]. Shiah *et al*.[64] found that miR-329 and miR-410 apparent silencing contribute to over expression of Wnt7b in oral squamous cell carcinoma (OSCC) and activate Wnt7b/β-catenin signaling pathway, which is similar to the classical pathway. Also, it promoted angiogenesis and the occurrence, proliferation and invasion of OSCC. These events indicated that Wnt7b participates in tumor invasion and metastasis through multiple pathways[65].

ROLE OF WNT7B IN CANCER THROUGH NON-CLASSICAL PATHWAYS

The Wnt7b activation of Wnt/β-catenin is a typical Wnt signaling pathway in tumor development invasion and metastasis. There are fewer reports on the Wnt7b-mediated atypical Wnt pathway. The atypical Wnt pathway included Wnt/Ca+ and planar cell polar pathways, which mainly activated JNK kinase, calmodulin-dependent kinase II (CaMK) and protein kinase C. In the studies of castration-resistant prostate cancer (CRPC), it was found that β-catenin signaling is usually highly expressed in advanced cancer rather than early stage[66] and β-catenin activation in androgen receptor (AR)-positive CRPC usually depends on AR instead of classic Wnt[67]. This is due to β-catenin is mainly present in the cell membrane and cytoplasm, but not in the nucleus in Wnt7b knockout prostate[68] cancer C4-2B. In fact, Wnt7b is able to phosphorylate PKC prototype MARCKs, thereby reducing PKCα and PKCδ. Interestingly, AR has the ability to skip Wnt7b directly on PKCα and PKCδ to cause functional compensation[69]. Phosphorylation of MARCKS effectively reduced by knockdown of Wnt7b and PKCα or PKCδ implys that Wnt7b is upstream of PKC isozyme[69,70]. Not only in CRPC, in ER-/HER2+(human epidermal growth factor receptor 2) breast cancer, a cascade of WNT/HER2 pathways that mediate tumor cell growth via AR targeting Wnt7b and HER3 is also formed, but whether the response is related to PKC is not mentioned[12]. However, the response to Wnt7b in breast and prostate cancer has been shown to be highly correlated with bone cell regulation and pathology. The secretion of Wnt and ET-1 by cancer cells blocks DKK1 and increases the formation of new bones. This process required the involvement of the Wnt7b receptor LRP5[71-73]. Therefore, targeting the AR/Wnt7b/PKC signaling cascade to inhibit tumor proliferation and bone metastasis may be a relatively effective and promising mechanism.

Given that Wnt7b plays a pivotal role in cancer through atypical pathways, it is suggested that there may be some cytokines that are closely related to the non-canonical pathway of Wnt7b. Here, the correlation of STAT3 and PKC theta were focused with the non-classical pathway of Wnt7b. Signal transducers and transcription activator 3 (STAT3) are acute phase response factor in interleukin-6 (IL-6) signaling[74]. The STAT3 signaling pathway played critical roles in the various of human cancers, including NSCLC, leukemia and breast cancer which are related to Wnt7b[75,76]. Studies demonstrated that there is a certain interaction between STAT3 and β-catenin that is different from the classical pathway. In the studies of ALK-positive anaplastic large cell lymphoma and malignant glioma, it was found that down-regulation of β-catenin reduced the expression of STAT3 and pSTAT3[77,78]. It is also proposed that the β-catenin/TCF4 complex can directly bind to the STAT3 gene promoter[79]. In addition, studies have found that direct inhibition of STAT3 signaling down-regulates the WNT/β-catenin signaling pathway and inhibits transcription of the target genes cyclin D1 and c-Myc, leading to glioma cell death[80]. It confirmed that in the presence of Wnt5a/b ligand, phosphorylation of the Fzd2 tyr552 promoted junctions of Fzd2 and FYN kinase SH2, which promoted phosphorylation of STAT3 tyr705 into the nucleus and regulation of downstream cytokines in the non-canonical pathway of Wnt5a/b-fzd2-fyn-STAT3. Whether there is a similar relationship between Wnt7b and STAT3 and the interaction mechanism between stat3 and β-catenin are still rather vague[57]. The PKC-θ belonged to the novel protein kinase C family, which plays an important role in regulating cell proliferation, differentiation, apoptosis and angiogenesis[81]. Studies have shown that PKC-θ is associated with the development, invasion and metastasis of triple-negative breast cancer and gastrointestinal stromal tumors [53,82-84]. The specific mechanism of the PKC isoform in the Wnt/Ca2+pathway has not been characterized. It has been documented that Wnt3a can positively regulate the Wnt/β-catenin classical pathway by up-regulating[85] PKC-θ. At the same time, PKC-θ imbalance directly affect the TGF-β and NF-κB path STAT3 ways to promote EMT[84].

CONCLUSION

Growing literatures have reported the momentous function of Wnt ligands in tumors and highlighted that, Wnt ligands or components of Wnt pathway might be a potential target for the invasion and metastasis of malignant tumors. Nevertheless, there is a "non-canonical" pathway of Wnt7b acting as a synergistical or compensatory role and thus many details of how Wnt7b acts in invasion and metastasis of malignant tumors warrant further investigation. However, on the basis of present knowledge, it was found that Wnt7b offers many targets for therapeutic intervention in invasion and metastasis of malignant tumors.

SIGNIFICANT STATEMENT

This study first summarized the relationship between high expression of Wnt7b and tumor lesion, clinicopathological characteristics and poor prognosis. In addition, this study explained the relationship between wnt7b and TGF-β, VEGF, MicroRNAs, EMT, PKC and STAT3. Thus a new theory on the mechanism of "canonical or non-canonical" Wnt7b signal pathway at cellular and molecular level may be arrived at.

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