

Review Article

Regulation of Carcinogenesis induced by abnormality of WNT/ β -catenin Signaling Pathway

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ABSTRACT

Keywords

Wnt/ β -catenin, abnormality, carcinogenesis, drugs, cancer treatment.

Stem cells development, Wnt/ β -catenin signaling pathway has crucial impact in regulation of self-renewal, proliferation, differentiation and cell death process. Simultaneously, alteration in Wnt signaling pathways are induced enormous abnormalities in development process including carcinogenesis and homeostasis. In cancer stem cells, aberrant Wnt/ β -catenin signal has major role in self-renewal and proliferation. Abnormality of β -catenin signal stimulated different variety of cancer and also β -catenin signaling molecules such as APC, Axin, GSK-3 and others were involved in cancer stem cells development. Developments of new drugs are especially involved in inhibition of overexpression of β -catenin in tumorigenesis. Diagnostic purpose, activation/inactivation of tumor suppressor genes and oncogenes are necessary for cancer treatment.

Introduction

Wnt1 (Wingless and int-1) gene, originally identified as a oncogene in mouse mammary tumor (Nusse and Varmus, 1982). Wnt signaling pathway involved in stem cells development and human diseases, commonly known as cancers. In 1990s, Wnt/ β -catenin molecules involved in the carcinogenesis, such APC interact with β -catenin to stimulated signaling pathway. Activation of mutation and overexpression of β -catenin leads many cancers and human disorders (Clevers and

Nusse, 2012). Many Wnt/ β -catenin signaling factors involved in human cancers, such factors are APC, Axin, β -TrCP, DKKs, SFRPs, WIF-1, DVLs, GSK-3, TCFs, LEF and finally β -catenin (Luo *et al.*, 2007; Ochoa-Hernandez *et al.*, 2012).

Wnt/ β -catenin Signaling Pathway

Wnt proteins are regulated β -catenin signaling pathway for stem cells and organ developments. Wnt/ β -catenin proteins

were involved in self-renewal, proliferation and maintenance of stem cells. In Wnt signaling, extracellular modulating factors such as Dkk1, WIF-1, SFRP and Dkk1, most common Wnt antagonist to bind LRP5/6 and inhibited Wnt/ β -catenin Signaling (Sonderegger, 2010).

In deficiency of Wnt factors including Wnt1, Wnt2, Wnt2b, Wnt3, Wnt3a, Wnt8a, Wnt8b and Wnt10a and it was stimulated phosphorylation of β -catenin. The cytoplasmic β -catenin proteins combined with Axin, APC and GSK-3 then phosphorylation of β -catenin induced by CK1 and GSK-3. Finally, degradation of β -catenin was stimulated through β -TrCP complex resulting low concentration of β -catenin in cytosol (Zhang *et al.*, 2013).

Secretion of Wnt signaling factors were induced β -catenin signaling. Wnt factors are bind to FZD and it was triggered destruction of Axin/APC/GSK-3 complex. Demolition of β -catenin was activated Dvl and Dvl bind to the FZD followed by Wnt FZD complex formation. Resulting, enormous amount of β -catenin then β -catenin was transferred into the nucleus. Activated β -catenin was wipeout Groucho and HDAC complex.

Here, β -catenin act as a transcriptional co-regulator and bind to the TCF/LEF complex. The active complex of β -catenin and TCF/LEF regulated transcriptional activation of target genes such as c-Myc, Nanog, CD-44, Oct-4, Sox-2, c-Jun and Cyclin D1. Other Wnt target genes were noted at the Wnt home page (<http://www.stanford.edu/~wrnusse/wntwindow.html>) (Lyashenko *et al.*, 2011; Zeng *et al.*, 2008).

Wnt/ β -catenin Signaling in Cancer and Cancer Stem Cells

As a central pathway of both development and cancer, Wnt signaling pathway regulated self-renewal, proliferation and maintained both of normal and cancer stem cells. Mutation and over expression of β -catenin leads many cancers including breast, lung, prostate, colorectal, liver and skin cancer [Table] (Polakis, 2000).

Breast cancer and cancer stem cells

Aberrant expression and mutation of β -catenin was induced breast carcinogenesis. In mammary tumorigenesis, both of mouse and human breast cancer is critical. Wnt signaling was first discovered in mammary tumor when mouse mammary tumor was identified and integrated into int-1 locus. Overexpression of Wnt1 was induced breast tumor via Wnt/ β -catenin signaling. Despite, the strong evidence of Wnt/ β -catenin in mouse mammary tumor model, it was very importance of Wnt signal in human breast cancer. Enormous reports have identified deregulation of Wnt/ β -catenin signaling pathway in breast cancer. Mutation and aberrant expression of β -catenin was associated with triple-negative and basal breast cancer (Valkenburg *et al.*, 2011).

Colorectal cancer

Wnt/ β -catenin signaling was first linked to human colon cancer by the observation of APC mutation. Aberrations of Wnt signaling have been identified 90% in colon cancer. The absence of APC protein leads the chronic activation of Wnt signaling, resulting in the secretion of adenomas, known as adenocarcinoma. Genetic observation in APC mutant, clearly demonstrate the role of APC

mutant in formation of tumor via Wnt signaling pathway. This mutant APC allows β -catenin to accumulate in cytosol and continuously active Wnt/ β -catenin to form colon cancer. Although β -catenin and APC mutation leads colonic carcinogenesis and downregulation of other tumor suppressor gene also involved in development of colon cancer (Giles *et al.*, 2003).

Prostate Cancer

Prostate cancer is most common cancer for American males. Wnt signals are up-regulated in prostate cancer. Increased expression level of Wnt1, Wnt5a, Wnt7a, Wnt11 involved in prostate cancer aggressive and metastasis. In prostate cells, androgen receptor were controlled the prostate tumor growth. Androgen receptors bind to the β -catenin and stimulated transcriptional activity. In prostate cancer, overexpression and mutation of β -catenin similarly bind to the androgen receptors and activated transcriptional activity then produce enormous cell fate. β -catenin activity is also regulated by other molecules in prostate cancer (Chen *et al.*, 2008).

Liver Cancer

In liver, Wnt signaling play crucial role in proliferation during development and also important function in adult liver. Despite, aberrant reactivation of Wnt/ β -catenin signaling was stimulated the enormous accumulation of β -catenin in cytosol lead to many different tumors of liver. Mutation of Axin and β -catenin continuously induced the activation of β -catenin in hepatocellular carcinoma and hepatoblastomas. Simultaneous mutation of β -catenin and H-ras leads to 100% of hepatocellular carcinoma. Finally,

abnormal regulation of Wnt signaling pathways have crucial role in the progression of hepatocellular carcinoma (Chen *et al.*, 2008; Behari, 2010).

Skin Cancer

Wnt signals involved in hair morphogenesis and mutation of β -catenin regulated abnormal hair follicle morphogenesis. Tumor initiation depends on overexpression and mutation of β -catenin signaling. Pilomatricoma one of the skin cancer caused by mutation of β -catenin. Nuclear β -catenin and overexpression level of Axin was also involved in skin cancer. Aberrant expression of β -catenin was reported in melanoma and non-melanoma skin cancer. Activated β -catenin or upregulation of Wnt/ β -catenin signaling was induced transcriptional activation of target genes c-myc and c-jun. These gene and Wnt factors including Wnt3, Wnt4 and Wnt10b were found in skin carcinogenesis (Bhatia and Spiegelman, 2005).

Other types of cancer

The mutant of β -catenin gene (CTNNB1) involved in many tumor. β -catenin and APC mutation involved in multiple myeloma and Wnt5a also expressed in human melanoma. In female and male organs, abnormality Wnt signaling stimulated ovarian carcinomas. Other many types of cancer stimulated by aberrant expression and mutation of β -catenin such as, lung cancer, endometrial cancer, glioblastoma, medulloblastoma, basal cell carcinoma, head and neck squamous cell carcinoma, bladder cancer, gastric cancer, oral cancer, esophageal cancer, retinoblastoma, pancreatic cancer and renal cell carcinoma (Giles *et al.*, 2003).

Table.1 Expression of Wnt/ β -catenin signaling molecules in Cancer development

Wnt Molecules		Nature of defect	Types of cancer	Reference
APC		Loss of function (LOF) and mutation	Familial adenomatous polyposis, colorectal, breast, cervical, oral, pancreatic, prostate, intestinal, liver, lung, medulloblastoma germinoma, myeloma and melanoma	Yao <i>et al.</i> , 2011; Li <i>et al.</i> , 2012
Axin	Axin-1	LOF and mutation	Hepatocellular carcinoma, medulloblastoma, colorectal cancer, esophageal squamous cell carcinoma, ovarian adenocarcinoma, adenoid cystic carcinoma, Prostate cancer, breast cancer and melanoma	Logan and Nusse, 2004; Salahshor and Woodgett, 2005
	Axin-2	LOF and mutation	Familial tooth agenesis and colorectal cancer, melanoma, Hepatocellular carcinoma, ovarian adenocarcinoma, endometrial cancer, prostate cancer, breast and lung cancer	Logan and Nusse, 2004; Salahshor and Woodgett, 2005
β -TrCP			Breast cancer, prostate cancer and colorectal cancer, liver cancer, ovarian cancer, neuroblastoma, gastric cancer, lung and thyroid cancer	Fuchs <i>et al.</i> , 2004; Kim <i>et al.</i> , 2007
DKK	DKK1	Overexpression	Breast cancer, prostate cancer, lung cancer, kidney cancer, melanomas, ovarian cancer, colon cancer, multiple myeloma, Hepatocellular carcinoma, colon cancer, gastric cancer, esophageal cancer, oral cancer, neuroblastoma, endometrial carcinoma, leukaemia, hepatoblastomas and Wilms tumors.	Forget <i>et al.</i> , 2007
	DKK2	Overexpression	Neuroblastoma, tumor angiogenesis, Ewing sarcoma, hepatocellular carcinoma, colorectal cancer, ovarian carcinoma, malignant melanoma, renal cell carcinoma, gastric cancer, Breast cancer, lung cancer, cervical cancer	Revet <i>et al.</i> , 2010; Park <i>et al.</i> , 2014
	DKK3	LOF or decreased expression	Medulloblastoma, cervical carcinoma, colon cancer, pancreatic cancer, esophageal cancer, Neuroblastoma, Hepatocellular carcinoma, non-small cell lung, breast, prostate, pancreatic, cervical, bladder, renal and leukemia	Revet <i>et al.</i> , 2010; Kuphal <i>et al.</i> , 2006
	DKK4	Overexpression	Hepatocellular carcinoma, colon cancer, breast cancer, gastric cancer	Kuphal <i>et al.</i> , 2006; Katoh and Katoh, 2005
SFRPs		Overexpression	lung cancers, breast and colorectal carcinomas, endometrial stromal sarcomas, prostate	Shi <i>et al.</i> , 2007

		carcinomas, and neuroblastomas, gastric cancer, ovarian carcinoma, Hepatocellular carcinoma, multiple myeloma, pancreatic cancer, breast cancer, esophageal adenocarcinoma,	
WIF-1	LOF or decreased expression	Breast, prostate, lung and bladder cancer, cervical cancer, esophageal squamous cell carcinoma, osteosarcoma, melanoma, chronic lymphocytic leukemia, gastric, colorectal and pancreatic cancer	Wissmann <i>et al.</i> , 2003
DVLs	Overexpression	Lymphoma, colorectal cancer, breast cancer, neuroblastoma, cervical carcinoma, lung cancer	Hegazy <i>et al.</i> , 2013
GSK-3	Overexpression	Oral cancer, ovarian cancer, multiple myeloma, colorectal cancer, chronic lymphocytic leukemia, gastric cancer, ovarian cancer, breast cancer, lung cancer, Prostate cancer, Hepatocellular carcinoma, neuroblastoma	Ryu <i>et al.</i> , 2012
TCFs	Increased expression	Colon cancer, lung cancer, melanoma, lymphoma, renal cell carcinoma, breast and ovarian, hepatocellular carcinoma, gastric carcinoma, prostate cancer, brain tumor,	Tiemessen <i>et al.</i> , 2012
LEF	Aberrant expression	Colon cancer, breast cancer, chronic lymphocytic leukemia, oral carcinoma, prostate, acute myeloid leukemia, oropharyngeal carcinoma, melanoma, lung adenocarcinoma	Nikuseva-Martic <i>et al.</i> , 2013
β -catenin	Overexpression and mutation	colorectal cancer, hepatocellular carcinoma, lung cancer, endometrial cancer, malignant breast tumor, ovarian cancer, glioblastoma, melanoma, medulloblastoma, basal cell carcinoma, head and neck squamous cell carcinoma, prostate cancer, bladder cancer, esophageal cancer, retinoblastoma, gastric cancer, multiple myeloma, oral cancer, pancreatic cancer, renal cell carcinoma	Morin, 1999; Zeng <i>et al.</i> , 2008; Zang <i>et al.</i> , 2001

Fig.1 Off-State of Wnt/ β -catenin signaling pathway

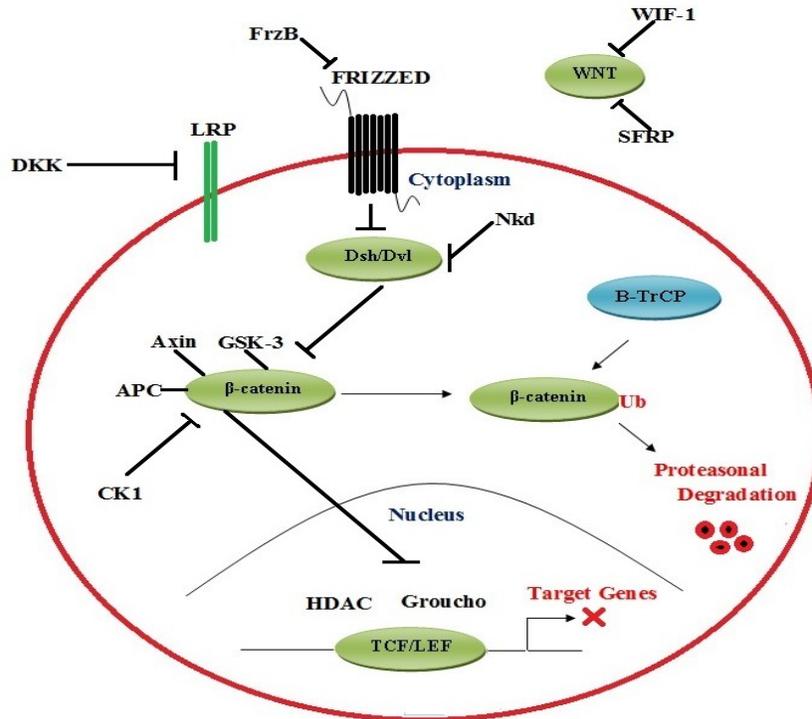
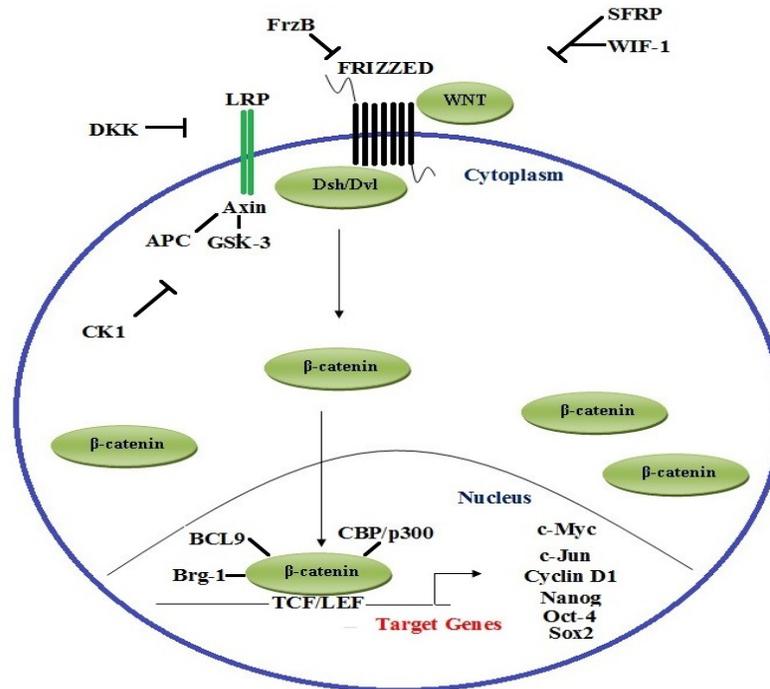


Fig.2 On-State of Wnt/ β -catenin signaling pathway



Wnt/ β -catenin signals are central pathway of stem cells and organ development. In cancer and cancer stem cells, abnormality of Wnt/ β -catenin has crucial role in cancer development. Aberrant expression and mutation of β -catenin continuously stimulated many types of cancer. Deregulation of Wnt/ β -catenin signaling has crucial impact in cancer stem cells self-renewal and proliferation. Critically, mutant β -catenin, Axin, APC plays important role in cancer development. In clinical level, specific drugs were not developed against cancer and cancer stem cell self-renewal and proliferation carried out by overexpression and mutant β -catenin signaling. Future research, specialized drug will synthesis against mutant and overexpression of β -catenin involved in variety of cancer and specially, drug will target to cancer stem cells development.

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