**Name of Journal:** *World Journal of Clinical Oncology*

**Manuscript NO:** 64718

**Manuscript Type:** REVIEW

**Intestinal Wnt in the transition from physiology to oncology**

Swoboda J *et al*. Intestinal Wnt from physiology to oncology

Julia Swoboda, Patrick Mittelsdorf, Yuan Chen, Ralf Weiskirchen, Johannes Stallhofer, Silke Schüle, Nikolaus Gassler

**Julia Swoboda, Patrick Mittelsdorf, Yuan Chen, Nikolaus Gassler,** Section Pathology, Institute of Forensic Medicine, Jena University Hospital, Jena 07747, Germany

**Ralf Weiskirchen,** Institute of Molecular Pathobiochemistry, Experimental Gene Therapy and Clinical Chemistry, RWTH University Hospital Aachen, Aachen 52074, Germany

**Johannes Stallhofer,** Department of Internal Medicine IV (Gastroenterology, Hepatology, and Infectious Diseases), Jena University Hospital, Jena 07747, Germany

**Silke Schüle,** Department of General, Visceral and Vascular Surgery, Jena University Hospital, Jena 07747, Germany

**Author contributions:** Swoboda J wrote the paper; Mittelsdorf P designed the figures and helped to draft the manuscript; Chen Y, Weiskirchen R, Stallhofer J and Schüle S participated in drafting the article and critically revising it; Gassler N conceived the concept and also contributed to figures and correction.

**Corresponding author: Nikolaus Gassler, MA, MD, Professor,** Section Pathology, Institute of Forensic Medicine, Jena University Hospital, Am Klinikum 1, Jena 07747, Germany. nikolaus.gassler@med.uni-jena.de

**Received:** February 23, 2021

**Revised:** September 7, 2021

**Accepted:** February 19, 2022

**Published online:** March 24, 2022

**Abstract**

Adult stem cells are necessary for self-renewal tissues and regeneration after damage. Especially in the intestine, which self-renews every few days, they play a key role in tissue homeostasis. Therefore, complex regulatory mechanisms are needed to prevent hyperproliferation, which can lead in the worst case to carcinogenesis or under-activation of stem cells, which can result in dysfunctional epithelial. One main regulatory signaling pathway is the Wnt/β-catenin signaling pathway. It is a highly conserved pathway, with β-catenin, a transcription factor, as target protein. Translocation of β-catenin from cytoplasm to nucleus activates the transcription of numerous genes involved in regulating stem cell pluripotency, proliferation, cell differentiation and regulation of cell death. This review presents a brief overview of the Wnt/β-catenin signaling pathway, the regulatory mechanism of this pathway and its role in intestinal homeostasis. Additionally, this review highlights the molecular mechanisms and the histomorphological features of Wnt hyperactivation. Furthermore, the central role of the Wnt signaling pathway in intestinal carcinogenesis as well as its clinical relevance in colorectal carcinoma are discussed.

**Key Words:** Wnt signaling; Beta-catenin; Intestine; Colorectal cancer; Cell signaling; Intestinal stem cells

**©The** **Author(s) 2022.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Citation:** Swoboda J, Mittelsdorf P, Chen Y, Weiskirchen R, Stallhofer J, Schüle S, Gassler N. Intestinal Wnt in the transition from physiology to oncology. *World J Clin Oncol* 2022; 13(3): 168-185

**URL:** https://www.wjgnet.com/2218-4333/full/v13/i3/168.htm

**DOI:** https://dx.doi.org/10.5306/wjco.v13.i3.168

**Core Tip:** Wnt signaling pathway is a key regulator of intestinal stem cells. Mutations in this pathway are frequently found in adenomas and carcinomas of the colorectum. Therefore, it represents a potential target for anticancer therapy. This review sums up the physiological role and the regulatory mechanism of Wnt signaling in the human intestine, and moreover, discusses the central role of the Wnt signaling pathway in intestinal carcinogenesis, the morphological features associated with Wnt hyperactivation and clinical relevance of Wnt in the colorectal carcinoma.

**INTRODUCTION**

The gastrointestinal epithelia are tissues that self-renew every few days. Therefore, pluripotent stem cells are needed, which have the potential to develop into different epithelial cells. These highly complex mechanisms need complex fine-tuning. An overactivation of pluripotent stem cells could lead to hyperproliferation and in the worst case to cancer development. Conversely, under-activation could lead to insufficient development of the epithelia with dysfunction of the epithelia. One main regulatory signaling responsible for intestinal epithelial development is Wnt signaling.

Since 1976 it has been known that the Wingless (*WNT*) gene in Drosophila not only influences development, but also provokes abnormalities of the mesothorax[1]. In recent decades, other genes of the Wnt family have been found and the signaling pathways around Wnt in humans have also become more and more clear. Today 19 *WNT* genes in humans are known and the Wnt pathway is known to play a critical role in embryonic development and tissue homeostasis[2]. An imbalance in Wnt signaling can lead to several diseases including carcinogenesis, neurodegenerative, metabolic and cardiovascular diseases[3]. In addition to the canonical Wnt/β-catenin pathway, which is the main focus of this review, there is also the noncanonical pathway and the noncanonical Wnt/calcium pathway[4].

This work focuses on the regulation and the role of the canonical Wnt/β-catenin signaling pathway in physiological epithelial differentiation and the molecular activities of Wnt contributing to autonomous hyperproliferation and injured cell death as hallmarks of carcinogenesis.

**WNT/β-CATENIN SIGNALING PATHWAY**

The most common Wnt pathway and evolutionarily conserved pathway is the canonical Wnt/β-catenin signaling (Figure 1). It consists of the transmembrane complex (Lrp5/6 and Frizzled), a destruction complex [Axin, Adenomatous polyposis coli (APC), glycogen synthase kinase-3 (GSK3), casein kinase 1 (CK1), protein phosphatase 2A (PP2A)] and β-catenin[5-7]. In the absence of the Wnt ligand, β-catenin is phosphorylated by the kinases CK1 and GSK3[8]. The phosphorylation leads to the ubiquitination and degradation of β-catenin. If Wnt binds to the transmembrane complex, the protein Disheveled is activated and turns down the destruction complex, resulting in accumulation of β-catenin in the cytoplasm[9,10]. Then, β-catenin is translocated into the nucleus and acts there as a transcription factor together with P300, B-cell CLL/lymphoma 9, pygo and T-cell factor/lymphoid enhancer-binding factor (TCF/LEF) as cofactors[11-13]. Moreover, there are inhibitors of this pathway like Dickkopf 1 (Dkk1), which binds to Lrp5 and inhibits the binding of Wnt at the transmembrane complex[14,15].

The role of Wnt/β-catenin signaling in the development of the gastrointestinal tract becomes clear when we look at the main genes which are regulated by the Wnt signaling pathway. Nuclear β-catenin activates genes which code for proteins involved in important pathways as well as processes including embryogenesis, proliferation, cell differentiation and the regulation of cell death (Table 1)[16-18].

**THE NECESSITY OF WNT SIGNALING IN INTESTINAL MUCOSAL PHYSIOLOGY**

In the intestinal tract, the canonical Wnt is an essential and fundamental molecular cascade to establish and constitute the mucosal barrier. However, in the different segments of the intestinal tract, the Wnt shows different cellular and molecular players as well as facets that are characteristic for each compartment. Wnt signaling is required in all parts for stem cell renewal, while Wnt overactivation in the stomach can lead to intestinal shift. Mutations in the Wnt ligands affect all parts of the intestine[19,20]. These points are addressed further in the following paragraphs.

***Stomach***

The stomach can be divided, based on its local glands, into two main parts: The corpus/fundus and the antrum. The corpus and fundus contain oxyntic glands with chief cells, parietal cells and endocrine cells, while the antrum glands mainly contain mucous and endocrine cells[21]. Wnt/β-catenin signaling was required for the development of the embryonic fundus and in the β-catenin-deficient epithelium, parietal cells were absent[22]. In the antrum glands, Lgr5+ and Axin2+ stem cells were found[23]. Both proteins are regulated throughout Wnt signaling. Wnts are necessary for the maintenance of Lgr5+ cells and are necessary for the zymogenic cell line from Lgr5+ cells[24]. Moreover, they suppress the differentiation along the pit cell lineage. The Wnt ligands in the stomach will be secreted by pericyte-like stromal cells[25]. These cells are conserved and exist in the colon as well as in the stomach. Besides, activation of Wnt signaling in the stomach can lead to an intestinal fate in the stomach. Therefore, the mesenchymal transcription factor Barx1 represses the Wnt signaling and inhibits an intestinal shift of the stomach epithelium[26].

***Small intestine***

The small intestine consists of finger-like villi with an absorptive function and crypts of Lieberkühn (Figure 2). In the crypts, two different populations of intestinal stem cells (ISC) are located[27]. At the bottom of the crypts are columnar ISCs which express Lgr5, have a high division rate and are preferred for the renewal of the intestinal epithelia[28]. These cells can be activated throughout Wnt. On the other hand, there are quiescent ISCs that have a slow division rate, are less vulnerable to radiation and Wnt signaling is not activated. These cells are located above the Paneth cells and are also called +4 cells[29]. The role of these cells has not been fully investigated yet. But in the absence of columnar ISCs, quiescent ISCs can be activated and assume the tasks of columnar ISCs[30]. The localization of the subpopulation of ISC in the crypt is controlled by the surrounding mesenchymal cells through bone morphogenetic protein (BMP) signaling[27]. The regulation of the ISC occurs through Wnt3A which is secreted by Paneth cells[31].

Paneth cells are located in the base of the crypt of the small intestine next to Lgr5+ cells. Their differentiation is induced by SOX9, a transcriptional target and a critical regulator of Wnt signaling[32]. In contrast to other differentiated intestine cells, they do not migrate upwards to the top of the villus tip and their lifetime is, at 30 d, much longer[33]. Their main role is to synthesize and secrete defensins, anti-microbial peptides and trophic factors. Nevertheless, they seem to have an impact on crypt homeostasis.

Above the Paneth cells and stem cells is the transit-amplifying zone. The progenitor cells of the differentiated enterocytes are settled here, which can divide themselves two to five times[34,35]. All differentiated cells with the exception of Paneth cells migrate from the crypts upwards to the villi. The main parts of differentiated cells are enterocytes, which make up 80%-90% and have an absorptive function. In addition to them, there are tuft cells, goblet cells, enteroendocrine cells and microfold cells that are also termed M cells[35,36].

That Wnt signaling is essential for intestinal development has been already shown in the work of Pinto *et al*[37]. Overexpression of the Wnt inhibitor Dkk1 leads to a loss of crypts and reduced epithelial proliferation[37]. Furthermore, inhibition of Dkk leads to a reduced rate of fission of crypts in postnatal growth[38]. A negative autoregulatory feedback loop of Wnt signaling prevents a hyperactivation of Wnt signaling[28,39].

***Colon***

The colon has, in contrast to the small intestine, crypts, but no villi. The so-called colonocytes are functionally equivalent to the enterocytes[35]. Like the small intestine, the colon epithelia renew themselves through crypt-based columnar ISCs[35]. The work of Davies *et al*[40] revealed that Wnt activity is lower in the colon than in the small intestine. This may be influenced by the fact that instead of Paneth cells the colon epithelia have deep secretory cells with similar functions to Paneth cells, but in contrast to Paneth cells, they do not secrete Wnt ligands[35,41]. Furthermore, *in vitro* studies show that the reaction of Wnt-signaling activation also differs between the left and the right colon[42]. In embryonic development, a Wnt3A gradient plays an important role in hindgut extension and colon formation[43]. Like the small intestine, the colon epithelia include goblet cells, tuft cells and enteroendocrine cells[35].

**THE COMPLEX REGULATION NETWORK OF WNT SIGNALING**

As mentioned above, the Wnt signaling pathway is a highly conserved pathway and essential for intestinal homeostasis. To preserve this homeostasis, precise fine-tuning is absolutely necessary. The regulation of Wnt ligands occurs on different pathway levels. The mechanisms involved in this regulation are explained below and summed up in Figure 3.

***Notch signaling pathway***

Notch signaling is one of the most important signaling pathways in terms of adjacent cellular communication and regulation of gastrointestinal stem cells[44]. It plays a crucial role in determining whether a cell develops into a secretory or an absorptive cell[44]. Deletion of NOTCH1 and NOTCH2 leads to hyperplasia of secretory cells[45]. It is not surprising that Wnt and Notch signaling act closely together and regulate each other[46,47]. The amount of Notch correlates here inversely with the amount of β-catenin[48,49]. On the other hand, Disheveled, which is part of the Wnt signaling, inhibits Notch signaling[50,51]. As Notch signaling requires cell-cell contact, Paneth cells are important for controlling the Notch signaling of small ISC[52]. In conclusion, Notch signaling determines cell fate to absorptive cell lines, while Wnt signaling drives cells to secretory cell lines[35,53].

***Caudal-related homeobox transcription factor 2***

Caudal-related homeobox transcription factor 2 (CDX2) is essential for human development. In the gastrointestinal tract, it determines gastric and intestinal development[54]. In adult mice, the absence of CDX2 leads to a cessation of intestinal differentiation[54]. In various works it has been shown that CDX2 activates Axin 2, which is part of the destruction complex in Wnt/β-catenin signaling[55,56]. Yu *et al*[56] showed in their work that CDX2 upregulates not only Axin 2 but also GSK-3β, which is also part of the destruction complex. The absence of CDX2, which in colorectal cancer is directly correlated with a higher tumor grade, leads to an activation of Wnt signaling[57].

***BMPs***

BMPs belong to the transforming growth factor-β (TGF-β) family. They are produced by mesenchymal cells especially at the tip of the villus and generate a contrary gradient with Wnt through the crypt-villus axis[58]. At the crypt base, BMP signaling is repressed by BMP inhibitors like gremlin and chordin-like 1 secreted by smooth muscle cells or myofibroblasts[59]. BMP represses ISC proliferation, while the influence of BMP on Wnt signaling is the subject of controversial debate. The work of He *et al*[60] postulates that BMP inhibits Wnt signaling, while the work of Qi *et al*[61] describes a direct suppression of Lgr5+ cells through BMP without changes in the Wnt target genes.

***Hippo signaling pathway***

Hippo signaling is a highly conserved pathway and important for intestinal homeostasis and regeneration. Inactivation of Hippo signaling leads to an activation of the transcription factor Yes-associated protein 1 (YAP1), which has the highest activity at the bottom of the crypts[62]. YAP1 is an oncogene that is a facultative regulator of stem cell homeostasis and an essential regulator for the regeneration of the intestinal epithelial after injury[62]. Hippo and Wnt signaling are closely linked to each other[63]. YAP1 increases the transcriptional activity of β-catenin, while active Hippo signaling leads to the formation of the destruction complex of Wnt signaling[64,65].

***Hepatocyte nuclear factor 4***

Hepatocyte nuclear factor 4 (HNF4) is a transcription factor family that mainly regulates metabolism in cells. Especially fatty acids have a high impact on ISC homeostasis[66]. Chen *et al*[67] show in *in vitro* studies that HNF4α and HNF4γ activate genes involved in fatty acid oxidation and that HNF4 is necessary for stem cell renewal in the intestine. Studies about the interaction of HNF4 and Wnt are rare, few studies indicate that HNF4 may regulate Wnt signaling. The study by Yao *et al*[68] demonstrated that HNF4α is downregulated in human colon carcinoma and showed in *in vitro* experiments that HNF4α suppresses Wnt/β-catenin signaling. These results coincide with the data shown in hepatocellular carcinoma[69].

***Posttranslational modification of Wnt ligands***

Wnt ligands need posttranslational modifications before they can activate Wnt signaling. In the endoplasmic reticulum, Wnt ligands were glycosylated and lipidated[70]. These modifications are essential for intracellular transport, secretion of Wnt ligands and signaling[71,72].

Wnt signaling could also be inhibited by posttranslational palmitoylation. Acyl-CoA synthetase 5 (ACSL5), a mitochondrial enzyme, activates long-chain fatty acids, while binding a thioester. ACSL5-dependent palmitoylation of Wnt2β leads to an accumulation of Wnt2β in the mitochondrion and a decrease in Wnt signaling activity[73].

Furthermore, the degradation of Wnt components by the proteasome can be regulated *via* ubiquitination through ligases. For example a phosphor switch in the E3 ubiquitin ligase RNF43 leads to a lack of degradation of Frizzled and therefore to Wnt activation[74]. The ligase RNF43 itself is inhibited by receptor Lgr4[75]. Park *et al*[76] summed up the different regulation possibilities of Wnt signaling throughout ubiquitination and deubiquitination. The ubiquitination is done by E3 Ligases while deubiquitination is done by deubiquitinating enzymes. In Wnt signaling, every protein component is targeted by ubiquitination or deubiquitination[76]. Therefore, it is an important regulator of Wnt signaling.

***Non-coding RNAs***

Long non-coding RNAs are over 200 nt long non-coding RNA molecules. As reviewed in Zarkou *et al*[77], they can act as a Wnt enhancer by transcriptional activation of genes coding for Wnt proteins or by interaction with transcription factors regulating Wnt signaling.

MicroRNAs (miRNAs) are small 18-25 nt long non-coding RNA molecules and can bind on their target messenger-RNA (mRNA) and suppress translation. Rahmani *et al*[78] summed up about 17 miRNAs that target mRNAs encoding for proteins of Wnt signaling. Here, they can act as an activator of Wnt signaling by suppressing translation of mRNA encoding for the destruction complex or as a suppressor of Wnt signaling, by inhibiting translation of mRNAs encoding for transmembrane complex or β-catenin. Kim *et al*[79] examined the crosstalk between stress-driven ribosome dysfunction and Wnt signaling. A proteinkinase R-activating ribosomal insult leads to changes in the Wnt and connective tissue growth factor crosstalk, which leads to progression in cancer stemness.

***Other pathways***

Despite the above-described pathways, growing evidence demonstrates that other pathways including the mitogen-activated protein kinase (MAPK) pathway, TGF-β signaling, and phosphoinositide 3-kinase/protein kinase B (PI3K/AKT) pathways involved in cell proliferation and survival have an influence on Wnt signaling[80]. It is reported that MAPK signaling regulates Wnt activity on stemness phenotypes in colorectal carcinoma cells[80,81]. Moreover, it has been found that Wnt and TGF-β pathways interact with each other to regulate genes participating in epithelial to mesenchymal transition (EMT)[82]. Hu *et al*[83] depict that epidermal growth factor receptor mediated PI3K/AKT activation enhances Wnt signaling activity through promoting β-catenin translocation, leading to increased tumor cell invasiveness.

**HYPERACTIVATION OF WNT SIGNALING DRIVES PATHOPHYSIOLOGY**

In spite of these regulatory mechanisms, Wnt hyperactivation is not always avoidable. In this context, controlled activation must be distinguished from autonomous activation. Controlled activation is triggered by a stimulus outside the cell and determined through the presence of the stimulus, while autonomous activation is mainly triggered through modifications of proteins involved in the pathway and independently of the regulatory mechanism. The detailed mechanisms which lead to hyperactivation of Wnt signaling and the histomorphological correlation will be discussed hereafter.

***Molecular mechanisms resulting in Wnt hyperactivation***

As mentioned above, Wnt signaling is a complex regulated signaling pathway and many possibilities lead to hyperactivation of Wnt signaling in the intestine. Especially Wnt activation, while the loss of *APC* gene is well-studied *in vitro* and *in vivo*. In Drosophila, *APC* loss induced intestinal tumorigenesis[84]. A germline mutation in the *APC* gene with a loss-of-function mutation leads to familial adenomatous polyposis, representing a hereditary disease characterized by hundreds of colorectal adenomas[85]. But hyperactivation is not always accompanied by pathological tissue growth. In intestinal epithelial after injury, Wnt is also hyperactivated and enables regeneration[86]. Nevertheless, there is a fine line between Wnt activation for tissue regeneration and tissue hyperplasia. Ahmed *et al*[87] show in mice that Wnt and Notch signaling balance transmissible murine colonic hyperplasia and colitis induced by *citrobacter rodentium*. In the chronically inflamed intestine such as bowel disease, Wnt signaling is activated[88]. These patients had an increased risk of developing dysplasia and colorectal carcinoma[89]. Abnormal β-catenin expression was more closely linked to E-cadherin alterations in inflammatory bowel disease-related cancers than in sporadic cancers suggesting that specific alterations in this pathway may differ in these two cancer groups[90].

As long as Wnt signaling is controlled by other pathways, hyperproliferation of epithelial is stoppable. Problematic is uncontrolled Wnt activation, which leads to a permanent-growth stimulus. This could be caused by loss-of-function mutations in the genes encoding for the destruction complex. As mentioned above, familial adenomatous polyposis is a good example of this. But growth stimulation alone is not sufficient for carcinoma development. Fearon and Vogelstein generate the model of the adenoma-carcinoma-sequence[91]. They postulate that stepwise genetic alterations in oncogenes and tumor suppressor genes lead to hyperproliferative epithelial, low-grade and high-grade adenoma to carcinoma development. Besides *APC* mutations, which are hypothesized as a key event in adenoma development, gain-of-function mutations in *KRAS* and loss of functions in *P16-INK4*, *TP53* and *Smad4* are described in the model of multiple step carcinogenesis[92]. It is assumed that this model applies to 80% of colorectal carcinoma[93]. Nonetheless, not only *APC* mutations but also mutations in *KRAS* influence Wnt/β-catenin signaling[84]. In cell culture, KRAS stabilizes β-catenin through inhibition of GSK-3β, while others postulate that KRAS mutations activate Wnt signaling through DNA demethylation[93,94]. Interestingly, *APC* mutation and Wnt activation is a common finding in colorectal cancer, but not in carcinoma of the small intestine, even though Wnt activity in the small intestine is higher than in the colon[40,95]. That suggests that in colorectal carcinogenesis the Wnt activation is not triggered by a regulatory activation of Wnt signaling, but through an autonomous, uncontrolled activation of the Wnt signaling pathway.

In the stomach, bile acid reflux leads to an epigenetic downregulation of Dkk1, an inhibitor of Wnt signaling[96]. The bile acid-induced downregulation of Dkk1 is correlated with gastric intestinal metaplasia and might be triggered by Wnt activation. Other studies have demonstrated high expression of Dkk1 in gastric carcinomas[97].

***Morphological changes caused by mutations associated with Wnt activation***

The genotypic changes in colorectal adenomas lead to phenotypic changes (Figure 4). Adenoma with the classical adenoma-carcinoma-sequence often present macroscopically or endoscopically as polypoid lesions, while tumors with CpG island hypermethylation and *BRAF* mutations often present as flat mucosal lesions[92]. *APC* mutations are more often in adenomas with villous or tubulovillous formation, which are reminiscent of small intestinal villi, but *APC* mutation is also found in tubular adenomas which had elongated crypts[98]. Furthermore, Paneth cell metaplasia is also a common finding in conventional adenoma, following the adenoma-carcinoma-sequence. Joo *et al*[99] examined colonic epithelial neoplasms for Paneth cell metaplasia and Paneth cells were found in 38.5% of the conventional adenoma. This Paneth cell metaplasia was always associated with positive nuclear β-catenin staining[99]. The adenoma cells also show, depending on their grading, enlarged, hyperchromatic nuclei and loss of polarity and decreased numbers of goblet and absorptive cell lines[100]. In conclusion, hyperactivation of Wnt in the colon shifts the phenotype to a small intestinal-like phenotype.

As in the intestine, APC downregulation occurs in gastric adenomas[101]. In the stomach, the downregulation of APC is mostly caused by hypermethylation of the APC promoter and might be triggered by *Helicobacter pylori* infection[102]. Koushyar *et al*[103] summed up the parts of Wnt signaling which are deregulated in gastric cancer. In gastric cancer organoids, Wnt inactivation leads to a shift from morphological poorly carcinoma not other specified to signet-ring cell carcinoma[104].

**CLINICAL RELEVANCE OF WNT ACTIVATION IN THE INTESTINE**

***Clinical relevance of Wnt activation in gastric cancer***

In studies, Wnt signaling was upregulated in more than 80% of the examined gastric cancers and may mark Lgr5 stem cells[105]. The detailed mechanism which leads to Wnt activation is similar to colorectal cancer and is reviewed in detail by Chiurillo[106]. Mao *et al*[107] examined that Wnt1 overexpression accelerated the growth of gastric cancer. Wnt/β-catenin signaling inhibitors suppress gastric tumor growth in a mice model[108].

***Clinical relevance of Wnt activation in the small intestine***

Chen *et al*[109] showed cells of the Paneth cell lineage are present in intestinal adenomas. They secrete Wnt 3 and a deletion of Paneth cells leads to reduced growth of adenomas in the small intestine in APCmin mice. The authors concluded that Wnt3 is required for early tumorigenesis in the small bowel.

***Clinical relevance of Wnt activation in colorectal cancer***

In recent decades, the role of genetic aberration as a prognostic value has moved increasingly to the fore. It is therefore evident that APC mutations, which occur in the majority of microsatellite stable colorectal cancers, are examined to determine whether they had a prognostic value of colorectal cancer. Jorissen *et al*[110]analyzed over seven hundred patients with sporadic colorectal cancer and found that wild-type *APC* correlates with poor prognosis (5-year survival) in microsatellite stable proximal colon cancer. On the other hand, some studies indicate that nuclear β-catenin promotes metastasis of colon cancer, which usually display poor prognosis, by EMT[111,112].

As mentioned above, mutations that activate Wnt/β-catenin signaling are common genetic events in colorectal cancer and usually occur in an early state of carcinogenesis. Therefore, Wnt inactivation is a possible target for preventing tumor progression and as a potential treatment of colorectal cancer. 5-aminosalicylic acid (5-ASA) is a well-established treatment against inflammatory bowel disease, especially in ulcerative colitis. Therefore, it has not only anti-inflammatory but also anti-proliferative effects[113]. Several cohort studies and case-control studies have demonstrated that 5-ASA treatment is associated with a reduced colorectal cancer risk in patients with ulcerative colitis[114-116]. Therefore, guidelines recommend 5-ASA treatment for ulcerative colitis patients also under the aspect of cancer prevention. The anti-proliferative effect is forced by PP2A-dependent accumulation of nuclear β-catenin[117]. Munding *et al*[118] examined the role of the chemopreventive effects of 5-ASA *in vivo*. After three years, there were no significant differences regarding the progression of adenomas between the patients treated with 5-ASA and the placebo group. But in the group treated with 5-ASA, a significant decrease in nuclear β-catenin expression was found[118]. Further studies with a longer treatment time were necessary because the development of carcinoma through the adenoma-carcinoma sequence takes about ten to fifteen years[119]. Serafino *et al*[120] examined in their study the β-catenin expression and the expression of the β-catenin regulated proteins c-Myc and Cyclin D1 in bowel disease and found elevated expression levels of these proteins especially in low-grade and high-grade dysplasia. These results emphasize the potential benefit of Wnt signaling inactivation as a predictive cancer therapy.

As reviewed by Zhu *et al*[121], Wnt activation has an impact on the resistance to chemotherapy in colorectal adenocarcinoma. Hu *et al*[122] determined that Wnt activation through exosomal Wnt secretion of fibroblasts leads to an increase in chemoresistance of cancer stem cells. Zhang *et al*[123] also identified the tumor microenvironment as a crucial factor in Wnt-induced chemoresistance. The increased chemoresistance in Wnt upregulated cancers is not only caused by enhancing the expression of antiapoptotic proteins, but also by enhancing the expression of multidrug resistance proteins[123,124]. Zhong *et al*[125] summarized different studies where chemoresistance is associated with Wnt activation in conventional radiochemotherapy, but also in targeted and immunotherapy. Wnt signaling seems to have a big impact on the response to cancer therapy. Hence, the development of a personalized therapy targeting components of the Wnt signaling pathway in treatment of cancer is required.

**WNT/β-CATENIN SIGNALING AS A POTENTIAL TARGET IN THE PREVENTION AND TREATMENT OF INTESTINAL CANCER**

Application of Wnt inhibitors might be a possible therapeutic strategy to inactivate the Wnt pathway in cancer, for example obviation of binding of Wnt to Frizzled, stabilization of Dkk or destruction complex, inhibition of the transmembrane complex or Disheveled, application of β-catenin antagonist and antagonist of β-catenin cofactors, *etc*. Different drugs targeting Wnt pathway are currently in clinical trials, as reviewed in detail in Caspi *et al*[126]. Kleeman *et al*[127] postulate that there may be a difference in the therapeutic approach in ligand-dependent and ligand-independent tumors. Therefore, the localization of the mutation should be taken into account in the choice of Wnt signaling-targeting therapy. Ligand-dependent tumors should be targeted to the ligands or the transmembrane complex. In ligand-independent tumors, such as APC mutated tumors, targeting transmembrane complex is useless. A therapeutic option in these tumors is increased degradation of β-catenin. This is achieved by a stabilization of the destruction complex or directly by an increase of β-catenin degradation. One way to stabilize the destruction complex is an increased polymerization of conductin/axin2[128]. *In vitro* it represses the growth of colorectal cancer cells[128]. An opportunity to strengthen the degradation of β-catenin is *via* the proteasome through binding of molecules, which induces proteolysis. Kessler *et al*[129] examined potential binding sites of β-catenin proteolysis targeting chimeras (PROTACs). The first PROTACs are tested in mice and showed, in APCmin/+ mice, prevention and regression of colorectal cancer[130]. The E3 Ligase, TRIM58 enhances β-catenin degradation in gastric cancer and is a potential therapeutic target[131]. A different approach would be oncolytic viruses. *In vitro* and in a mice model, the adenovirus CD55-Smad4 represses tumor proliferation in metastasis by, inter alia, suppression of Wnt signaling[132]. Adenoviruses that inhibit tumor growth by repressing the Wnt pathway have also been developed for other carcinomas such as hepatocellular carcinoma[133]. Another possible therapeutic approach in Wnt-activated tumors would be the inhibition of the ribosome biogenesis. Raveux *et al*[134] show that ribosome biogenesis dysfunction alleviates Wnt-driven tumor initiation and reduces cancer cell proliferation. In a study, kinase inhibitors in gastric cancer were screened for Wnt pathway inhibition and 34 kinases inhibit Wnt signaling more than 50%[135]. Potential targets to inhibit Wnt/β-catenin signaling are summarized in Table 2.

However, it must be noted that there could be a YAP/TAZ-dependent transcriptional reprogramming which leads to a lineage reversion and a Wnt-independent tumor growth, which can lead to failure of Wnt signaling inhibitors[136].

Development of therapeutic approaches by targeting Wnt signaling main players is challenging though it brings new hope for the management of colorectal cancer in the future.

**CONCLUSION**

The Wnt/β-catenin signaling pathway is a highly regulated pathway and essential for intestinal homeostasis. Disruption of this homeostasis with Wnt signaling hyperactivation can lead to tumor development and indeed Wnt activation is common in human colorectal cancer. The prognostic value of Wnt activation in colorectal cancer has not been fully elucidated yet. Furthermore, components of the Wnt signaling pathway have been brought into focus as possible targets in anti-cancer therapy and as possible adjuvant treatment for chemoresistant cancers.

**REFERENCES**

1 **Sharma RP**, Chopra VL. Effect of the Wingless (wg1) mutation on wing and haltere development in Drosophila melanogaster. *Dev Biol* 1976; **48**: 461-465 [PMID: 815114 DOI: 10.1016/0012-1606(76)90108-1]

2 **Nusse R**. Wnt signaling in disease and in development. *Cell Res* 2005; **15**: 28-32 [PMID: 15686623 DOI: 10.1038/sj.cr.7290260]

3 **Ng LF**, Kaur P, Bunnag N, Suresh J, Sung ICH, Tan QH, Gruber J, Tolwinski NS. WNT Signaling in Disease. *Cells* 2019; **8** [PMID: 31382613 DOI: 10.3390/cells8080826]

4 **Duchartre Y**, Kim YM, Kahn M. The Wnt signaling pathway in cancer. *Crit Rev Oncol Hematol* 2016; **99**: 141-149 [PMID: 26775730 DOI: 10.1016/j.critrevonc.2015.12.005]

5 **Parker TW**, Neufeld KL. APC controls Wnt-induced β-catenin destruction complex recruitment in human colonocytes. *Sci Rep* 2020; **10**: 2957 [PMID: 32076059 DOI: 10.1038/s41598-020-59899-z]

6 **Kimelman D**, Xu W. beta-catenin destruction complex: insights and questions from a structural perspective. *Oncogene* 2006; **25**: 7482-7491 [PMID: 17143292 DOI: 10.1038/sj.onc.1210055]

7 **MacDonald BT**, He X. Frizzled and LRP5/6 receptors for Wnt/β-catenin signaling. *Cold Spring Harb Perspect Biol* 2012; **4** [PMID: 23209147 DOI: 10.1101/cshperspect.a007880]

8 **Cruciat CM**. Casein kinase 1 and Wnt/β-catenin signaling. *Curr Opin Cell Biol* 2014; **31**: 46-55 [PMID: 25200911 DOI: 10.1016/j.ceb.2014.08.003]

9 **Klingensmith J**, Nusse R, Perrimon N. The Drosophila segment polarity gene dishevelled encodes a novel protein required for response to the wingless signal. *Genes Dev* 1994; **8**: 118-130 [PMID: 8288125 DOI: 10.1101/gad.8.1.118]

10 **Schaefer KN**, Pronobis MI, Williams CE, Zhang S, Bauer L, Goldfarb D, Yan F, Major MB, Peifer M. Wnt regulation: exploring Axin-Disheveled interactions and defining mechanisms by which the SCF E3 ubiquitin ligase is recruited to the destruction complex. *Mol Biol Cell* 2020; **31**: 992-1014 [PMID: 32129710 DOI: 10.1091/mbc.E19-11-0647]

11 **Cantù C**, Felker A, Zimmerli D, Prummel KD, Cabello EM, Chiavacci E, Méndez-Acevedo KM, Kirchgeorg L, Burger S, Ripoll J, Valenta T, Hausmann G, Vilain N, Aguet M, Burger A, Panáková D, Basler K, Mosimann C. Mutations in *Bcl9* and *Pygo* genes cause congenital heart defects by tissue-specific perturbation of Wnt/β-catenin signaling. *Genes Dev* 2018; **32**: 1443-1458 [PMID: 30366904 DOI: 10.1101/gad.315531.118]

12 **Rieger ME**, Zhou B, Solomon N, Sunohara M, Li C, Nguyen C, Liu Y, Pan JH, Minoo P, Crandall ED, Brody SL, Kahn M, Borok Z. p300/β-Catenin Interactions Regulate Adult Progenitor Cell Differentiation Downstream of WNT5a/Protein Kinase C (PKC). *J Biol Chem* 2016; **291**: 6569-6582 [PMID: 26833564 DOI: 10.1074/jbc.M115.706416]

13 **Doumpas N**, Lampart F, Robinson MD, Lentini A, Nestor CE, Cantù C, Basler K. TCF/LEF dependent and independent transcriptional regulation of Wnt/β-catenin target genes. *EMBO J* 2019; **38** [PMID: 30425074 DOI: 10.15252/embj.201798873]

14 **Bafico A**, Liu G, Yaniv A, Gazit A, Aaronson SA. Novel mechanism of Wnt signalling inhibition mediated by Dickkopf-1 interaction with LRP6/Arrow. *Nat Cell Biol* 2001; **3**: 683-686 [PMID: 11433302 DOI: 10.1038/35083081]

15 **Semënov MV**, Tamai K, Brott BK, Kühl M, Sokol S, He X. Head inducer Dickkopf-1 is a ligand for Wnt coreceptor LRP6. *Curr Biol* 2001; **11**: 951-961 [PMID: 11448771 DOI: 10.1016/s0960-9822(01)00290-1]

16 **Herbst A**, Jurinovic V, Krebs S, Thieme SE, Blum H, Göke B, Kolligs FT. Comprehensive analysis of β-catenin target genes in colorectal carcinoma cell lines with deregulated Wnt/β-catenin signaling. *BMC Genomics* 2014; **15**: 74 [PMID: 24467841 DOI: 10.1186/1471-2164-15-74]

17 **Alexandre C**, Baena-Lopez A, Vincent JP. Patterning and growth control by membrane-tethered Wingless. *Nature* 2014; **505**: 180-185 [PMID: 24390349 DOI: 10.1038/nature12879]

18 **Chin AM**, Tsai YH, Finkbeiner SR, Nagy MS, Walker EM, Ethen NJ, Williams BO, Battle MA, Spence JR. A Dynamic WNT/β-CATENIN Signaling Environment Leads to WNT-Independent and WNT-Dependent Proliferation of Embryonic Intestinal Progenitor Cells. *Stem Cell Reports* 2016; **7**: 826-839 [PMID: 27720905 DOI: 10.1016/j.stemcr.2016.09.004]

19 **O'Connell AE**, Zhou F, Shah MS, Murphy Q, Rickner H, Kelsen J, Boyle J, Doyle JJ, Gangwani B, Thiagarajah JR, Kamin DS, Goldsmith JD, Richmond C, Breault DT, Agrawal PB. Neonatal-Onset Chronic Diarrhea Caused by Homozygous Nonsense WNT2B Mutations. *Am J Hum Genet* 2018; **103**: 131-137 [PMID: 29909964 DOI: 10.1016/j.ajhg.2018.05.007]

20 **Zhang YJ**, Jimenez L, Azova S, Kremen J, Chan YM, Elhusseiny AM, Saeed H, Goldsmith J, Al-Ibraheemi A, O'Connell AE, Kovbasnjuk O, Rodan L, Agrawal PB, Thiagarajah JR. Novel variants in the stem cell niche factor WNT2B define the disease phenotype as a congenital enteropathy with ocular dysgenesis. *Eur J Hum Genet* 2021; **29**: 998-1007 [PMID: 33526876 DOI: 10.1038/s41431-021-00812-1]

21 **Kim TH**, Shivdasani RA. Stomach development, stem cells and disease. *Development* 2016; **143**: 554-565 [PMID: 26884394 DOI: 10.1242/dev.124891]

22 **McCracken KW**, Aihara E, Martin B, Crawford CM, Broda T, Treguier J, Zhang X, Shannon JM, Montrose MH, Wells JM. Wnt/β-catenin promotes gastric fundus specification in mice and humans. *Nature* 2017; **541**: 182-187 [PMID: 28052057 DOI: 10.1038/nature21021]

23 **Fischer AS**, Sigal M. The Role of Wnt and R-spondin in the Stomach During Health and Disease. *Biomedicines* 2019; **7** [PMID: 31248166 DOI: 10.3390/biomedicines7020044]

24 **Sayols S**, Klassek J, Werner C, Möckel S, Ritz S, Mendez-Lago M, Soshnikova N. Signalling codes for the maintenance and lineage commitment of embryonic gastric epithelial progenitors. *Development* 2020; **147** [PMID: 32878924 DOI: 10.1242/dev.188839]

25 **Kim JE**, Fei L, Yin WC, Coquenlorge S, Rao-Bhatia A, Zhang X, Shi SSW, Lee JH, Hahn NA, Rizvi W, Kim KH, Sung HK, Hui CC, Guo G, Kim TH. Single cell and genetic analyses reveal conserved populations and signaling mechanisms of gastrointestinal stromal niches. *Nat Commun* 2020; **11**: 334 [PMID: 31953387 DOI: 10.1038/s41467-019-14058-5]

26 **Kim BM**, Buchner G, Miletich I, Sharpe PT, Shivdasani RA. The stomach mesenchymal transcription factor Barx1 specifies gastric epithelial identity through inhibition of transient Wnt signaling. *Dev Cell* 2005; **8**: 611-622 [PMID: 15809042 DOI: 10.1016/j.devcel.2005.01.015]

27 **Li L**, Clevers H. Coexistence of quiescent and active adult stem cells in mammals. *Science* 2010; **327**: 542-545 [PMID: 20110496 DOI: 10.1126/science.1180794]

28 **Mah AT**, Yan KS, Kuo CJ. Wnt pathway regulation of intestinal stem cells. *J Physiol* 2016; **594**: 4837-4847 [PMID: 27581568 DOI: 10.1113/JP271754]

29 **Potten CS**, Booth C, Pritchard DM. The intestinal epithelial stem cell: the mucosal governor. *Int J Exp Pathol* 1997; **78**: 219-243 [PMID: 9505935 DOI: 10.1046/j.1365-2613.1997.280362.x]

30 **Tian H**, Biehs B, Warming S, Leong KG, Rangell L, Klein OD, de Sauvage FJ. A reserve stem cell population in small intestine renders Lgr5-positive cells dispensable. *Nature* 2011; **478**: 255-259 [PMID: 21927002 DOI: 10.1038/nature10408]

31 **Farin HF**, Van Es JH, Clevers H. Redundant sources of Wnt regulate intestinal stem cells and promote formation of Paneth cells. *Gastroenterology* 2012; **143**: 1518-1529.e7 [PMID: 22922422 DOI: 10.1053/j.gastro.2012.08.031]

32 **Bastide P**, Darido C, Pannequin J, Kist R, Robine S, Marty-Double C, Bibeau F, Scherer G, Joubert D, Hollande F, Blache P, Jay P. Sox9 regulates cell proliferation and is required for Paneth cell differentiation in the intestinal epithelium. *J Cell Biol* 2007; **178**: 635-648 [PMID: 17698607 DOI: 10.1083/jcb.200704152]

33 **Clevers HC**, Bevins CL. Paneth cells: maestros of the small intestinal crypts. *Annu Rev Physiol* 2013; **75**: 289-311 [PMID: 23398152 DOI: 10.1146/annurev-physiol-030212-183744]

34 **Umar S**. Intestinal stem cells. *Curr Gastroenterol Rep* 2010; **12**: 340-348 [PMID: 20683682 DOI: 10.1007/s11894-010-0130-3]

35 **Beumer J**, Clevers H. Cell fate specification and differentiation in the adult mammalian intestine. *Nat Rev Mol Cell Biol* 2021; **22**: 39-53 [PMID: 32958874 DOI: 10.1038/s41580-020-0278-0]

36 **Clevers H**. The intestinal crypt, a prototype stem cell compartment. *Cell* 2013; **154**: 274-284 [PMID: 23870119 DOI: 10.1016/j.cell.2013.07.004]

37 **Pinto D**, Gregorieff A, Begthel H, Clevers H. Canonical Wnt signals are essential for homeostasis of the intestinal epithelium. *Genes Dev* 2003; **17**: 1709-1713 [PMID: 12865297 DOI: 10.1101/gad.267103]

38 **Dudhwala ZM**, Hammond PD, Howarth GS, Cummins AG. Intestinal stem cells promote crypt fission during postnatal growth of the small intestine. *BMJ Open Gastroenterol* 2020; **7** [PMID: 32586946 DOI: 10.1136/bmjgast-2020-000388]

39 **van der Flier LG**, Clevers H. Stem cells, self-renewal, and differentiation in the intestinal epithelium. *Annu Rev Physiol* 2009; **71**: 241-260 [PMID: 18808327 DOI: 10.1146/annurev.physiol.010908.163145]

40 **Davies PS**, Dismuke AD, Powell AE, Carroll KH, Wong MH. Wnt-reporter expression pattern in the mouse intestine during homeostasis. *BMC Gastroenterol* 2008; **8**: 57 [PMID: 19055726 DOI: 10.1186/1471-230X-8-57]

41 **Humphries A**, Wright NA. Colonic crypt organization and tumorigenesis. *Nat Rev Cancer* 2008; **8**: 415-424 [PMID: 18480839 DOI: 10.1038/nrc2392]

42 **Adam RS**, van Neerven SM, Pleguezuelos-Manzano C, Simmini S, Léveillé N, de Groot NE, Holding AN, Markowetz F, Vermeulen L. Intestinal region-specific Wnt signalling profiles reveal interrelation between cell identity and oncogenic pathway activity in cancer development. *Cancer Cell Int* 2020; **20**: 578 [PMID: 33292279 DOI: 10.1186/s12935-020-01661-6]

43 **Garriock RJ**, Chalamalasetty RB, Zhu J, Kennedy MW, Kumar A, Mackem S, Yamaguchi TP. A dorsal-ventral gradient of Wnt3a/β-catenin signals controls mouse hindgut extension and colon formation. *Development* 2020; **147** [PMID: 32156757 DOI: 10.1242/dev.185108]

44 **Demitrack ES**, Samuelson LC. Notch regulation of gastrointestinal stem cells. *J Physiol* 2016; **594**: 4791-4803 [PMID: 26848053 DOI: 10.1113/JP271667]

45 **Carulli AJ**, Keeley TM, Demitrack ES, Chung J, Maillard I, Samuelson LC. Notch receptor regulation of intestinal stem cell homeostasis and crypt regeneration. *Dev Biol* 2015; **402**: 98-108 [PMID: 25835502 DOI: 10.1016/j.ydbio.2015.03.012]

46 **Hayward P**, Kalmar T, Arias AM. Wnt/Notch signalling and information processing during development. *Development* 2008; **135**: 411-424 [PMID: 18192283 DOI: 10.1242/dev.000505]

47 **Hurlbut GD**, Kankel MW, Lake RJ, Artavanis-Tsakonas S. Crossing paths with Notch in the hyper-network. *Curr Opin Cell Biol* 2007; **19**: 166-175 [PMID: 17317139 DOI: 10.1016/j.ceb.2007.02.012]

48 **Acosta H**, López SL, Revinski DR, Carrasco AE. Notch destabilises maternal beta-catenin and restricts dorsal-anterior development in Xenopus. *Development* 2011; **138**: 2567-2579 [PMID: 21610033 DOI: 10.1242/dev.061143]

49 **Kwon C**, Cheng P, King IN, Andersen P, Shenje L, Nigam V, Srivastava D. Notch post-translationally regulates β-catenin protein in stem and progenitor cells. *Nat Cell Biol* 2011; **13**: 1244-1251 [PMID: 21841793 DOI: 10.1038/ncb2313]

50 **Collu GM**, Hidalgo-Sastre A, Acar A, Bayston L, Gildea C, Leverentz MK, Mills CG, Owens TW, Meurette O, Dorey K, Brennan K. Dishevelled limits Notch signalling through inhibition of CSL. *Development* 2012; **139**: 4405-4415 [PMID: 23132247 DOI: 10.1242/dev.081885]

51 **Axelrod JD**, Matsuno K, Artavanis-Tsakonas S, Perrimon N. Interaction between Wingless and Notch signaling pathways mediated by dishevelled. *Science* 1996; **271**: 1826-1832 [PMID: 8596950 DOI: 10.1126/science.271.5257.1826]

52 **Mei X**, Gu M, Li M. Plasticity of Paneth cells and their ability to regulate intestinal stem cells. *Stem Cell Res Ther* 2020; **11**: 349 [PMID: 32787930 DOI: 10.1186/s13287-020-01857-7]

53 **Kaemmerer E**, Jeon MK, Berndt A, Liedtke C, Gassler N. Targeting Wnt Signaling *via* Notch in Intestinal Carcinogenesis. *Cancers (Basel)* 2019; **11** [PMID: 31003440 DOI: 10.3390/cancers11040555]

54 **Stringer EJ**, Duluc I, Saandi T, Davidson I, Bialecka M, Sato T, Barker N, Clevers H, Pritchard CA, Winton DJ, Wright NA, Freund JN, Deschamps J, Beck F. Cdx2 determines the fate of postnatal intestinal endoderm. *Development* 2012; **139**: 465-474 [PMID: 22190642 DOI: 10.1242/dev.070722]

55 **Boyd M**, Hansen M, Jensen TG, Perearnau A, Olsen AK, Bram LL, Bak M, Tommerup N, Olsen J, Troelsen JT. Genome-wide analysis of CDX2 binding in intestinal epithelial cells (Caco-2). *J Biol Chem* 2010; **285**: 25115-25125 [PMID: 20551321 DOI: 10.1074/jbc.M109.089516]

56 **Yu J**, Liu D, Sun X, Yang K, Yao J, Cheng C, Wang C, Zheng J. CDX2 inhibits the proliferation and tumor formation of colon cancer cells by suppressing Wnt/β-catenin signaling *via* transactivation of GSK-3β and Axin2 expression. *Cell Death Dis* 2019; **10**: 26 [PMID: 30631044 DOI: 10.1038/s41419-018-1263-9]

57 **Dalerba P**, Sahoo D, Paik S, Guo X, Yothers G, Song N, Wilcox-Fogel N, Forgó E, Rajendran PS, Miranda SP, Hisamori S, Hutchison J, Kalisky T, Qian D, Wolmark N, Fisher GA, van de Rijn M, Clarke MF. CDX2 as a Prognostic Biomarker in Stage II and Stage III Colon Cancer. *N Engl J Med* 2016; **374**: 211-222 [PMID: 26789870 DOI: 10.1056/NEJMoa1506597]

58 **McCarthy N**, Manieri E, Storm EE, Saadatpour A, Luoma AM, Kapoor VN, Madha S, Gaynor LT, Cox C, Keerthivasan S, Wucherpfennig K, Yuan GC, de Sauvage FJ, Turley SJ, Shivdasani RA. Distinct Mesenchymal Cell Populations Generate the Essential Intestinal BMP Signaling Gradient. *Cell Stem Cell* 2020; **26**: 391-402.e5 [PMID: 32084389 DOI: 10.1016/j.stem.2020.01.008]

59 **Kosinski C**, Li VS, Chan AS, Zhang J, Ho C, Tsui WY, Chan TL, Mifflin RC, Powell DW, Yuen ST, Leung SY, Chen X. Gene expression patterns of human colon tops and basal crypts and BMP antagonists as intestinal stem cell niche factors. *Proc Natl Acad Sci U S A* 2007; **104**: 15418-15423 [PMID: 17881565 DOI: 10.1073/pnas.0707210104]

60 **He XC**, Zhang J, Tong WG, Tawfik O, Ross J, Scoville DH, Tian Q, Zeng X, He X, Wiedemann LM, Mishina Y, Li L. BMP signaling inhibits intestinal stem cell self-renewal through suppression of Wnt-beta-catenin signaling. *Nat Genet* 2004; **36**: 1117-1121 [PMID: 15378062 DOI: 10.1038/ng1430]

61 **Qi Z**, Li Y, Zhao B, Xu C, Liu Y, Li H, Zhang B, Wang X, Yang X, Xie W, Li B, Han JJ, Chen YG. BMP restricts stemness of intestinal Lgr5+ stem cells by directly suppressing their signature genes. *Nat Commun* 2017; **8**: 13824 [PMID: 28059064 DOI: 10.1038/ncomms13824]

62 **Hong AW**, Meng Z, Guan KL. The Hippo pathway in intestinal regeneration and disease. *Nat Rev Gastroenterol Hepatol* 2016; **13**: 324-337 [PMID: 27147489 DOI: 10.1038/nrgastro.2016.59]

63 **Li N**, Lu N, Xie C. The Hippo and Wnt signalling pathways: crosstalk during neoplastic progression in gastrointestinal tissue. *FEBS J* 2019; **286**: 3745-3756 [PMID: 31342636 DOI: 10.1111/febs.15017]

64 **Kriz V**, Korinek V. Wnt, RSPO and Hippo Signalling in the Intestine and Intestinal Stem Cells. *Genes (Basel)* 2018; **9** [PMID: 29316729 DOI: 10.3390/genes9010020]

65 **Ward D**, Montes Olivas S, Fletcher A, Homer M, Marucci L. Cross-talk between Hippo and Wnt signalling pathways in intestinal crypts: Insights from an agent-based model. *Comput Struct Biotechnol J* 2020; **18**: 230-240 [PMID: 33489001 DOI: 10.1016/j.csbj.2019.12.015]

66 **Mihaylova MM**, Cheng CW, Cao AQ, Tripathi S, Mana MD, Bauer-Rowe KE, Abu-Remaileh M, Clavain L, Erdemir A, Lewis CA, Freinkman E, Dickey AS, La Spada AR, Huang Y, Bell GW, Deshpande V, Carmeliet P, Katajisto P, Sabatini DM, Yilmaz ÖH. Fasting Activates Fatty Acid Oxidation to Enhance Intestinal Stem Cell Function during Homeostasis and Aging. *Cell Stem Cell* 2018; **22**: 769-778.e4 [PMID: 29727683 DOI: 10.1016/j.stem.2018.04.001]

67 **Chen L**, Vasoya RP, Toke NH, Parthasarathy A, Luo S, Chiles E, Flores J, Gao N, Bonder EM, Su X, Verzi MP. HNF4 Regulates Fatty Acid Oxidation and Is Required for Renewal of Intestinal Stem Cells in Mice. *Gastroenterology* 2020; **158**: 985-999.e9 [PMID: 31759926 DOI: 10.1053/j.gastro.2019.11.031]

68 **Yao HS**, Wang J, Zhang XP, Wang LZ, Wang Y, Li XX, Jin KZ, Hu ZQ, Wang WJ. Hepatocyte nuclear factor 4α suppresses the aggravation of colon carcinoma. *Mol Carcinog* 2016; **55**: 458-472 [PMID: 25808746 DOI: 10.1002/mc.22294]

69 **Wu N**, Zhang YL, Wang HT, Li DW, Dai HJ, Zhang QQ, Zhang J, Ma Y, Xia Q, Bian JM, Hang HL. Overexpression of hepatocyte nuclear factor 4α in human mesenchymal stem cells suppresses hepatocellular carcinoma development through Wnt/β-catenin signaling pathway downregulation. *Cancer Biol Ther* 2016; **17**: 558-565 [PMID: 27124543 DOI: 10.1080/15384047.2016.1177675]

70 **Kaemmerer E**, Gassler N. Wnt Lipidation and Modifiers in Intestinal Carcinogenesis and Cancer. *Cancers (Basel)* 2016; **8** [PMID: 27438855 DOI: 10.3390/cancers8070069]

71 **Takada R**, Satomi Y, Kurata T, Ueno N, Norioka S, Kondoh H, Takao T, Takada S. Monounsaturated fatty acid modification of Wnt protein: its role in Wnt secretion. *Dev Cell* 2006; **11**: 791-801 [PMID: 17141155 DOI: 10.1016/j.devcel.2006.10.003]

72 **Kurayoshi M**, Yamamoto H, Izumi S, Kikuchi A. Post-translational palmitoylation and glycosylation of Wnt-5a are necessary for its signalling. *Biochem J* 2007; **402**: 515-523 [PMID: 17117926 DOI: 10.1042/BJ20061476]

73 **Klaus C**, Schneider U, Hedberg C, Schütz AK, Bernhagen J, Waldmann H, Gassler N, Kaemmerer E. Modulating effects of acyl-CoA synthetase 5-derived mitochondrial Wnt2B palmitoylation on intestinal Wnt activity. *World J Gastroenterol* 2014; **20**: 14855-14864 [PMID: 25356045 DOI: 10.3748/wjg.v20.i40.14855]

74 **Tsukiyama T**, Zou J, Kim J, Ogamino S, Shino Y, Masuda T, Merenda A, Matsumoto M, Fujioka Y, Hirose T, Terai S, Takahashi H, Ishitani T, Nakayama KI, Ohba Y, Koo BK, Hatakeyama S. A phospho-switch controls RNF43-mediated degradation of Wnt receptors to suppress tumorigenesis. *Nat Commun* 2020; **11**: 4586 [PMID: 32934222 DOI: 10.1038/s41467-020-18257-3]

75 **Park S**, Wu L, Tu J, Yu W, Toh Y, Carmon KS, Liu QJ. Unlike LGR4, LGR5 potentiates Wnt-β-catenin signaling without sequestering E3 Ligases. *Sci Signal* 2020; **13** [PMID: 33262293 DOI: 10.1126/scisignal.aaz4051]

76 **Park HB**, Kim JW, Baek KH. Regulation of Wnt Signaling through Ubiquitination and Deubiquitination in Cancers. *Int J Mol Sci* 2020; **21** [PMID: 32486158 DOI: 10.3390/ijms21113904]

77 **Zarkou V**, Galaras A, Giakountis A, Hatzis P. Crosstalk mechanisms between the WNT signaling pathway and long non-coding RNAs. *Noncoding RNA Res* 2018; **3**: 42-53 [PMID: 30159439 DOI: 10.1016/j.ncrna.2018.04.001]

78 **Rahmani F**, Avan A, Hashemy SI, Hassanian SM. Role of Wnt/β-catenin signaling regulatory microRNAs in the pathogenesis of colorectal cancer. *J Cell Physiol* 2018; **233**: 811-817 [PMID: 28266708 DOI: 10.1002/jcp.25897]

79 **Kim KH**, Lee SJ, Kim J, Moon Y. Dynamic Malignant Wave of Ribosome-Insulted Gut Niche *via* the Wnt-CTGF/CCN2 Circuit. *iScience* 2020; **23**: 101076 [PMID: 32361596 DOI: 10.1016/j.isci.2020.101076]

80 **Wei G**, Gao N, Chen J, Fan L, Zeng Z, Gao G, Li L, Fang G, Hu K, Pang X, Fan HY, Clevers H, Liu M, Zhang X, Li D. Erk and MAPK signaling is essential for intestinal development through Wnt pathway modulation. *Development* 2020; **147** [PMID: 32747435 DOI: 10.1242/dev.185678]

81 **Horst D**, Chen J, Morikawa T, Ogino S, Kirchner T, Shivdasani RA. Differential WNT activity in colorectal cancer confers limited tumorigenic potential and is regulated by MAPK signaling. *Cancer Res* 2012; **72**: 1547-1556 [PMID: 22318865 DOI: 10.1158/0008-5472.CAN-11-3222]

82 **Cheruku HR,** Mohamedali A, Cantor DI, Tan SH, Nice EC, Baker MS. Transforming growth factor-β, MAPK and Wnt signaling interactions in colorectal cancer. *EuPA Open Proteomics* 2015; **8**: 104-115 [DOI: 10.1016/j.euprot.2015.06.004]

83 **Hu T**, Li C. Convergence between Wnt-β-catenin and EGFR signaling in cancer. *Mol Cancer* 2010; **9**: 236 [PMID: 20828404 DOI: 10.1186/1476-4598-9-236]

84 **Wang C**, Zhao R, Huang P, Yang F, Quan Z, Xu N, Xi R. APC loss-induced intestinal tumorigenesis in Drosophila: Roles of Ras in Wnt signaling activation and tumor progression. *Dev Biol* 2013; **378**: 122-140 [PMID: 23570874 DOI: 10.1016/j.ydbio.2013.03.020]

85 **Half E**, Bercovich D, Rozen P. Familial adenomatous polyposis. *Orphanet J Rare Dis* 2009; **4**: 22 [PMID: 19822006 DOI: 10.1186/1750-1172-4-22]

86 **Cordero JB**, Sansom OJ. Wnt signalling and its role in stem cell-driven intestinal regeneration and hyperplasia. *Acta Physiol (Oxf)* 2012; **204**: 137-143 [PMID: 21439026 DOI: 10.1111/j.1748-1716.2011.02288.x]

87 **Ahmed I**, Chandrakesan P, Tawfik O, Xia L, Anant S, Umar S. Critical roles of Notch and Wnt/β-catenin pathways in the regulation of hyperplasia and/or colitis in response to bacterial infection. *Infect Immun* 2012; **80**: 3107-3121 [PMID: 22710872 DOI: 10.1128/IAI.00236-12]

88 **Moparthi L**, Koch S. Wnt signaling in intestinal inflammation. *Differentiation* 2019; **108**: 24-32 [PMID: 30718056 DOI: 10.1016/j.diff.2019.01.002]

89 **Mark-Christensen A**, Laurberg S, Haboubi N. Dysplasia in Inflammatory Bowel Disease: Historical Review, Critical Histopathological Analysis, and Clinical Implications. *Inflamm Bowel Dis* 2018; **24**: 1895-1903 [PMID: 29668897 DOI: 10.1093/ibd/izy075]

90 **Aust DE**, Terdiman JP, Willenbucher RF, Chew K, Ferrell L, Florendo C, Molinaro-Clark A, Baretton GB, Löhrs U, Waldman FM. Altered distribution of beta-catenin, and its binding proteins E-cadherin and APC, in ulcerative colitis-related colorectal cancers. *Mod Pathol* 2001; **14**: 29-39 [PMID: 11211307 DOI: 10.1038/modpathol.3880253]

91 **Fearon ER**, Vogelstein B. A genetic model for colorectal tumorigenesis. *Cell* 1990; **61**: 759-767 [PMID: 2188735 DOI: 10.1016/0092-8674(90)90186-i]

92 **Bosman F**, Yan P. Molecular pathology of colorectal cancer. *Pol J Pathol* 2014; **65**: 257-266 [PMID: 25693079 DOI: 10.5114/pjp.2014.48094]

93 **Li J**, Mizukami Y, Zhang X, Jo WS, Chung DC. Oncogenic K-ras stimulates Wnt signaling in colon cancer through inhibition of GSK-3beta. *Gastroenterology* 2005; **128**: 1907-1918 [PMID: 15940626 DOI: 10.1053/j.gastro.2005.02.067]

94 **Wong CC**, Xu J, Bian X, Wu JL, Kang W, Qian Y, Li W, Chen H, Gou H, Liu D, Yat Luk ST, Zhou Q, Ji F, Chan LS, Shirasawa S, Sung JJ, Yu J. In Colorectal Cancer Cells With Mutant KRAS, SLC25A22-Mediated Glutaminolysis Reduces DNA Demethylation to Increase WNT Signaling, Stemness, and Drug Resistance. *Gastroenterology* 2020; **159**: 2163-2180.e6 [PMID: 32814111 DOI: 10.1053/j.gastro.2020.08.016]

95 **Schrock AB**, Devoe CE, McWilliams R, Sun J, Aparicio T, Stephens PJ, Ross JS, Wilson R, Miller VA, Ali SM, Overman MJ. Genomic Profiling of Small-Bowel Adenocarcinoma. *JAMA Oncol* 2017; **3**: 1546-1553 [PMID: 28617917 DOI: 10.1001/jamaoncol.2017.1051]

96 **Lu W**, Ni Z, Tong M, Jiang S, Zhang J, Feng C, Han C, Yuan T, Wang N, Zhao J, Sun N, Liu C, Jia Q, Wu Q, Ning H, Shi Y. DKK1 is epigenetically downregulated by promoter methylation and inhibits bile acid-induced gastric intestinal metaplasia. *Biochem Biophys Res Commun* 2020; **523**: 780-786 [PMID: 31952791 DOI: 10.1016/j.bbrc.2019.12.109]

97 **Guan E**, Tian F, Liu Z. A novel risk score model for stomach adenocarcinoma based on the expression levels of 10 genes. *Oncol Lett* 2020; **19**: 1351-1367 [PMID: 31966067 DOI: 10.3892/ol.2019.11190]

98 **De Benedetti L**, Sciallero S, Gismondi V, James R, Bafico A, Biticchi R, Masetti E, Bonelli L, Heouaine A, Picasso M. Association of APC gene mutations and histological characteristics of colorectal adenomas. *Cancer Res* 1994; **54**: 3553-3556 [PMID: 8012980]

99 **Joo M**, Shahsafaei A, Odze RD. Paneth cell differentiation in colonic epithelial neoplasms: evidence for the role of the Apc/beta-catenin/Tcf pathway. *Hum Pathol* 2009; **40**: 872-880 [PMID: 19269007 DOI: 10.1016/j.humpath.2008.12.003]

100 **Bosman FT**, Carneiro F, Hruban RH, Theise ND. WHO classification of tumours of the digestive system. *WHO Classification of Tumours* 2010; **3**

101 **Wang ZK**, Liu J, Liu C, Wang FY, Chen CY, Zhang XH. Hypermethylation of adenomatous polyposis coli gene promoter is associated with novel Wnt signaling pathway in gastric adenomas. *J Gastroenterol Hepatol* 2012; **27**: 1629-1634 [PMID: 22741528 DOI: 10.1111/j.1440-1746.2012.07219.x]

102 **Wang Z**, Ye Y, Liu D, Yang X, Wang F. Hypermethylation of multiple Wnt antagonist genes in gastric neoplasia: Is H pylori infection blasting fuse? *Medicine (Baltimore)* 2018; **97**: e13734 [PMID: 30593147 DOI: 10.1097/MD.0000000000013734]

103 **Koushyar S**, Powell AG, Vincan E, Phesse TJ. Targeting Wnt Signaling for the Treatment of Gastric Cancer. *Int J Mol Sci* 2020; **21** [PMID: 32486243 DOI: 10.3390/ijms21113927]

104 **Togasaki K**, Sugimoto S, Ohta Y, Nanki K, Matano M, Takahashi S, Fujii M, Kanai T, Sato T. Wnt Signaling Shapes the Histologic Variation in Diffuse Gastric Cancer. *Gastroenterology* 2021; **160**: 823-830 [PMID: 33217450 DOI: 10.1053/j.gastro.2020.10.047]

105 **Tan SH**, Swathi Y, Tan S, Goh J, Seishima R, Murakami K, Oshima M, Tsuji T, Phuah P, Tan LT, Wong E, Fatehullah A, Sheng T, Ho SWT, Grabsch HI, Srivastava S, Teh M, Denil SLIJ, Mustafah S, Tan P, Shabbir A, So J, Yeoh KG, Barker N. AQP5 enriches for stem cells and cancer origins in the distal stomach. *Nature* 2020; **578**: 437-443 [PMID: 32025032 DOI: 10.1038/s41586-020-1973-x]

106 **Chiurillo MA**. Role of the Wnt/β-catenin pathway in gastric cancer: An in-depth literature review. *World J Exp Med* 2015; **5**: 84-102 [PMID: 25992323 DOI: 10.5493/wjem.v5.i2.84]

107 **Mao J**, Fan S, Ma W, Fan P, Wang B, Zhang J, Wang H, Tang B, Zhang Q, Yu X, Wang L, Song B, Li L. Roles of Wnt/β-catenin signaling in the gastric cancer stem cells proliferation and salinomycin treatment. *Cell Death Dis* 2014; **5**: e1039 [PMID: 24481453 DOI: 10.1038/cddis.2013.515]

108 **Yu Z**, Jiang X, Qin L, Deng H, Wang J, Ren W, Li H, Zhao L, Liu H, Yan H, Shi W, Wang Q, Luo C, Long B, Zhou H, Sun H, Jiao Z. A novel UBE2T inhibitor suppresses Wnt/β-catenin signaling hyperactivation and gastric cancer progression by blocking RACK1 ubiquitination. *Oncogene* 2021; **40**: 1027-1042 [PMID: 33323973 DOI: 10.1038/s41388-020-01572-w]

109 **Chen Q**, Suzuki K, Sifuentes-Dominguez L, Miyata N, Song J, Lopez A, Starokadomskyy P, Gopal P, Dozmorov I, Tan S, Ge B, Burstein E. Paneth cell-derived growth factors support tumorigenesis in the small intestine. *Life Sci Alliance* 2021; **4** [PMID: 33372038 DOI: 10.26508/Lsa.202000934]

110 **Jorissen RN**, Christie M, Mouradov D, Sakthianandeswaren A, Li S, Love C, Xu ZZ, Molloy PL, Jones IT, McLaughlin S, Ward RL, Hawkins NJ, Ruszkiewicz AR, Moore J, Burgess AW, Busam D, Zhao Q, Strausberg RL, Lipton L, Desai J, Gibbs P, Sieber OM. Wild-type APC predicts poor prognosis in microsatellite-stable proximal colon cancer. *Br J Cancer* 2015; **113**: 979-988 [PMID: 26305864 DOI: 10.1038/bjc.2015.296]

111 **Yue B**, Liu C, Sun H, Liu M, Song C, Cui R, Qiu S, Zhong M. A Positive Feed-Forward Loop between LncRNA-CYTOR and Wnt/β-Catenin Signaling Promotes Metastasis of Colon Cancer. *Mol Ther* 2018; **26**: 1287-1298 [PMID: 29606502 DOI: 10.1016/j.ymthe.2018.02.024]

112 **Ormanns S**, Neumann J, Horst D, Kirchner T, Jung A. WNT signaling and distant metastasis in colon cancer through transcriptional activity of nuclear β-Catenin depend on active PI3K signaling. *Oncotarget* 2014; **5**: 2999-3011 [PMID: 24930890 DOI: 10.18632/oncotarget.1626]

113 **Reinacher-Schick A**, Seidensticker F, Petrasch S, Reiser M, Philippou S, Theegarten D, Freitag G, Schmiegel W. Mesalazine changes apoptosis and proliferation in normal mucosa of patients with sporadic polyps of the large bowel. *Endoscopy* 2000; **32**: 245-254 [PMID: 10718391 DOI: 10.1055/s-2000-135]

114 **Velayos FS**, Loftus EV Jr, Jess T, Harmsen WS, Bida J, Zinsmeister AR, Tremaine WJ, Sandborn WJ. Predictive and protective factors associated with colorectal cancer in ulcerative colitis: A case-control study. *Gastroenterology* 2006; **130**: 1941-1949 [PMID: 16762617 DOI: 10.1053/j.gastro.2006.03.028]

115 **Velayos FS**, Terdiman JP, Walsh JM. Effect of 5-aminosalicylate use on colorectal cancer and dysplasia risk: a systematic review and metaanalysis of observational studies. *Am J Gastroenterol* 2005; **100**: 1345-1353 [PMID: 15929768 DOI: 10.1111/j.1572-0241.2005.41442.x]

116 **Magro F**, Gionchetti P, Eliakim R, Ardizzone S, Armuzzi A, Barreiro-de Acosta M, Burisch J, Gecse KB, Hart AL, Hindryckx P, Langner C, Limdi JK, Pellino G, Zagórowicz E, Raine T, Harbord M, Rieder F; European Crohn’s and Colitis Organisation [ECCO]. Third European Evidence-based Consensus on Diagnosis and Management of Ulcerative Colitis. Part 1: Definitions, Diagnosis, Extra-intestinal Manifestations, Pregnancy, Cancer Surveillance, Surgery, and Ileo-anal Pouch Disorders. *J Crohns Colitis* 2017; **11**: 649-670 [PMID: 28158501 DOI: 10.1093/ecco-jcc/jjx008]

117 **Bos CL**, Diks SH, Hardwick JC, Walburg KV, Peppelenbosch MP, Richel DJ. Protein phosphatase 2A is required for mesalazine-dependent inhibition of Wnt/beta-catenin pathway activity. *Carcinogenesis* 2006; **27**: 2371-2382 [PMID: 16728434 DOI: 10.1093/carcin/bgl071]

118 **Munding J**, Ziebarth W, Pox CP, Ladigan S, Reiser M, Hüppe D, Brand L, Schmiegel W, Tannapfel A, Reinacher-Schick AC. The influence of 5-aminosalicylic acid on the progression of colorectal adenomas *via* the β-catenin signaling pathway. *Carcinogenesis* 2012; **33**: 637-643 [PMID: 22198215 DOI: 10.1093/carcin/bgr306]

119 **Day DW**, Morson BC. The adenoma-carcinoma sequence. *Major Probl Pathol* 1978; **10**: 58-71 [PMID: 359943]

120 **Serafino A**, Moroni N, Zonfrillo M, Andreola F, Mercuri L, Nicotera G, Nunziata J, Ricci R, Antinori A, Rasi G, Pierimarchi P. WNT-pathway components as predictive markers useful for diagnosis, prevention and therapy in inflammatory bowel disease and sporadic colorectal cancer. *Oncotarget* 2014; **5**: 978-992 [PMID: 24657851 DOI: 10.18632/oncotarget.1571]

121 **Zhu GX**, Gao D, Shao ZZ, Chen L, Ding WJ, Yu QF. Wnt/β‑catenin signaling: Causes and treatment targets of drug resistance in colorectal cancer (Review). *Mol Med Rep* 2021; **23** [PMID: 33300082 DOI: 10.3892/mmr.2020.11744]

122 **Hu YB**, Yan C, Mu L, Mi YL, Zhao H, Hu H, Li XL, Tao DD, Wu YQ, Gong JP, Qin JC. Exosomal Wnt-induced dedifferentiation of colorectal cancer cells contributes to chemotherapy resistance. *Oncogene* 2019; **38**: 1951-1965 [PMID: 30390075 DOI: 10.1038/s41388-018-0557-9]

123 **Zhang ZM**, Wu JF, Luo QC, Liu QF, Wu QW, Ye GD, She HQ, Li BA. Pygo2 activates MDR1 expression and mediates chemoresistance in breast cancer *via* the Wnt/β-catenin pathway. *Oncogene* 2016; **35**: 4787-4797 [PMID: 26876203 DOI: 10.1038/onc.2016.10]

124 **Cao F**, Yin LX. miR-122 enhances sensitivity of hepatocellular carcinoma to oxaliplatin *via* inhibiting MDR1 by targeting Wnt/β-catenin pathway. *Exp Mol Pathol* 2019; **106**: 34-43 [PMID: 30539797 DOI: 10.1016/j.yexmp.2018.10.009]

125 **Zhong Z**, Virshup DM. Wnt Signaling and Drug Resistance in Cancer. *Mol Pharmacol* 2020; **97**: 72-89 [PMID: 31787618 DOI: 10.1124/mol.119.117978]

126 **Caspi M**, Wittenstein A, Kazelnik M, Shor-Nareznoy Y, Rosin-Arbesfeld R. Therapeutic targeting of the oncogenic Wnt signaling pathway for treating colorectal cancer and other colonic disorders. *Adv Drug Deliv Rev* 2021; **169**: 118-136 [PMID: 33346022 DOI: 10.1016/j.addr.2020.12.010]

127 **Kleeman SO**, Koelzer VH, Jones HJ, Vazquez EG, Davis H, East JE, Arnold R, Koppens MA, Blake A, Domingo E, Cunningham C, Beggs AD, Pestinger V, Loughrey MB, Wang LM, Lannagan TR, Woods SL, Worthley D, Consortium SC, Tomlinson I, Dunne PD, Maughan T, Leedham SJ. Exploiting differential Wnt target gene expression to generate a molecular biomarker for colorectal cancer stratification. *Gut* 2020; **69**: 1092-1103 [PMID: 31563876 DOI: 10.1136/gutjnl-2019-319126]

128 **Bernkopf DB**, Brückner M, Hadjihannas MV, Behrens J. An aggregon in conductin/axin2 regulates Wnt/β-catenin signaling and holds potential for cancer therapy. *Nat Commun* 2019; **10**: 4251 [PMID: 31534175 DOI: 10.1038/s41467-019-12203-8]

129 **Kessler D**, Mayer M, Zahn SK, Zeeb M, Wöhrle S, Bergner A, Bruchhaus J, Ciftci T, Dahmann G, Dettling M, Döbel S, Fuchs JE, Geist L, Hela W, Kofink C, Kousek R, Moser F, Puchner T, Rumpel K, Scharnweber M, Werni P, Wolkerstorfer B, Breitsprecher D, Baaske P, Pearson M, McConnell DB, Böttcher J. Getting a Grip on the Undrugged: Targeting β-Catenin with Fragment-Based Methods. *ChemMedChem* 2021; **16**: 1420-1424 [PMID: 33275320 DOI: 10.1002/cmdc.202000839]

130 **Liao H**, Li X, Zhao L, Wang Y, Wang X, Wu Y, Zhou X, Fu W, Liu L, Hu HG, Chen YG. A PROTAC peptide induces durable β-catenin degradation and suppresses Wnt-dependent intestinal cancer. *Cell Discov* 2020; **6**: 35 [PMID: 32550000 DOI: 10.1038/s41421-020-0171-1]

131 **Liu X**, Long Z, Cai H, Yu S, Wu J. TRIM58 suppresses the tumor growth in gastric cancer by inactivation of β-catenin signaling *via* ubiquitination. *Cancer Biol Ther* 2020; **21**: 203-212 [PMID: 31747856 DOI: 10.1080/15384047.2019.1679554]

132 **Xiao B**, Zhang L, Liu H, Fang H, Wang C, Huang B, Liu X, Zhou X, Wang Y. Oncolytic Adenovirus CD55-Smad4 Suppresses Cell Proliferation, Metastasis, and Tumor Stemness in Colorectal Cancer by Regulating Wnt/β-Catenin Signaling Pathway. *Biomedicines* 2020; **8** [PMID: 33322272 DOI: 10.3390/biomedicines8120593]

133 **Zhang J**, Lai W, Li Q, Yu Y, Jin J, Guo W, Zhou X, Liu X, Wang Y. A novel oncolytic adenovirus targeting Wnt signaling effectively inhibits cancer-stem like cell growth *via* metastasis, apoptosis and autophagy in HCC models. *Biochem Biophys Res Commun* 2017; **491**: 469-477 [PMID: 28698142 DOI: 10.1016/j.bbrc.2017.07.041]

134 **Raveux A**, Stedman A, Coqueran S, Vandormael-Pournin S, Owens N, Romagnolo B, Cohen-Tannoudji M. Compensation between Wnt-driven tumorigenesis and cellular responses to ribosome biogenesis inhibition in the murine intestinal epithelium. *Cell Death Differ* 2020; **27**: 2872-2887 [PMID: 32355182 DOI: 10.1038/s41418-020-0548-6]

135 **Bhaskar Rao D**, Devanandan HJ, Ganesan K. Identification of kinases and kinase inhibitors for the differential targeting of Wnt/β-catenin signaling in gastric cancer subtypes. *Drug Dev Res* 2021; **82**: 1182-1192 [PMID: 34002415 DOI: 10.1002/ddr.21833]

136 **Han T**, Goswami S, Hu Y, Tang F, Zafra MP, Murphy C, Cao Z, Poirier JT, Khurana E, Elemento O, Hechtman JF, Ganesh K, Yaeger R, Dow LE. Lineage Reversion Drives WNT Independence in Intestinal Cancer. *Cancer Discov* 2020; **10**: 1590-1609 [PMID: 32546576 DOI: 10.1158/2159-8290.CD-19-1536]

137 **Shi F**, Cheng YF, Wang XL, Edge AS. Beta-catenin up-regulates Atoh1 expression in neural progenitor cells by interaction with an Atoh1 3' enhancer. *J Biol Chem* 2010; **285**: 392-400 [PMID: 19864427 DOI: 10.1074/jbc.M109.059055]

138 **Castillo-Azofeifa D**, Fazio EN, Nattiv R, Good HJ, Wald T, Pest MA, de Sauvage FJ, Klein OD, Asfaha S. Atoh1+ secretory progenitors possess renewal capacity independent of Lgr5+ cells during colonic regeneration. *EMBO J* 2019; **38** [PMID: 30635334 DOI: 10.15252/embj.201899984]

139 **Jho EH**, Zhang T, Domon C, Joo CK, Freund JN, Costantini F. Wnt/beta-catenin/Tcf signaling induces the transcription of Axin2, a negative regulator of the signaling pathway. *Mol Cell Biol* 2002; **22**: 1172-1183 [PMID: 11809808 DOI: 10.1128/MCB.22.4.1172-1183.2002]

140 **Lapham A**, Adams JE, Paterson A, Lee M, Brimmell M, Packham G. The Bcl-w promoter is activated by beta-catenin/TCF4 in human colorectal carcinoma cells. *Gene* 2009; **432**: 112-117 [PMID: 19124064 DOI: 10.1016/j.gene.2008.12.002]

141 **Kim PJ**, Plescia J, Clevers H, Fearon ER, Altieri DC. Survivin and molecular pathogenesis of colorectal cancer. *Lancet* 2003; **362**: 205-209 [PMID: 12885482 DOI: 10.1016/S0140-6736(03)13910-4]

142 **Kim JS**, Crooks H, Dracheva T, Nishanian TG, Singh B, Jen J, Waldman T. Oncogenic beta-catenin is required for bone morphogenetic protein 4 expression in human cancer cells. *Cancer Res* 2002; **62**: 2744-2748 [PMID: 12019147]

143 **Tetsu O**, McCormick F. Beta-catenin regulates expression of cyclin D1 in colon carcinoma cells. *Nature* 1999; **398**: 422-426 [PMID: 10201372 DOI: 10.1038/18884]

144 **Wassermann S**, Scheel SK, Hiendlmeyer E, Palmqvist R, Horst D, Hlubek F, Haynl A, Kriegl L, Reu S, Merkel S, Brabletz T, Kirchner T, Jung A. p16INK4a is a beta-catenin target gene and indicates low survival in human colorectal tumors. *Gastroenterology* 2009; **136**: 196-205.e2 [PMID: 18951899 DOI: 10.1053/j.gastro.2008.09.019]

145 **Lickert H**, Domon C, Huls G, Wehrle C, Duluc I, Clevers H, Meyer BI, Freund JN, Kemler R. Wnt/(beta)-catenin signaling regulates the expression of the homeobox gene Cdx1 in embryonic intestine. *Development* 2000; **127**: 3805-3813 [PMID: 10934025]

146 **Zhao T**, Gan Q, Stokes A, Lassiter RN, Wang Y, Chan J, Han JX, Pleasure DE, Epstein JA, Zhou CJ. β-catenin regulates Pax3 and Cdx2 for caudal neural tube closure and elongation. *Development* 2014; **141**: 148-157 [PMID: 24284205 DOI: 10.1242/dev.101550]

147 **Niida A**, Hiroko T, Kasai M, Furukawa Y, Nakamura Y, Suzuki Y, Sugano S, Akiyama T. DKK1, a negative regulator of Wnt signaling, is a target of the beta-catenin/TCF pathway. *Oncogene* 2004; **23**: 8520-8526 [PMID: 15378020 DOI: 10.1038/sj.onc.1207892]

148 **Pendás-Franco N**, García JM, Peña C, Valle N, Pálmer HG, Heinäniemi M, Carlberg C, Jiménez B, Bonilla F, Muñoz A, González-Sancho JM. DICKKOPF-4 is induced by TCF/beta-catenin and upregulated in human colon cancer, promotes tumour cell invasion and angiogenesis and is repressed by 1alpha,25-dihydroxyvitamin D3. *Oncogene* 2008; **27**: 4467-4477 [PMID: 18408752 DOI: 10.1038/onc.2008.88]

149 **Batlle E**, Henderson JT, Beghtel H, van den Born MM, Sancho E, Huls G, Meeldijk J, Robertson J, van de Wetering M, Pawson T, Clevers H. Beta-catenin and TCF mediate cell positioning in the intestinal epithelium by controlling the expression of EphB/ephrinB. *Cell* 2002; **111**: 251-263 [PMID: 12408869 DOI: 10.1016/s0092-8674(02)01015-2]

150 **Beisner J**, Teltschik Z, Ostaff MJ, Tiemessen MM, Staal FJ, Wang G, Gersemann M, Perminow G, Vatn MH, Schwab M, Stange EF, Wehkamp J. TCF-1-mediated Wnt signaling regulates Paneth cell innate immune defense effectors HD-5 and -6: implications for Crohn's disease. *Am J Physiol Gastrointest Liver Physiol* 2014; **307**: G487-G498 [PMID: 24994854 DOI: 10.1152/ajpgi.00347.2013]

151 **Li Y**, Bavarva JH, Wang Z, Guo J, Qian C, Thibodeau SN, Golemis EA, Liu W. HEF1, a novel target of Wnt signaling, promotes colonic cell migration and cancer progression. *Oncogene* 2011; **30**: 2633-2643 [PMID: 21317929 DOI: 10.1038/onc.2010.632]

152 **Kay SK**, Harrington HA, Shepherd S, Brennan K, Dale T, Osborne JM, Gavaghan DJ, Byrne HM. The role of the Hes1 crosstalk hub in Notch-Wnt interactions of the intestinal crypt. *PLoS Comput Biol* 2017; **13**: e1005400 [PMID: 28245235 DOI: 10.1371/journal.pcbi.1005400]

153 **Rodilla V**, Villanueva A, Obrador-Hevia A, Robert-Moreno A, Fernández-Majada V, Grilli A, López-Bigas N, Bellora N, Albà MM, Torres F, Duñach M, Sanjuan X, Gonzalez S, Gridley T, Capella G, Bigas A, Espinosa L. Jagged1 is the pathological link between Wnt and Notch pathways in colorectal cancer. *Proc Natl Acad Sci U S A* 2009; **106**: 6315-6320 [PMID: 19325125 DOI: 10.1073/pnas.0813221106]

154 **Mann B**, Gelos M, Siedow A, Hanski ML, Gratchev A, Ilyas M, Bodmer WF, Moyer MP, Riecken EO, Buhr HJ, Hanski C. Target genes of beta-catenin-T cell-factor/Lymphoid-enhancer-factor signaling in human colorectal carcinomas. *Proc Natl Acad Sci U S A* 1999; **96**: 1603-1608 [PMID: 9990071 DOI: 10.1073/pnas.96.4.1603]

155 **Wisdom R**, Johnson RS, Moore C. c-Jun regulates cell cycle progression and apoptosis by distinct mechanisms. *EMBO J* 1999; **18**: 188-197 [PMID: 9878062 DOI: 10.1093/emboj/18.1.188]

156 **Barker N**, van Es JH, Kuipers J, Kujala P, van den Born M, Cozijnsen M, Haegebarth A, Korving J, Begthel H, Peters PJ, Clevers H. Identification of stem cells in small intestine and colon by marker gene Lgr5. *Nature* 2007; **449**: 1003-1007 [PMID: 17934449 DOI: 10.1038/nature06196]

157 **Boon EM**, van der Neut R, van de Wetering M, Clevers H, Pals ST. Wnt signaling regulates expression of the receptor tyrosine kinase met in colorectal cancer. *Cancer Res* 2002; **62**: 5126-5128 [PMID: 12234972]

158 **He TC**, Sparks AB, Rago C, Hermeking H, Zawel L, da Costa LT, Morin PJ, Vogelstein B, Kinzler KW. Identification of c-MYC as a target of the APC pathway. *Science* 1998; **281**: 1509-1512 [PMID: 9727977 DOI: 10.1126/science.281.5382.1509]

159 **Jung HC**, Kim K. Identification of MYCBP as a beta-catenin/LEF-1 target using DNA microarray analysis. *Life Sci* 2005; **77**: 1249-1262 [PMID: 15979100 DOI: 10.1016/j.lfs.2005.02.009]

160 **Ungerbäck J**, Elander N, Grünberg J, Sigvardsson M, Söderkvist P. The Notch-2 gene is regulated by Wnt signaling in cultured colorectal cancer cells. *PLoS One* 2011; **6**: e17957 [PMID: 21437251 DOI: 10.1371/journal.pone.0017957]

161 **Dehner M**, Hadjihannas M, Weiske J, Huber O, Behrens J. Wnt signaling inhibits Forkhead box O3a-induced transcription and apoptosis through up-regulation of serum- and glucocorticoid-inducible kinase 1. *J Biol Chem* 2008; **283**: 19201-19210 [PMID: 18487207 DOI: 10.1074/jbc.M710366200]

162 **Blache P**, van de Wetering M, Duluc I, Domon C, Berta P, Freund JN, Clevers H, Jay P. SOX9 is an intestine crypt transcription factor, is regulated by the Wnt pathway, and represses the CDX2 and MUC2 genes. *J Cell Biol* 2004; **166**: 37-47 [PMID: 15240568 DOI: 10.1083/jcb.200311021]

163 **Konsavage WM Jr**, Kyler SL, Rennoll SA, Jin G, Yochum GS. Wnt/β-catenin signaling regulates Yes-associated protein (YAP) gene expression in colorectal carcinoma cells. *J Biol Chem* 2012; **287**: 11730-11739 [PMID: 22337891 DOI: 10.1074/jbc.M111.327767]

164 **Wei W**, Chua MS, Grepper S, So SK. Blockade of Wnt-1 signaling leads to anti-tumor effects in hepatocellular carcinoma cells. *Mol Cancer* 2009; **8**: 76 [PMID: 19778454 DOI: 10.1186/1476-4598-8-76]

165 **Shah K**, Panchal S, Patel B. Porcupine inhibitors: Novel and emerging anti-cancer therapeutics targeting the Wnt signaling pathway. *Pharmacol Res* 2021; **167**: 105532 [PMID: 33677106 DOI: 10.1016/j.phrs.2021.105532]

166 **Dunbar K**, Valanciute A, Lima ACS, Vinuela PF, Jamieson T, Rajasekaran V, Blackmur J, Ochocka-Fox AM, Guazzelli A, Cammareri P, Arends MJ, Sansom OJ, Myant KB, Farrington SM, Dunlop MG, Din FVN. Aspirin Rescues Wnt-Driven Stem-like Phenotype in Human Intestinal Organoids and Increases the Wnt Antagonist Dickkopf-1. *Cell Mol Gastroenterol Hepatol* 2021; **11**: 465-489 [PMID: 32971322 DOI: 10.1016/j.jcmgh.2020.09.010]

167 **Novellasdemunt L**, Kucharska A, Jamieson C, Prange-Barczynska M, Baulies A, Antas P, van der Vaart J, Gehart H, Maurice MM, Li VS. NEDD4 and NEDD4L regulate Wnt signalling and intestinal stem cell priming by degrading LGR5 receptor. *EMBO J* 2020; **39**: e102771 [PMID: 31867777 DOI: 10.15252/embj.2019102771]

168 **Nile AH**, de Sousa E Melo F, Mukund S, Piskol R, Hansen S, Zhou L, Zhang Y, Fu Y, Gogol EB, Kömüves LG, Modrusan Z, Angers S, Franke Y, Koth C, Fairbrother WJ, Wang W, de Sauvage FJ, Hannoush RN. A selective peptide inhibitor of Frizzled 7 receptors disrupts intestinal stem cells. *Nat Chem Biol* 2018; **14**: 582-590 [PMID: 29632413 DOI: 10.1038/s41589-018-0035-2]

169 **Gurney A**, Axelrod F, Bond CJ, Cain J, Chartier C, Donigan L, Fischer M, Chaudhari A, Ji M, Kapoun AM, Lam A, Lazetic S, Ma S, Mitra S, Park IK, Pickell K, Sato A, Satyal S, Stroud M, Tran H, Yen WC, Lewicki J, Hoey T. Wnt pathway inhibition *via* the targeting of Frizzled receptors results in decreased growth and tumorigenicity of human tumors. *Proc Natl Acad Sci U S A* 2012; **109**: 11717-11722 [PMID: 22753465 DOI: 10.1073/pnas.1120068109]

170 **Grandy D**, Shan J, Zhang X, Rao S, Akunuru S, Li H, Zhang Y, Alpatov I, Zhang XA, Lang RA, Shi DL, Zheng JJ. Discovery and characterization of a small molecule inhibitor of the PDZ domain of dishevelled. *J Biol Chem* 2009; **284**: 16256-16263 [PMID: 19383605 DOI: 10.1074/jbc.M109.009647]

171 **Alula KM**, Delgado-Deida Y, Jackson DN, Venuprasad K, Theiss AL. Nuclear partitioning of Prohibitin 1 inhibits Wnt/β-catenin-dependent intestinal tumorigenesis. *Oncogene* 2021; **40**: 369-383 [PMID: 33144683 DOI: 10.1038/s41388-020-01538-y]

172 **Mizutani A**, Yashiroda Y, Muramatsu Y, Yoshida H, Chikada T, Tsumura T, Okue M, Shirai F, Fukami T, Yoshida M, Seimiya H. RK-287107, a potent and specific tankyrase inhibitor, blocks colorectal cancer cell growth in a preclinical model. *Cancer Sci* 2018; **109**: 4003-4014 [PMID: 30238564 DOI: 10.1111/cas.13805]

173 **Tian M**, Wang X, Sun J, Lin W, Chen L, Liu S, Wu X, Shi L, Xu P, Cai X, Wang X. IRF3 prevents colorectal tumorigenesis *via* inhibiting the nuclear translocation of β-catenin. *Nat Commun* 2020; **11**: 5762 [PMID: 33188184 DOI: 10.1038/s41467-020-19627-7]

174 **Yan M**, Li G, An J. Discovery of small molecule inhibitors of the Wnt/β-catenin signaling pathway by targeting β-catenin/Tcf4 interactions. *Exp Biol Med (Maywood)* 2017; **242**: 1185-1197 [PMID: 28474989 DOI: 10.1177/1535370217708198]

**Footnotes**

**Conflict-of-interest statement:** The authors declare no conflicts of interest for this article.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review started:** February 23, 2021

**First decision:** July 29, 2021

**Article in press:** February 19, 2022

**Specialty type:** Oncology

**Country/Territory of origin:** Germany

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): B

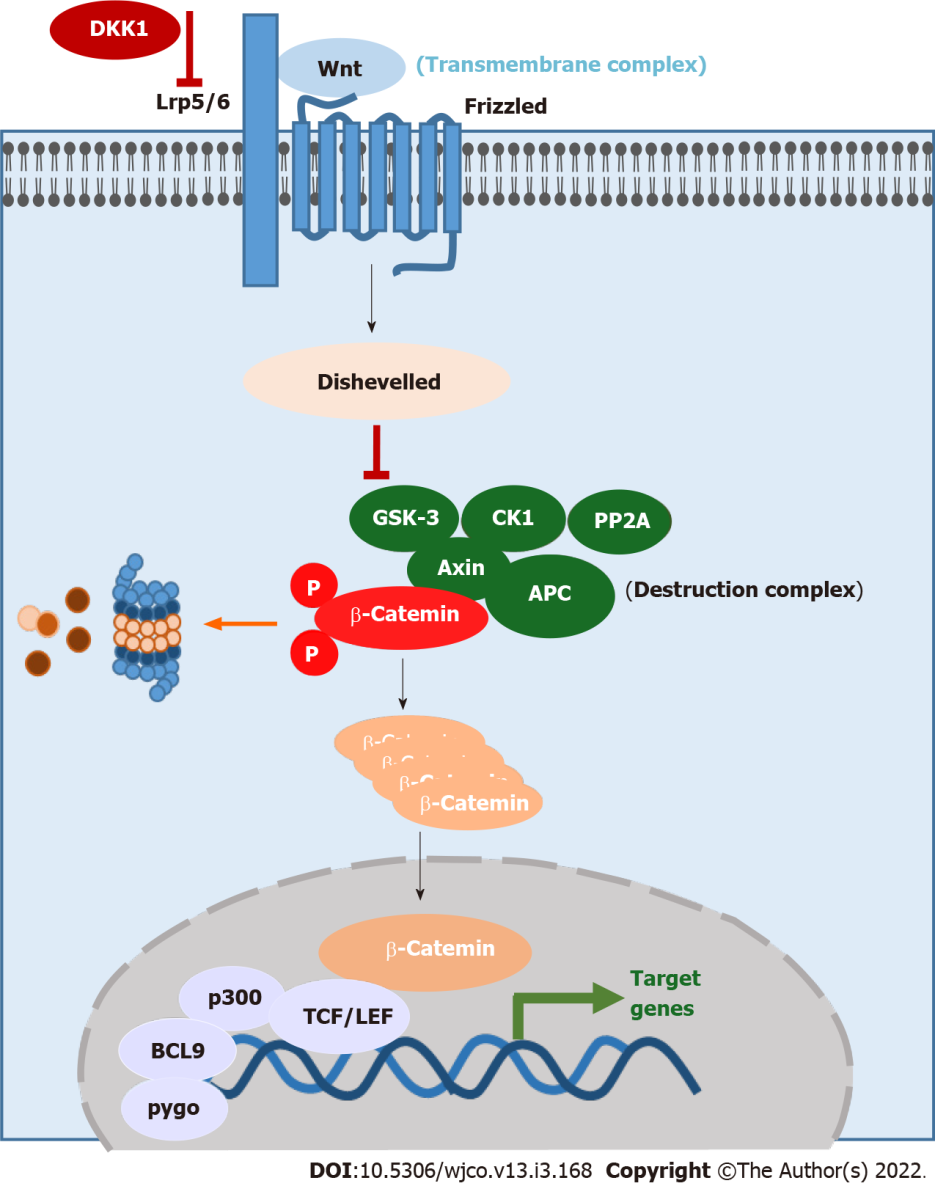
Grade C (Good): C

Grade D (Fair): D

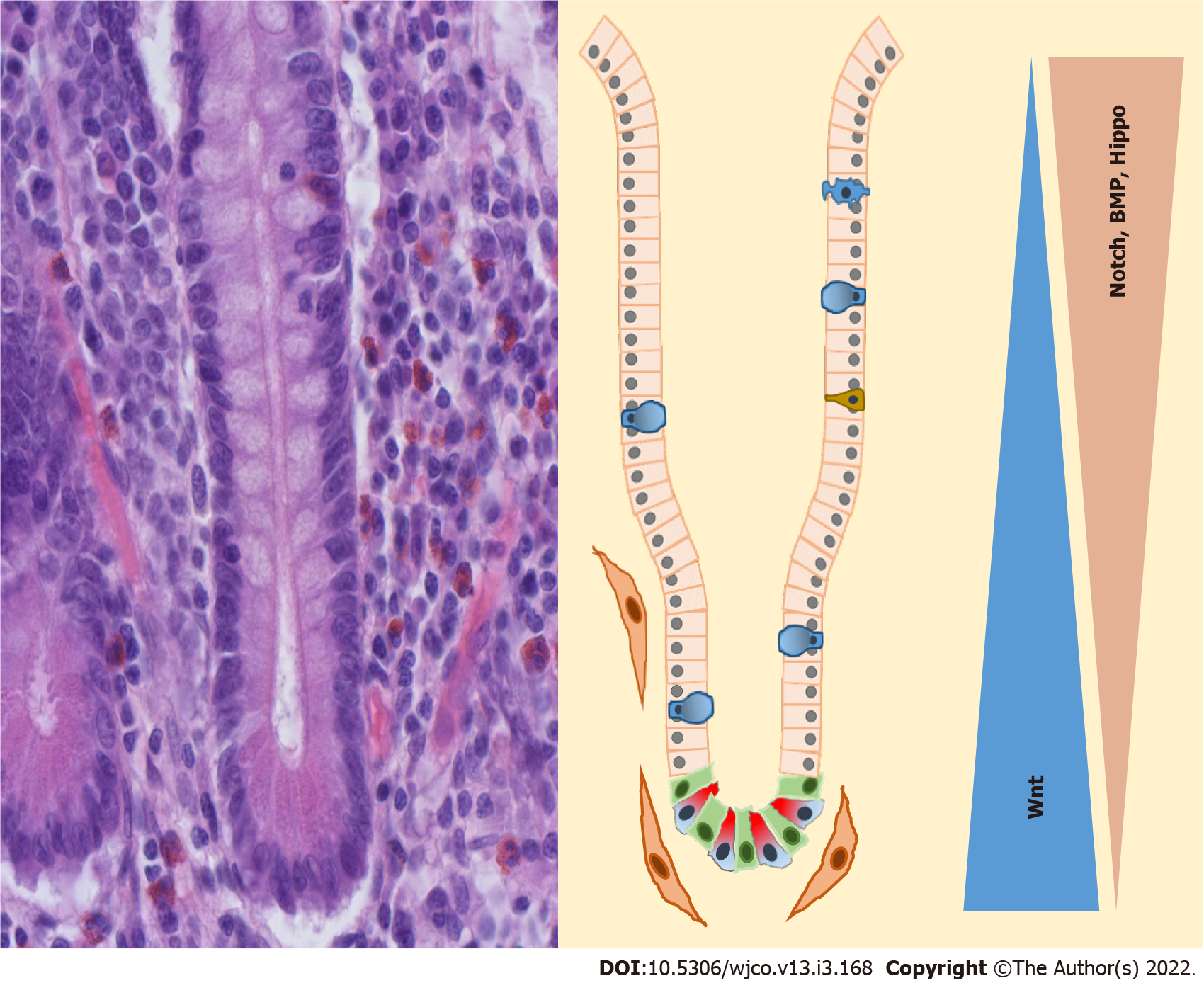
Grade E (Poor): 0

**P-Reviewer:** Feng R, Wang YG **S-Editor:** Wang JJ **L-Editor:** A **P-Editor:** Wang JJ

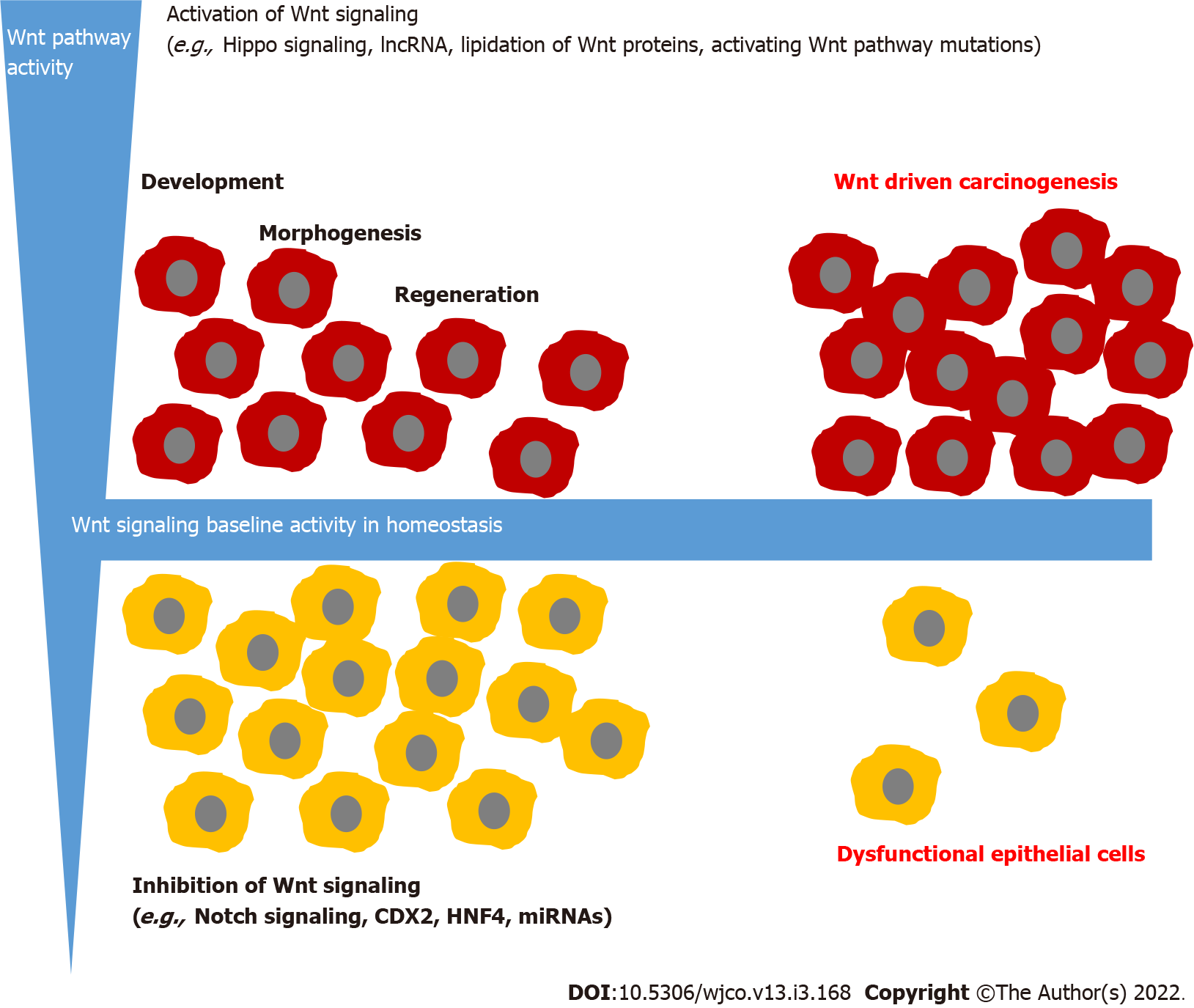
**Figure Legends**



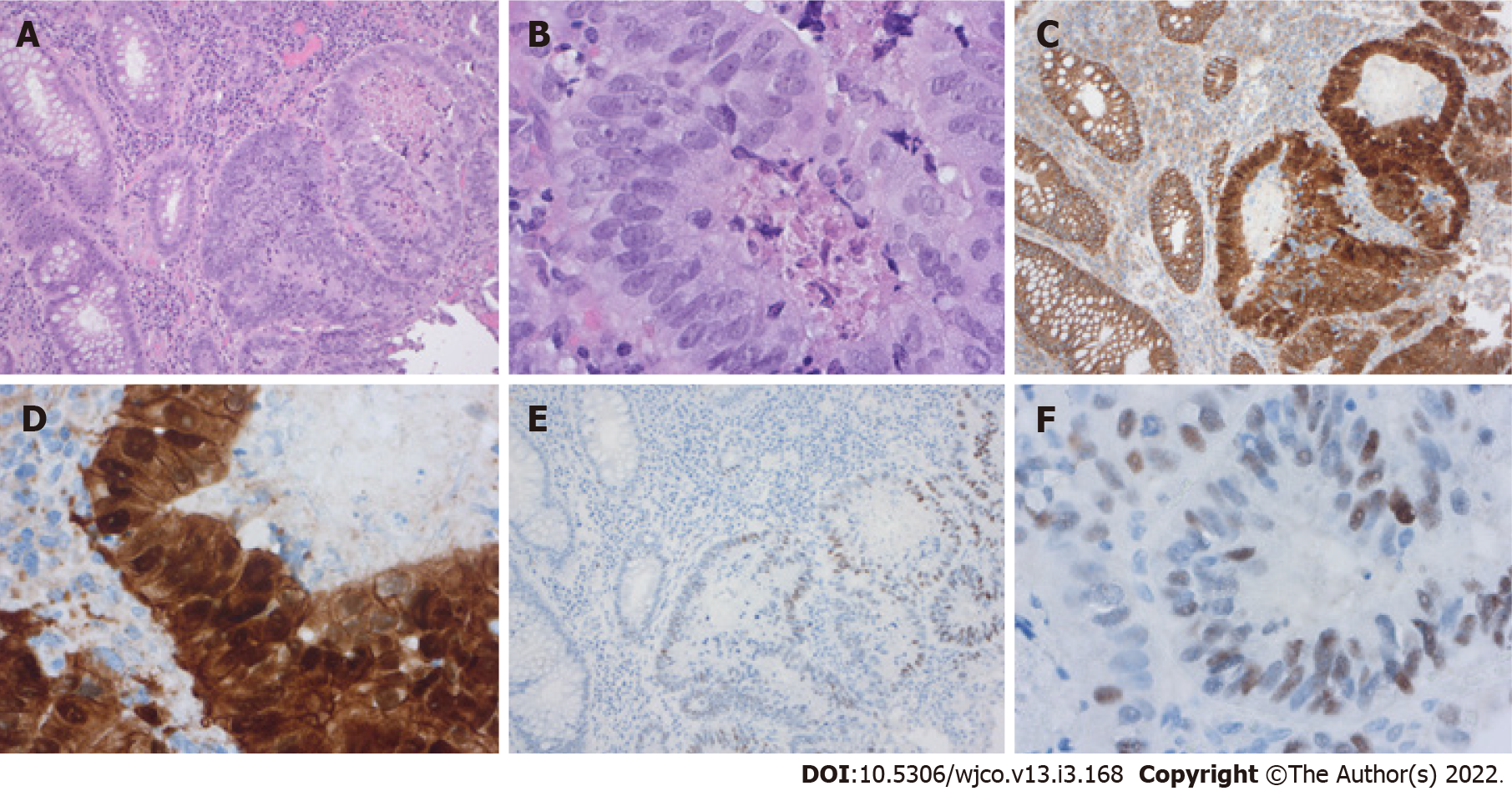
**Figure 1 Wnt signaling pathway.** Activated Wnt signaling pathway: Wnt ligand binds to the transmembrane complex and activates Disheveled, which turns down the destruction complex. β-catenin accumulates in the cytoplasm and translocates in the nucleus, where it acts with several cofactors as a transcription factor. Inactivated Wnt signaling pathway: β-catenin is phosphorylated by the destruction complex and gets degraded. Dkk1: Dickkopf 1; GSK-3: Glycogen synthase kinase-3; APC: Adenomatous polyposis coli; PP2A: Protein phosphatase 2A; TCF/LEF: T-cell factor/lymphoid enhancer-binding factor; BCL9: B-cell lymphoma 9.



**Figure 2 Small intestinal crypt of Lieberkühn with signaling pathway gradients.** On the left sight histology of a small intestinal crypt (400 × Hematoxylin eosin) and on the right a schematic drawing of a small intestinal crypt with intestinal stem cells (green), Paneth cells (red), goblet cells (light blue), tuft cell (blue) and neuroendocrine cell (yellow). BMP: Bone morphogenetic protein.



**Figure 3 Wnt signaling regulatory mechanisms in intestinal cell development.** Wnt signaling balances intestinal development, morphogenesis and regeneration due to a gradient of Wnt pathway activity in epithelial layers with major activated cells (red) and minor activated cells (yellow). In Wnt-driven carcinogenesis, the gradient of Wnt pathway activity is lost and major activated, neoplastic cells (red) dominate. lncRNA: Long non-coding RNA; miRNAs: MicroRNAs.



**Figure 4 Colorectal carcinoma.** A: Invasive growth and loss of polarity [100 × Hematoxylin eosin (HE)]; B: Cellular atypies (400 × HE); C: β-catenin staining (100 ×) membranous in normal epithelial, nuclear staining in dysplastic cells; D: β-catenin staining (400 ×) with partly extensive accumulation of β-catenin in the nucleus; E: Positive staining of c-myc (a target of β-catenin) in the dysplastic cells (100 ×); F: Positive nuclear staining of c-myc (400 ×).

**Table 1 Selection of assumed target genes of β-catenin**

|  |  |  |
| --- | --- | --- |
| **Gene** | **Function of the protein** | **Ref.** |
| ATOH1 | Transcription factor, secretory cell line differentiation | [137,138] |
| AXIN2 | Part of destruction complex Wnt signaling | [139] |
| BCL2 | Antiapoptotic | [140] |
| BIRC5 | Apoptosis inhibitor | [141] |
| BMP4 | Possible Wnt inhibitor | [142] |
| CCND1 | Cell proliferation | [143] |
| CDKN2A | Cell cycle inhibitor | [144] |
| CDX1 | Transcription factor, intestinal cell differentiation | [145] |
| CDX2 | Transcription factor, intestinal cell differentiation | [146] |
| DKK1/4 | Inhibitor of Wnt signaling | [147,148] |
| EPHB2/3 | Migration and proliferation in intestine epithelial | [149] |
| HD5/6 | Defensine, microbial defense | [150] |
| HEF1 | Supports activation of oncogenic signaling pathways | [151] |
| HES1 | Regulation of Notch signaling | [152] |
| JAG1 | Ligand of Notch signaling | [153] |
| JUN | Cell cycle progression, apoptosis inhibitor | [154,155] |
| LGR5 | Part of Wnt signaling | [156] |
| MDR1 | Plasma membrane protein involved in the drug resistance | [123,124] |
| MET | Differentiation of intestinal epithelium | [157] |
| MYC | Protooncogene | [158] |
| MYCBP | Control of transcriptional activity of c-MYC | [159] |
| NOTCH2 | Notch receptor | [160] |
| SGK1 | Inhibits pro-apoptotic transcription factors | [161] |
| SOX9 | Paneth cell differentiation | [32,162] |
| YAP | Transcription factor (Hippo signaling) activates genes involved in cell proliferation, suppresses apoptotic genes | [163] |

ATOH1: Atonal BHLH transcription factor 1; BCL2: B-cell lymphoma 2 ; BIRC5: Baculoviral IAP repeat containing 5; BMP4: Bone morphogenetic protein 4; CCND1: Cyclin D1; CDKN2A: Cyclin dependent kinase inhibitor 2A; CDX1: Caudal type homeobox 1; CDX2: Caudal type homeobox 2; DKK: Dickkopf; EPHB2/3: EPH receptor B2/3; HD5/6: Human alpha efensing 5/6; HEF1: Human enhancer of filamentation 1; HES1: Hairy and enhancer of split-1; JAG1: Jagged Canonical Notch Ligand 1; JUN: C-Jun N-terminal kinase; LGR5: Leucine-rich repeat-containing G-protein coupled receptor 5; MDR1: Multidrug-Resistance-1; MET: Tyrosine-protein kinase Met; MYC: Myc proto-oncogene, Bhlh transcription factor; MYCBP: MYC binding protein; NOTCH2: Notch Receptor 2; SGK1: Serum/glucocorticoid regulated kinase 1; SOX9: SRY-Box transcription factor 9; YAP: Yes-associated protein.

**Table 2 Selection of potential target opportunities to inhibit Wnt/β-catenin signaling**

|  |  |  |
| --- | --- | --- |
| **Target** | **Effect** | **Ref.** |
| **Ligand-dependent Wnt signaling activation** | | |
| Wnt ligands | Wnt inhibitors | [164] |
|  | Posttranslational modification | [165] |
| Dkk1 | Stabilization, increase of Dkk1 | [128,166] |
| Transmembrane complex | Inhibition of Lgr5/6 | [167] |
|  | Inhibition of Frizzled | [168,169] |
| Dishevelled | Inhibition | [170] |
| **Ligand independent Wnt signaling activation** | | |
| Destruction complex | Stabilization of the destruction complex | [171,172] |
| β-catenin | Increase of degradation | [130,131] |
| Inhibition of translocation to the nucleolus | [173] |
| β-catenin cofactors |  | [174] |
| Ribosome biogenesis |  | [134] |
| Oncolytic viruses |  | [132,133] |

Dkk1: Dickkopf 1.



Published by **Baishideng Publishing Group Inc**

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

**Telephone:** +1-925-3991568

**E-mail:** bpgoffice@wjgnet.com

**Help Desk:** https://www.f6publishing.com/helpdesk

https://www.wjgnet.com



**© 2022 Baishideng Publishing Group Inc. All rights reserved.**