

World Journal of *Clinical Oncology*

World J Clin Oncol 2022 March 24; 13(3): 159-236



EVIDENCE REVIEW

- 159 Evidence-based approach to the treatment of esophagogastric junction tumors
Schlottmann F, Casas MA, Molena D

REVIEW

- 168 Intestinal Wnt in the transition from physiology to oncology
Swoboda J, Mittelsdorf P, Chen Y, Weiskirchen R, Stallhofer J, Schüle S, Gassler N
- 186 From *Helicobacter pylori* infection to gastric cancer: Current evidence on the immune response
Lima de Souza Gonçalves V, Cordeiro Santos ML, Silva Luz M, Santos Marques H, de Brito BB, França da Silva FA, Souza CL, Oliveira MV, de Melo FF

MINIREVIEWS

- 200 Possible relationship between refractory celiac disease and malignancies
Demiroren K
- 209 Breast cancer in India: Present scenario and the challenges ahead
Mehrotra R, Yadav K
- 219 Immunotherapy in triple-negative breast cancer: A literature review and new advances
Valencia GA, Rioja P, Morante Z, Ruiz R, Fuentes H, Castaneda CA, Vidaurre T, Neciosup S, Gomez HL

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RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Ying-Yi Yuan*; Production Department Director: *Xu Guo*; Editorial Office Director: *Ze-Mao Gong*.

NAME OF JOURNAL

World Journal of Clinical Oncology

ISSN

ISSN 2218-4333 (online)

LAUNCH DATE

November 10, 2010

FREQUENCY

Monthly

EDITORS-IN-CHIEF

Hiten RH Patel, Stephen Safe, Jian-Hua Mao, Ken H Young

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/2218-4333/editorialboard.htm>

PUBLICATION DATE

March 24, 2022

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<https://www.wjgnet.com/bpg/GerInfo/288>

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<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>



Intestinal Wnt in the transition from physiology to oncology

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Specialty type: Oncology

Provenance and peer review:

Invited article; Externally peer reviewed.

Peer-review model: Single blind

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

Received: February 23, 2021

Peer-review started: February 23, 2021

First decision: July 29, 2021

Revised: September 7, 2021

Accepted: February 19, 2022

Article in press: February 19, 2022

Published online: March 24, 2022



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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

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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.

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>

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 Dishevelled 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.

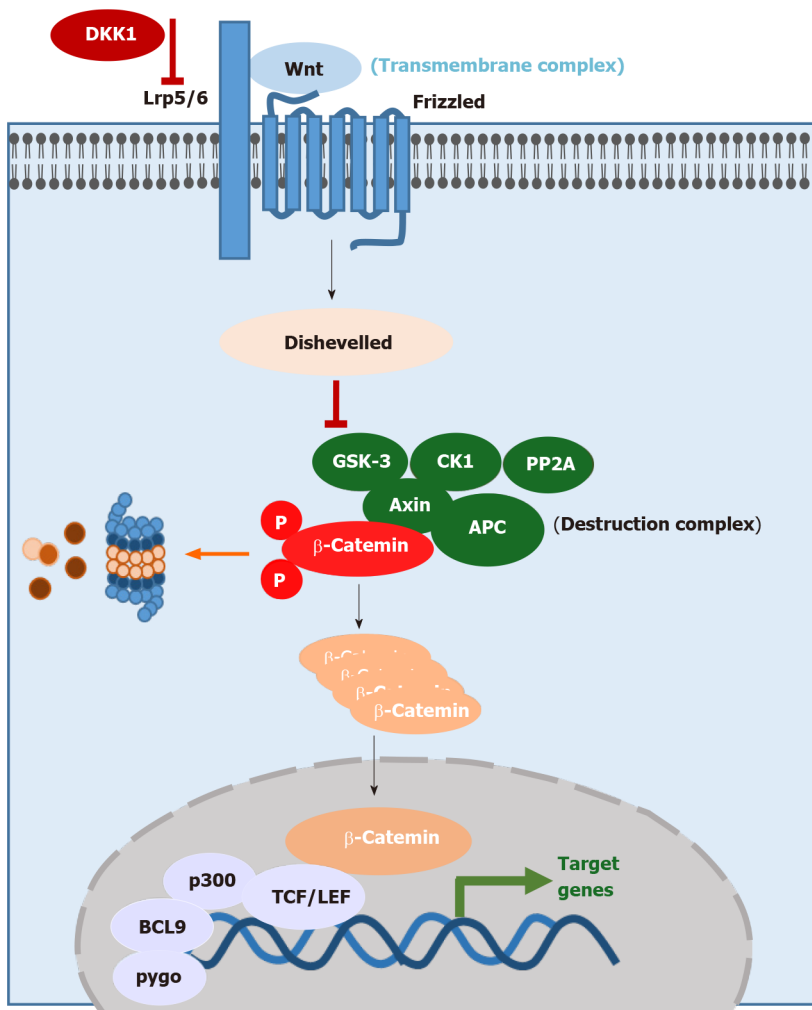
Table 1 Selection of assumed target genes of β -catenin

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 defensin 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.

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].



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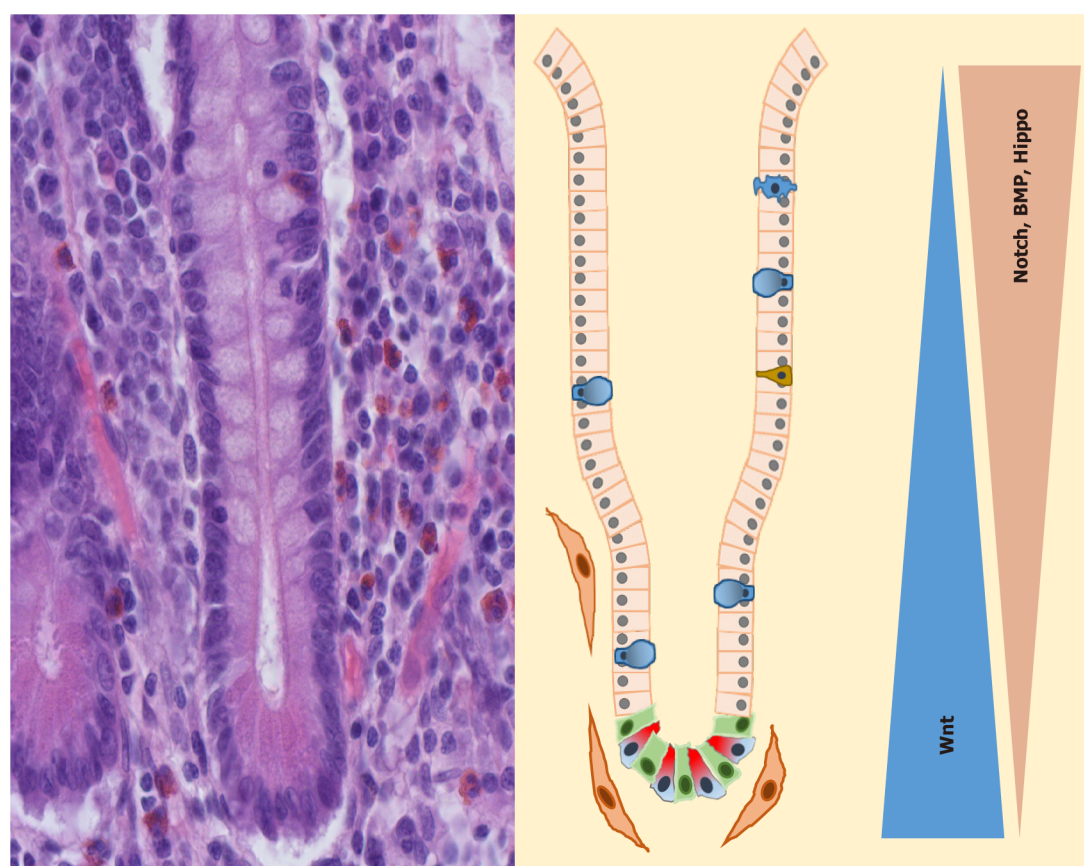
Figure 1 Wnt signaling pathway. Activated Wnt signaling pathway: Wnt ligand binds to the transmembrane complex and activates Dishevelled, which turns down the destruction complex. β -catenin accumulates in the cytoplasm and translocates in the nucleus, where it acts with several cofactors as a transcription 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.

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



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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.

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.

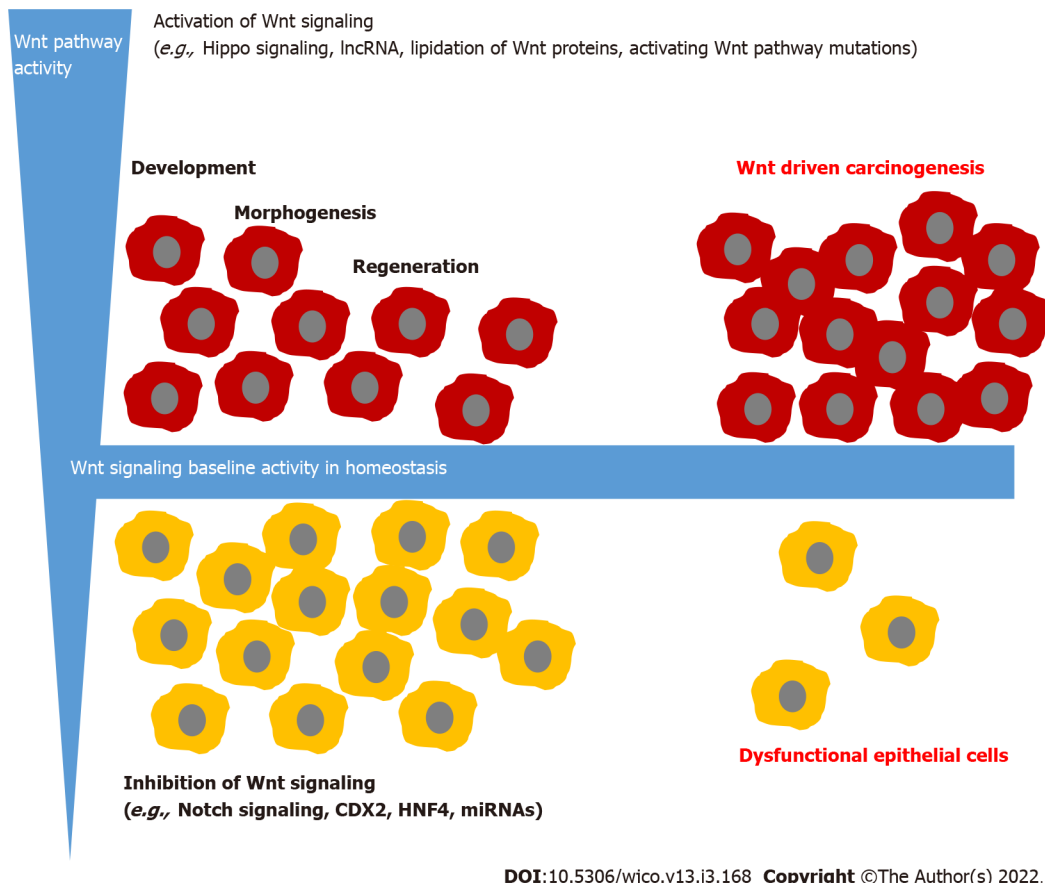


Figure 3 Wnt signaling regulatory mechanisms in intestinal cell development. Wnt signaling balances intestinal development, morphogenesis and regeneration due to a gradient of Wnt pathway activity in epithelial layers with major activated cells (red) and minor activated cells (yellow). In Wnt-driven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

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, Dishevelled, 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-3 β , 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 HNF4 α and HNF4 γ 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 HNF4 α is downregulated in human colon carcinoma and showed in *in vitro* experiments that HNF4 α 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 Wnt2 β leads to an accumulation of Wnt2 β 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.

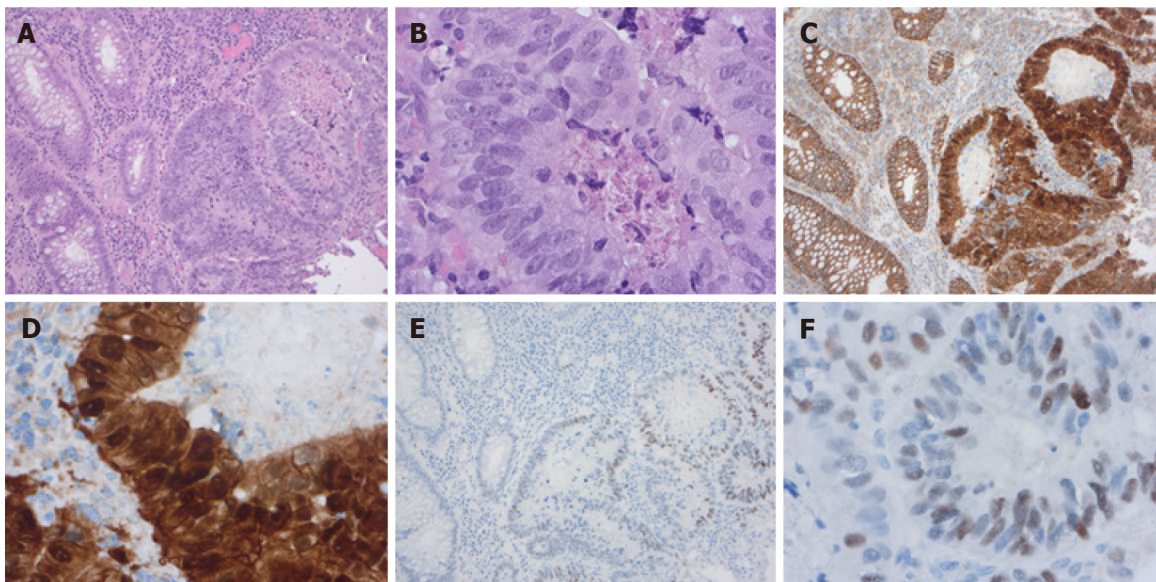
MicroRNAs (miRNAs) are small 18-25 nt long non-coding RNA molecules and can bind on their target messenger-RNA (mRNA) and suppress translation. Rahmani *et al*[78] summed up about 17 miRNAs that target mRNAs encoding for proteins of Wnt signaling. Here, they can act as an activator of Wnt signaling by 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 protein kinase 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,



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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 ×).

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 hyper-activation 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-3 β , 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 *APC^{min}* 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

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.

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 APC^{min/+} 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.

FOOTNOTES

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.

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

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S-Editor: Wang JJ

L-Editor: A

P-Editor: Wang JJ

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