Wnt/β-catenin signaling: Causes and treatment targets of drug resistance in colorectal cancer (Review)

GUI-XIAN ZHU[1,2], DIAN GAO[3], ZHAO-ZHAO SHAO[1], LI CHEN[1], WEN-JIE DING[1] and QIONG-FANG YU[1]

[1]Department of Gastroenterology and Hepatology, Second Affiliated Hospital of Nanchang University; [2]Second Clinical Medical College of Nanchang University; [3]Department of Pathogen Biology and Immunology, Medical College of Nanchang University, Nanchang, Jiangxi 330006, P.R. China

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Abstract. Colorectal cancer (CRC) is the third most common malignant tumor in humans. Chemotherapy is used for the treatment of CRC. However, the effect of chemotherapy remains unsatisfactory due to drug resistance. Growing evidence has shown that the presence of highly metastatic tumor stem cells, regulation of non-coding RNAs and the tumor microenvironment contributes to drug resistance mechanisms in CRC. Wnt/β-catenin signaling mediates the chemoresistance of CRC in these three aspects. Therefore, the present study analyzed the abundant evidence of the contribution of Wnt/β-catenin signaling to the development of drug resistance in CRC and discussed its possible role in improving the chemosensitivity of CRC, which may provide guidelines for its clinical treatment.

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Correspondence to: Dr Qiong-Fang Yu, Department of Gastroenterology and Hepatology, Second Affiliated Hospital of Nanchang University, 1 Minde Road, Nanchang, Jiangxi 330006, P.R. China
E-mail: qiongfangyu@yeah.net

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1. Introduction

Globally, colorectal cancer (CRC) is the third most commonly diagnosed malignant tumor and is the second leading cause of cancer-associated mortality (1). Overall, the incidence rate and mortality rate of CRC are rising rapidly in several low-income and middle-income countries (2). Although the mortality rate of CRC tends to be stable or declining in developed countries, it is still higher than that in low-income and middle-income countries (2). By 2030, the global CRC burden is expected to increase by 60%, reaching >2.2 million new cases and 1.1 million mortalities (3). The majority of newly-diagnosed CRC cases are classified as a sporadic form (4), and the occurrence and development of CRC is a long-term process. Conventional CRC begins with changes in the cell morphology of the colonic epithelium, which proliferates uncontrollably to form benign polyps. Gradually, it develops into a highly atypical hyperplastic advanced adenoma, which causes a loss of epithelial structure and function to form an invasive tumor (5,6).

A number of factors contribute to the formation of CRC. Genetic susceptibility is a major driver of early CRC occurrence. A study has demonstrated that CRC contains ≤80 mutations, of which <15 mutations are the driving force for tumorigenesis (7). The probability of developing CRC is also associated with personal features and habits, such as age, gender, race/ethnicity, chronic disease history, dietary factors, obesity, low physical activity, smoking and intestinal microflora (4,8,9). Chemotherapy based on 5-fluorouracil (5-FU) has been the main treatment method for patients with CRC since the 1950s (10-12). More chemotherapeutic drugs, such as oxaliplatin (L-OHP), irinotecan and capecitabine, have been developed in recent years and the emergence of monoclonal antibodies, such as bevacizumab and cetuximab, have greatly advanced chemotherapy for CRC (13). However, even if the current response rate to various systemic chemotherapy regimens reaches 50%, most patients develop resistance within 3-12 months (14,15). Drug resistance refers to the gradual decline in the response to drugs during the treatment of various diseases (16). Resistance to chemotherapy drugs is a major limitation in the use of chemotherapy (17). The failure of chemotherapy due to cancer progression and resistance underlies the majority of cancer-associated deaths (18). Therefore,

it is necessary to explore drug resistance mechanisms and reversal strategies of CRC chemotherapy.

Previous studies have demonstrated that tumor stem cells (CSCs), non-coding RNAs (ncRNAs) and disordered tumor microenvironment (TME) contribute to the resistance of CRC (19-22). Notably, Wnt/β-catenin signaling has been reported to regulate the formation of CRC via these three aspects (23,24). It is hypothesized that the dysregulation of the Wnt/β-catenin signaling is related to chemotherapy resistance in CRC. At present, numerous studies have sustained this view (25-27), but there is no systematic summary to the best of our knowledge. Therefore, the present authors have systematically reviewed the reported studies on Wnt/β-catenin signaling-mediated chemotherapy resistance of CRC, which may provide clinical reference for the future.

2. Method

Studies were retrieved from the Pubmed (https://pubmed.ncbi.nlm.nih.gov/) and Web of Science databases (https://www.webofknowledge.com) using 'Wnt', 'β-catenin', 'CRC', 'drug resistance' and 'multidrug resistance' (MDR) as key words. The retrieved literature ranged from 1980 to the present and the last search was performed on August 28, 2020. The present review focuses on the role of Wnt/β-catenin signaling in CRC resistance and the inhibition of Wnt/β-catenin signaling to study the regulation of CRC resistance.

3. Wnt/β-catenin signaling pathway

The Wnt gene was first identified in mouse mammary tumors in 1982 and was originally named the int1 gene (28). Subsequent investigation showed that the int gene serves an important role in embryo growth and development in mice, and its function is similar to the *Drosophila* wingless gene (29). The int1 gene and wingless gene are collectively referred to as the Wnt gene (29). The Wnt signaling pathway is one of the key signaling pathways in the regulation of cell proliferation and it serves a significant role in the pathological process of malignant tumors (30-34). The Wnt gene is composed of various glycoproteins, is a member of the coiled family of transmembrane receptors and is the coreceptor for lipoprotein receptor-related protein (LRP) family and other downstream components (35). There are currently 19 Wnt ligands in mammals that function via autocrine and paracrine pathways (36,37). These various Wnt ligands serve different roles in the development of organisms and the aberrant expression of Wnt ligand genes can lead to the occurrence and development of different types of tumors (Table I) (78). Wnt ligands are divided into two classes according to the different binding methods with downstream receptors. One group binds to the Frizzled (Fzd) and low-density lipoprotein-related receptor 5/6 (LRP/6) to activate canonical β-catenin-dependent pathways. The other group binds Fzd protein to activate the cyclic guanosine monophosphate protein and the noncanonical Wnt pathway (79). β-catenin is the central molecule in the canonical Wnt pathway that controls the switch of the Wnt signaling pathway. Therefore, it is also called Wnt/β-catenin signaling (80). Wnt ligands do not bind to the receptor in normal mature cells, and Wnt/β-catenin signaling is in an 'off' state (81). Adenomatous polyposis coli (APC) protein, framework protein Axin, glycogen synthase kinase 3β (GSK3β) and casein kinase 1 (CK1) form a complex that causes degradation of β-catenin (82). This complex degrades β-catenin, which is phosphorylated, modified by ubiquitin and ultimately degraded by the proteasome (83). Eventually, the concentration of β-catenin is decreased, nuclear translocation is suppressed, and downstream target genes, including c-Myc, cyclin D1, survivin and porous metalloproteinase, cannot be activated (83). When Wnt ligands bind to transmembrane Fzd receptors and LRP5/6, CK1 and GSK3β are attracted to LRP5/6 and function as phosphorylases of LRP5/6, which prevents formation of the protein complexes that degrade β-catenin (84). Continuously increasing concentrations of free β-catenin enter the nucleus via the nuclear pore membrane and bind to transcription factor/lymphocyte-enhancing factor (TCF/LEF) (85). Binding promotes the transcription of downstream target genes that affect cell proliferation, apoptosis, stromal lysis and angiogenesis (85). Wnt ligands bind to the receptor, and Wnt/β-catenin signaling is in an 'on' state (81). The details are shown in Fig. 1.

4. Wnt/β-catenin signaling in CRC drug resistance

The resistance of human tumors to anticancer drugs is primarily due to the inherent chemical resistance of tumor cells, generally attributed to gene mutation, gene amplification or epigenetic changes, which affect absorption, metabolism or the export of drugs by a single cell (19). CRC cells exhibit varied resistance to different chemotherapy drugs, including 5-FU, L-OHP and irinotecan, depending on enhanced intracellular metabolism, upregulation or changes in intracellular targets, increased dihydropyrimidine dehydrogenase and thymidine synthase activities, upregulated levels of the diminished form glutathione or increased nucleotide excision repair (86,87). Resistance to capecitabine is accomplished via methylation of the gene encoding thymidine phosphorylase and inactivation of capecitabine (88). For the checkpoint inhibitors, including ipilimumab, pembrolizumab and nivolumab, tumors primarily achieve resistance via tumor mutation and adaptation, decreased production or expression of neoantigens, overexpression of indoleamine 2,3-dioxygenase and decreased expression of phosphatase and tensin homolog (PTEN) (89). Ghadimi *et al* (90) reported that the Wnt transcription factor TCF7L2 is overexpressed in 5-FU-resistant primary rectal cancer. The stimulation of Wnt3a leads to the strong activation of Wnt/β-catenin signaling in SW480, SW837 and LS1034 CRC cells (91). At the same time, the activity of TCF/LEF reporter gene is rapidly increased, which results in resistance to 5-FU (91). The inhibition of β-catenin can avoid the therapeutic resistance caused by enhanced TCF/LEF gene activity (91). Another study also demonstrated that the sensitivity of CRC cells to 5-FU can be adjusted through Wnt/β-catenin signaling pathway (92). In addition, pharmacological or genetic inhibition of β-catenin can change the chemical sensitivity of SW480 and SW620 CRC cells to 5-FU and L-OHP by regulating the Wnt/β-catenin-Jagged 2-p21 axis (93). Silencing of the

Table I. Cancer types associated with the Wnt ligand genes.

Author, year	Gene	Function	Type of cancer	(Refs.)
He *et al*, 2004 Chen *et al*, 2004; Babaei *et al*, 2019 Jia *et al*, 2017; Bodnar *et al*, 2014	Wnt1	GOF	Non-small-cell lung, prostate, CRC, gastric and ovarian cancer	(38-42)
Huang *et al*, 2015; Katoh *et al*, 2001	Wnt2	GOF	Lung, prostate, gastric cancer and CRC	(43,44)
Nakashima *et al*, 2012; Wang *et al*, 2016 Nie *et al*, 2019	Wnt3	GOF	Lung, CRC and gastric cancer	(45-47)
Thiago *et al*, 2010 Zimmerman *et al*, 2013 Annavarapu *et al*, 2013	Wnt3a	LOF	B cell precursor acute lymphoblastic leukemia, multiple melanoma and alveolar rhabdomyosarcoma	(48-50)
Fox *et al*, 2013; Wang *et al*, 2014 Akaboshi *et al*, 2009	Wnt3a	GOF	Malignant mesothelioma, breast and pancreatic cancer	(51-53)
Zhao et al, 2019	Wnt4	GOF	Cervical cancer	(54)
McDonald *et al*, 2009; Li *et al*, 2010 Ying *et al*, 2008 Kremenevskaja *et al*, 2005 Thiele *et al*, 2016; Kurayoshi *et al*, 2006	Wnt5a	LOF	Prostate and breast cancer, neuroblastoma, leukemia, squamous cell carcinoma of the esophagus, CRC and thyroid cancer	(55-59)
Kurayoshi *et al*, 2006 Kurayoshi *et al*, 2006; Huang *et al*, 2005 Bo *et al*, 2013	Wnt5a	GOF	Prostate, gastric, pancreatic, ovarian and non-small-cell lung cancer	(59-62)
Navarrete-Meneses *et al*, 2017 Stewart *et al*, 2014	Wnt5b	GOF	Acute lymphoblastic leukemia	(63)
Kirikoshi *et al*, 2002	Wnt7a	LOF	Non-small cell lung cancer, CRC, pancreatic and gastric cancer	(64,65)
Huang *et al*, 2015; Kirikoshi *et al*, 2002 Vesel *et al*, 2017	Wnt7b	GOF	Breast cancer, adenocarcinoma and embryonal tumor	(43,65,66)
Li *et al*, 2019; Li *et al*, 2017; Hsu *et al*, 2012 Kirikoshi *et al*, 2001; Dong *et al*, 2017	Wnt10a	GOF	CRC, ovarian cancer, renal cell carcinoma, esophageal and gastric cancer and papillary thyroid carcinoma	(67-71)
Wend *et al*, 2013; Chen *et al*, 2013 Saitoh *et al*, 2001	Wnt10b	GOF	Triple-negative breast and endometrial cancer and gastric carcinogenesis	(72-74)
Bartis *et al*, 2013; Tian *et al*, 2018	Wnt11	GOF	Lung cancer and CRC	(75,76)
Toyama *et al*, 2010	Wnt11	LOF	Hepatocellular carcinoma	(77)

LOF, loss-of-function; GOF, gain-of-function; CRC, colorectal cancer.

T cell factor 4 (Tcf4) gene, which is a downstream effector of Wnt/β-catenin signaling, sensitizes SW1874, SW1396, SW480 and SW-Sc CRC to L-OHP. This sensitization effect may be due to different mechanisms, including the Tcf4 motif in the ATP-binding cassette subfamily B member 1 (ABCB1) promoter, defects in the nucleotide excision repair or double strand break repair system after Tcf4-silencing (87). Wnt inhibitors also improve chemosensitivity (94,95). Among these inhibitors, 4-acetylantroquinol B, which is isolated from the mycelia of *Ganoderma camphora*, negatively regulates the stem cell maintenance signaling transduction pathway LGR5/Wnt/β-catenin and is most effective in reducing stem-related chemical resistance (96). The present study mainly reviewed the molecular mechanisms of Wnt/β-catenin signaling through CSCs, ncRNAs and TME that mediate the chemotherapy resistance of CRC.

Wnt/β-catenin signaling and CSCs. CSCs are cells that promote the development of tumors, and have the ability to self-renew and have multiple differentiation potentials (97,98). CSCs have four known characteristics, including self-renewal, differentiation, tumorigenic and specific surface markers. These cells are responsible for tumor occurrence, development, metastasis, recurrence and drug resistance (20,99). CSCs are naturally chemoresistant. CSCs are functionally protected in the tissue stem cell niche during chemotherapy (100). The CSCs niche is mainly composed of fibroblasts and endothelial, mesenchymal and immune cells (101,102). These adjacent cells

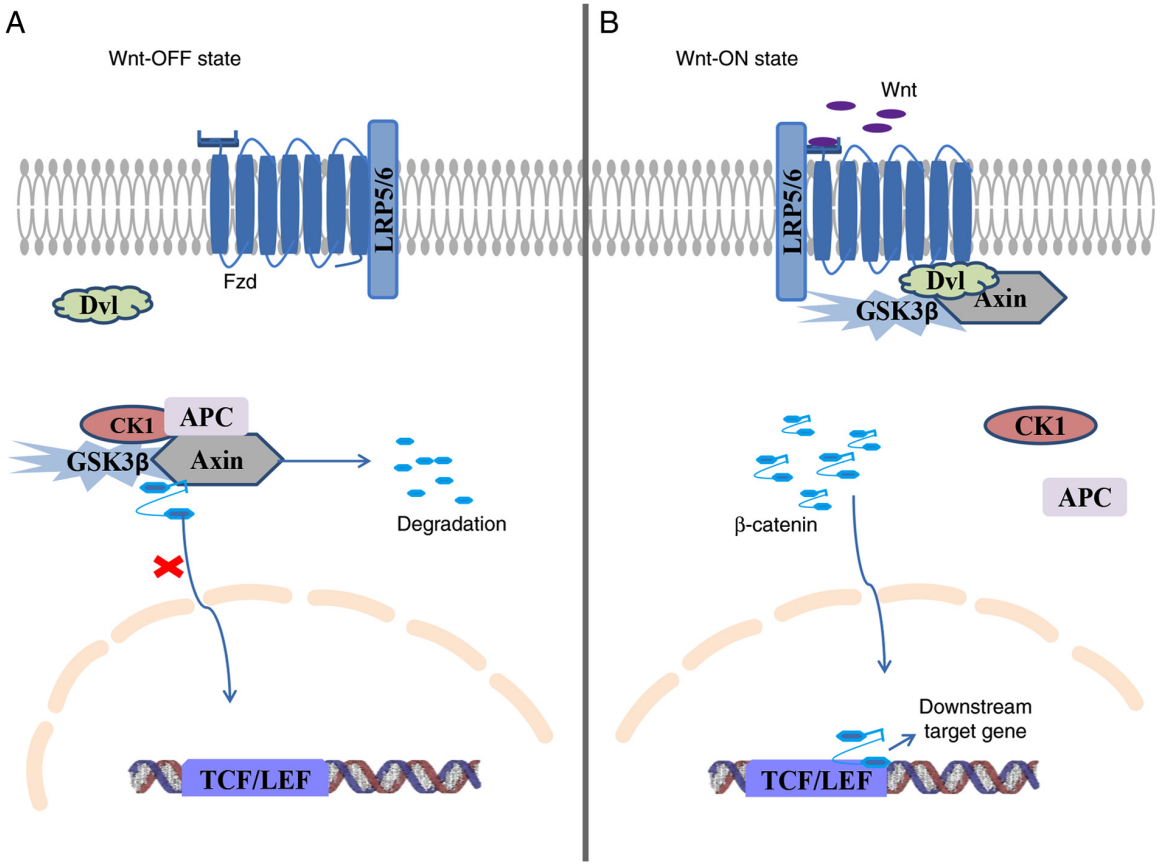

Figure 1. Schematic representation of the Wnt/β-catenin signaling pathway. (A) Wnt-off state. Cytoplasmic β-catenin is phosphorylated by a destructive complex composed of Axin, APC, GSK3β and CK1, then it is ubiquitinated and targeted for proteasome degradation. (B) Wnt-on state. Binding of Wnt ligands and its receptor Dvl determines the destruction of the β-catenin destruction complex, which induces the stability of β-catenin. β-catenin is transferred to the nucleus as a cofactor of TCF/LEF to activate Wnt target gene. Dvl, Dishevelled; APC, αdenomatous polyposis coli; GSK3β, glycogen synthase kinase 3β; CK1, casein kinase 1; Dvl, Fzd/LRP5/6/Dishevelled; TCF/LEF, transcription factor/lymphocyte-enhancing factor binding factor; Fzd, Frizzled; LRP5/6, low-density lipoprotein-related receptor 5/6.

promote the molecular signaling pathways required for the maintenance and survival of CSCs and trigger the endogenous drug resistance of CSCs (103). In addition, the extracellular matrix of niches can protect CSCs from the invasion of therapeutic drugs (100).

Wnt/β-catenin signaling is a necessary pathway for the initial activation, self-renewal and cloning ability of CSCs (104). Fevr *et al* (105) reported that tissue-specific and inducible β-catenin gene ablation blocks Wnt/β-catenin signaling and reduces the proliferation ability of CSCs. Wnt/β-catenin signaling regulates the expression of surface markers of CSCs (106,107). Leucine-rich repeat-containing G-protein-coupled receptor 5 (LGR5) is a target gene of the Wnt pathway and a marker of CSCs (107). Activation of Wnt/β-catenin signaling increases the level of the CSC cell surface marker LGR5 in the CRC cell lines HCT116, SW480 and DLD1 and enriches gene signatures associated with stemness and cancer relapse in CSCs (108). LGR5-positive CSCs are chemotherapy-resistant (109). The rapid proliferation of CSCs may transform LGR5-negative cells into LGR5-positive cells, which makes the cells enter a static state to escape the toxicity of drugs (110). However, CSCs of the CRC cell lines LoVo, HT29 and HCT116 also obtain drug resistance via the upregulation of drug-resistant drug pumps mediated by LGR5 (107). As CSCs and normal stem cells have very similar characteristics, most of these cells are in the G_0 phase of the cell cycle and express specific ATP-binding cassette proteins (ABC transporter) (111). The ABC transporter is a drug pump that mediates the outflow or uptake of a specific substrate. This mechanism takes place at cell membranes (including plasma membrane, endoplasmic reticulum, Golgi body, peroxisome and mitochondria) (112). ABC transporters expel numerous types of drugs from cancer cells and induce chemical resistance in numerous solid tumors (113,114). ABCB1 was the first cloned human ABC transporter (115). A study has shown that ABC inhibitors can inhibit ABC transporters with high potency and specificity and do not adversely affect the pharmacokinetics of therapeutic drugs that can kill cancer cells (116). NSC239225, as one of the ABC transporter inhibitors, can inhibit ABCB1 to increase the sensitivity of SW480TR CRC cells to some drugs, such as paclitaxel (PTX), doxorubicin and mitoxantrone. Its inhibitory effect is mainly achieved through stimulating ATP hydrolysis and directly binding to the iodoarylazidoprazosin (IAAP)-specific substrate binding site (117). Parguerenes I and II, which also act as ABC transporter inhibitors, can repress ABCB1 by modifying the extracellular substrate binding site of ABCB1, thereby reducing the resistance of SW620 and SW620 Ad300 CRC cells to PTX, Doxorubicin and vincristine (118). Studies have shown that Wnt/β-catenin signaling is closely

related to the ABC transporter of CSCs (25,119). Inhibition of Wnt/β-catenin signaling downregulates the expression of mRNA related to the ABC transporter, which makes SW480 CRC cells more sensitive to PTX and irinotecan (25). The ABCB1 level of SW620/AD CRC cells is also positively correlated with Wnt/β-catenin signaling transduction activity (120). Notably, Kugimiya *et al* (121) demonstrated that the downstream target gene of the Wnt/β-catenin signaling, c-Myc, makes COLO-320 CRC cells resistant to the chemical 5-FU by regulating the expression of ABCB5. This effect is primarily achieved by c-Myc-mediated regulation of the ABC transporter gene expression via binding to the upstream promoter (121). Wang *et al* (122) demonstrated that the transient receptor potential channel short transient receptor potential channel 5 (TRPC5)-induces an increase in [Ca^{2+}], promoting the transport of β-catenin to the nucleus, which serves an important role in ABCB1-induced resistance to 5-FU in CRC cells. Inhibition of TRPC5 using TRPC5-specific siRNA further inhibits the Wnt/β-catenin signaling pathway, reduces the induction of ABCB1 and reverses the resistance of HCT-8 and LoVo CRC cells to 5-FU (122).

Increased glycolysis is also an important cause of CSC drug resistance. The stem cell niche is an anoxic functional chamber that induces CSCs to reprogram for glycolysis (123). This effect promotes the expression of genes involved in apoptosis resistance, which enables the cells to survive in a hostile environment and avoid the influence of chemotherapy (123). Abnormal activation of Wnt/β-catenin signaling transduction is observed in a number of types of human cancer, which promotes glycolysis via the upregulation of solute carrier family 2, facilitated glucose transporter member 1 expression through its target gene c-Myc (124). The role of Wnt/β-catenin signaling transduction in promoting glycolysis is related to drug resistance (125)

Wnt/β-catenin signaling and ncRNAs. Unlike mRNA, ncRNAs lack the potential to encode proteins or peptides (126). ncRNAs are divided into microRNAs (miRNAs/miR) (20-24 nt) (127), long non-coding RNAs (lncRNA) (>200 nt) (128), extracellular RNAs (129), circular RNAs (crcRNA) (130) (100-10,000 nt) and intronic RNAs (131). Previous studies have demonstrated that lncRNAs and miRNA affect the chemotherapy sensitivity of CRC cells via regulation of the Wnt/β-catenin signaling pathway (Table II) (26,131,132). miRNAs regulate Wnt/β-catenin signaling by targeting Wnt ligands (133). Wnt10b is the downstream target of miR-148a, and miR-148a-overexpression inhibits Wnt10b expression and Wnt/β-catenin signaling activity, enhancing cisplatin resistance in SW480 CRC cells (26). Another study demonstrated that miR-103/107 prevents the ormation of the β-catenin complex by repressing Axis inhibition protein 2, which prolongs the duration of Wnt/β-catenin signaling and leads to the continuous induction of Wnt-responsive genes (131). Persistent effects of Wnt/β-catenin signaling stimulates multiple stem-like features in HCT116 and HT29 CRC cells, including chemical resistance (131). GSK3β is also an important component of the β-catenin complex. Inhibition of miR-224 upregulates GSK3β expression in Wnt/β-catenin signaling (134). Therefore, Wnt/β-catenin signaling activity and survivin (an apoptosis inhibitory gene) expression are inhibited, which reduces the adriamycin resistance of CRC SW480 cells (134,135). miR-506 also reverses the downstream target genes of MDR protein 1 (MDR1)/permeability-glycoprotein (P-gp)-mediated L-OHP resistance via inhibition of Wnt/β-catenin signaling (132). Wnt/β-catenin signaling also acts on some miRNAs to regulate the resistance to CRC (136-138). The P53 gene is a well-known tumor suppressor gene (136). Extensive research has reported that mutant p53 not only serves a key role in the transformation process of CRC, but also contributes to the invasiveness of CRC (137,138). Since the discovery of the P53 gene, the regulation of the p53 pathway has aroused interest (139). There is a negative regulatory relationship between wild-type P53 and MDR1, which enhances tumor cell sensitivity to 5-FU (140). Patients with mutant p53 genes are generally resistant to CRC therapies and have a poor prognosis (141). Kwak *et al* (142) reported that the ectopic expression of miR-552 enhances the resistance to drug-induced apoptosis and that miR-522 directly targets p53. Further genetic and pharmacological experiments showed that the Wnt/β-catenin signaling pathway and its main downstream target, c-Myc, increase the level of miR-552 (142). Therefore, Wnt regulates tumor suppressor genes via miRNAs, which leads to drug resistance. Wnt/β-catenin signaling also transactivates miR-372/373 (143). Overexpression of miR-372/373 enhances the stemness of CRC cells by enriching CD26/CD24, which promotes self-renewal, chemotherapy resistance and the invasion of CRC cells (144).

lncRNAs also affect the chemosensitivity of CRC by regulating the Wnt/β-catenin signaling (145-157). Han *et al* (145) used reverse transcription-quantitative PCR and functional testing of CRC tissues and cell lines and identified that lncRNA CRNDE activates the downstream targets β-catenin and TCF4 via binding to miR-181a-5p, which causes resistance to 5-FU and L-OHP. Xiao *et al* (146) demonstrated that lncRNA HOTAIR knockout and mir-203a-3p overexpression inhibited the Wnt/β-catenin signaling pathway, thereby inhibiting cell proliferation and reducing chemoresistance. Another study confirmed that lncRNA H19 increases proliferation via activation of the Wnt/β-catenin signaling, which promotes the resistance of HT-29 CRC to methotrexate (147). CRC-related lncRNA CCAL is another key regulator of CRC progression. Clinical data has demonstrated that patients with CRC with high CCAL expression have shorter overall survival rates, and promotes the resistance of CRC cells to L-OHP (148). A subsequent study showed that the CCAL promoter region possesses reduced methylation and increased acetylation in patients with CRC, which promotes its expression. Upregulated CCAL activates Wnt/β-catenin signaling via inhibition of activating enhancer-binding protein 2α, which upregulates MDR1P-gp and induces MDR (149).

Wnt/β-catenin signaling and TME. Previous studies of chemical resistance primarily focused on the tumor cells themselves, but TME has also received attention (150,151). Various cytokines secreted in the tumor microenvironment, including those from cancer-associated fibroblasts (CAFs), immune cells, inflammatory factors and chemokines, may interact with Wnt/β-catenin signaling to cause a heterogeneous distribution of β-catenin in cells (152-154). Clear colocalization between CAFs and tumor cells expressing nuclear β-catenin is observed in primary CRC samples (27). These findings indicate a close

Table II. ncRNAs regulate Wnt/β-catenin signaling in colorectal cancer drug resistance.

Author, year	ncRNAs	Dysregulation	Target	Mechanism	Function on drug resistance	(Refs.)
Shi *et al*, 2019	miR-148a	Upregulated	Wnt10b	Inhibiting the Wnt/β-catenin signaling	Increasing cisplatin-sensitivity	(26)
Chen *et al*, 2019	miR-103/107	Upregulated	Axin2	Prolonging the duration of Wnt/β-catenin signaling	Increasing drug resistance	(131)
Liang *et al*, 2017	miR-224	Upregulated	GSK-3β	Inhibiting Wnt/β-catenin signaling activity and survivin expression	Decreasing MDR	(134)
Zhou *et al*, 2017	miR-506	Upregulated	β-catenin	Inhibiting the expression of MDR1/P-gp of Wnt/β-catenin signaling	Enhancing L-OHP sensitivity	(132)
Kwak *et al*, 2018	miR-552	Upregulated	P53 gene	Activated by Wnt/c-Myc axis to inhibit p53	Increasing drug resistance	(142)
Wang *et al*, 2018	miR-372/373	Upregulated	/	Activated by Wnt/β-catenin signaling to enrich CD26/CD24	Increasing drug resistance	(144)
Han *et al*, 2017	CRNDE	Upregulated	miR-181a-5p	Activating β-catenin and TCF4	Causing resistance to 5-FU and L-OHP	(145)
Xiao *et al*, 2018	HOTAIR	Upregulated	miR-203a-3p	Activating Wnt/β-catenin signaling	Promoting cell resistance	(146)
Wu *et al*, 2017	H19	Upregulated	/	Activating Wnt/β-catenin signaling to activate proliferation	Promoting resistance to the MTX	(147)
Ma *et al*, 2016	CCAL	Upregulated	AP-2α	Activating Wnt/β-catenin signaling to upregulate MDR1P-gp expression	Inducing MDR	(149)

/ indicates that detailed information was not provided in the reference. miR, microRNA; ncRNAs, non-coding RNAs; Axin2, Axis inhibition protein2; GSK3β, glycogen synthetase 3β; MDR, multidrug resistance; 5-FU, 5-fluorouracil; MTX, methotrexate; CRNDE, long non-coding RNA CRNDE; TCF4, T cell factor4; H19, long non-coding RNA H19; HOTAIR, long non-coding RNA HOTAIR; CCAL, long non-coding RNA CCAL; AP-2α, activating enhancer-binding protein 2 α; MDR1P-gp, MDR1P-glycoprotein.

relationship between drug resistance and the tumor environment, especially CAFs (27). A study has demonstrated that exosomes are ideal carriers for the delivery of insoluble hydrophobic Wnt proteins (155). CAF-derived exosomes contribute to the secretion of Wnt ligands, promote the phenotypic recovery of differentiated CRC cells and the function of CSCs characteristics by carrying Wnt ligands. These ligands activate Wnt/β-catenin signaling to regulate Wnt activity (27). All of these actions contribute to drug resistance (Fig. 2). Hu *et al* (156) treated human SW480, SW620 and LoVo CRC cells with CAF-conditioned medium (CAFs-CM). The results showed that CAF secretes exosomes into CRC cells, which leads to a significant increase in miR-92a-3p levels in CRC cells. The increased expression of miR-92a-3p activates the Wnt/β-catenin pathway and inhibits mitochondrial apoptosis via direct inhibition of the tumor suppressor gene F-box/WD repeat-containing protein 7 and apoptosis regulator 1, which promotes the resistance of CRC cells to 5-FU/L-OHP (157). Similarly, periodin secreted by fibroblasts also activates Wnt/β-catenin signaling, which promotes differentiated CRC cells to restore CSCs characteristics and functions (158). DNA damage caused by chemotherapy promotes CAFs to produce numerous soluble factors, including Wnt16B and stable free radical polymerization 2 (SFRP2) (159). Wnt16B promotes tumor growth via activation of the canonical pathway in cancer cells, which reduces treatment sensitivity (159). SFRP2 acts as a synergistic effector that further enhances the drug resistance of Wnt16B/β-catenin (160). SFRP2 also participates in the non-canonical pathway, including angiogenesis, via activation of calcineurin/nuclear factor of activated T cells, cytoplasmic 3

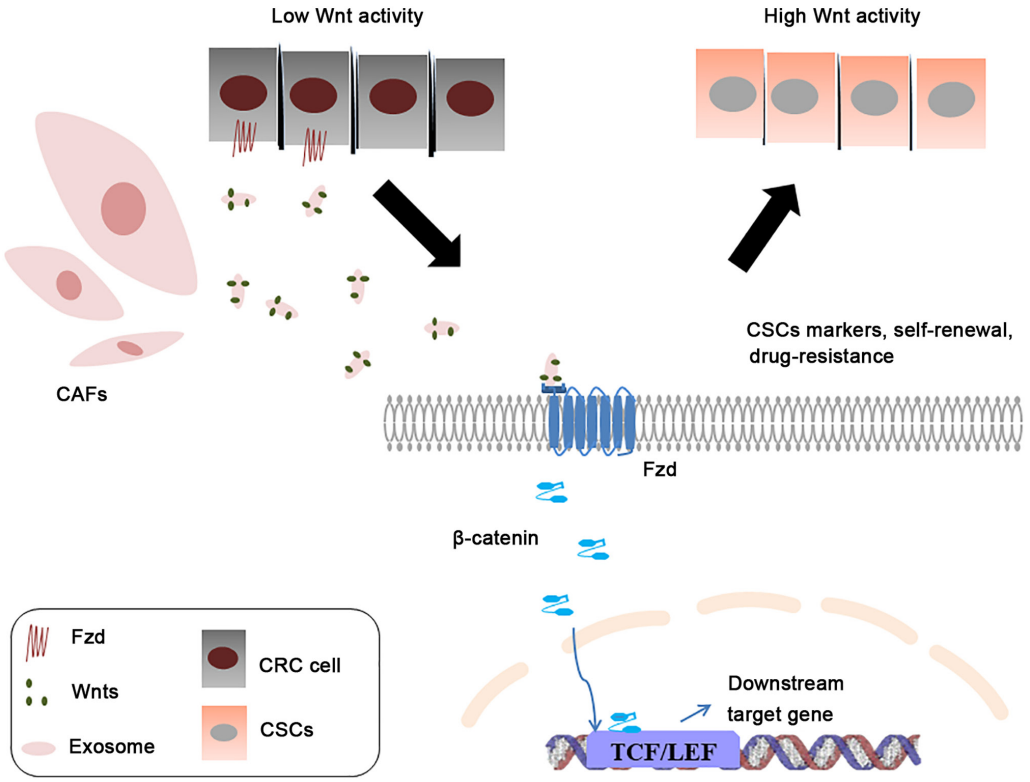

Figure 2. CAFs stimulate CRC cells to restore CSCs characteristics. CAFs are similar to CRC cells. CAFs secrete exosomes that carry Wnts, which stimulate differentiated CRC cells to restore their CSCs properties, including the expression of CSCs markers and increased Wnt activity. This process contributes to the development of drug resistance. CAFs, cancer-associated fibroblasts; CSCs, tumor stem cells; CRC, colorectal cancer; Fzd, Frizzled; TCF/LEF, transcription factor/lymphocyte-enhancing factor-binding factor; SFRP2, stable free radical polymerization 2.

signaling in endothelial cells, which indirectly promotes tumor development (Fig. 3) (160). Cancer-associated CAFs in CRC cells upregulate Wnt signaling-related genes, T-lymphoma infiltration and metastasis-inducing protein 1, and ultimately enhance the resistance of CRC by increasing the expression of tumor stem cells (161). BCL-9 serves a key role in promoting chemoresistance via the Wnt signaling pathway (162). Hypoxia in the TME leads to the upregulation of the key Wnt coactivator BCL-9 in a hypoxia-inducible factor-1α/2α-related manner (163). There is crosstalk between Wnt signaling and the hypoxia signaling pathway. This crosstalk synergistically acts on the development of CRC resistance (163).

Immunotherapy targeting TME is an important treatment for CRC (151). Programmed death-1 (PD-1) is a coinhibitory molecule on T cells. The interaction of PD-1 and its ligand PD-L1 affects the use of metabolic substrates and results in T cell failure and immune escape of tumor cells (164). Therefore, monoclonal antibodies that inhibit immune checkpoint receptors, including PD-1, are approved for the treatment of CRC (165). However, a significant proportion of patients remain clinically unresponsive to this treatment (166-168). The occurrence of this low sensitivity may be related to the reduction of pre-existing $CD8^+$ T cells that are negatively regulated by PD-1/PD-L1-mediated adaptive immune resistance (169,170). Notably, Wnt/β-catenin signaling results from the exclusion of $CD8^+$ T cells, which results in resistance to PD-1 inhibitors (171). Abnormal Wnt/β-catenin signaling activation in CRC significantly increases the infiltration of regulatory T cells (Tregs), effective inhibitors of $CD8^+$ T cells. Tregs promote resistance by negating the function of cytotoxic $CD8^+$ T cells (172). In addition to Tregs, dendritic cells (DCs) represent another important component of the immune cells that regulate tumor cell resistance (94). Tumor-resident $CD103^+$ DCs are necessary for the recruitment of $CD8^+$ T cells (171). Blockade of Wnt/β-catenin signaling in CRC cells increases DC infiltration, which leads to a significant increase in active $CD8^+$ T cells in CRC models and the consequent sensitizing of cancer cells to PD-1 inhibitors (172). Overall, these studies suggest that Wnt/β-catenin signaling mediates CRC resistance to immunotherapy via the regulation of immune cells in TME and provides a promising strategy for cancer therapy via the inhibition of Wnt/β-catenin signaling.

5. Wnt inhibitors reduce the resistance of CRC

A number of Wnt inhibitors avoid resistance to drug recognition and work in conjunction with current clinical front-line drugs for CRC. Several studies are focused on Wnt inhibitors in 5-FU resistance (56,94,173). Coumarin Esculetin (EST) reduces the release of E-cadherin, vimentin, β-catenin, c-Myc, cyclin D1, Wnt3a and VEGF, which inhibit Wnt/β-catenin signaling (174). *In vitro* and *in vivo* experiments have shown that EST combined with 5-FU enhances the sensitivity of HT-29, SW480, HCT-116 and Caco-2 CRC cells to 5-FU (174). Similarly, the use of the multikinase inhibitor regorafenib increases miR-34a levels and reverses 5-FU resistance and the cancer-initiating cell phenotype by degrading Wnt/β-catenin in HCT-116R and DLD-1R CRC cells (175). *In vitro* experimental

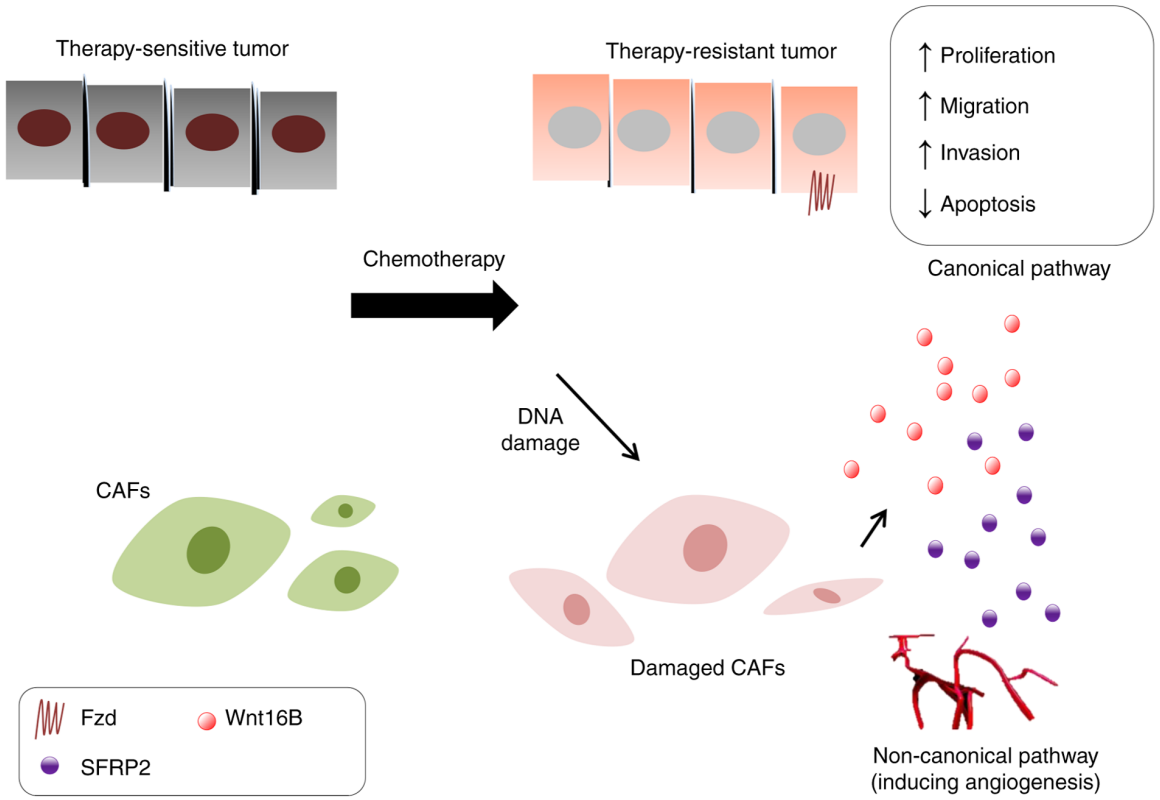

Figure 3. CAFs act on the Wnt pathway to promote tumor development. DNA damage caused by chemotherapy may result in CAF production of Wnt16B and SFRP2. Wnt16B promotes tumor growth via activation of the canonical pathway in cancer cells, which reduces treatment sensitivity. SFRP2 acts as a synergistic effector. SFRP2 may also participate in non-canonical pathways, such as angiogenesis, which indirectly promotes tumor development. CAFs, cancer-associated fibroblasts; Fzd, Frizzled; SFRP2, stable free radical polymerization 2.

results showed that the inhibition of the Wnt/β-catenin signaling cascade using the tankyrase inhibitor XAV939 overcomes the resistance of CRC cells carrying short APCs to 5-FU (176). The upregulation of guanylate-binding protein-1 enhances the killing effect of PTX in PTX-sensitive CRC cells and PTX-resistant CRC cells via inhibition of Wnt/β-catenin signaling in the CRC cell lines DLD-1, HT29, DiFi, T84 and HCT116 (177). Wu *et al* (178) reported that the synergistic use of cinnamaldehyde and L-OHP inhibits hypoxia-activated Wnt/β-catenin signaling, reverses EMT, actives CSC and diminishes the occurrence of L-OHP resistance. Patients with CRC with KRAS mutations are not sensitive to cetuximab and panitumumab (179). The potent and selective Wnt/β-catenin inhibitor KYA1797K activates GSK3β and degrades small β-catenin and Ras molecules to increase the sensitivity of tumors bearing KRAS mutations to cetuximab and panitumumab (180). These results indicate that Wnt signaling leads to chemoresistance in CRC. These studies highlight that the use of Wnt inhibitors affects the chemical sensitivity of cells to other drugs, which provides new approaches for the clinical treatment of CRC.

6. The role of Wnt/β-catenin signaling crosstalk in resistance

Activation of the checkpoint kinase 1 (CHK1) pathway enhances the drug sensitivity of CRC. He *et al* (181) performed microarray analysis on CRC-resistant cells and reported that Wnt signaling activation leads to 5-FU resistance via inhibition of the CHK1 pathway in TP53 wild-type cells, such as HCT-8. In addition, period circadian protein homolog 3 and dishevelled-3 are common members of the Wnt/β-catenin pathway and the Notch signaling pathway, which are involved in chemoresistance (182). Experimental inhibition or enhancement of the expression of these genes act on the Wnt/β-catenin signaling and Notch signaling pathways simultaneously to improve drug sensitivity (182,183). These findings highlight the fact that the Wnt/β-catenin signaling pathway and other signaling pathways exhibit crosstalk, synergistic and antagonistic effects in the occurrence of CRC resistance. Common members between these different signaling pathways should be identified as targets to overcome the occurrence of CRC resistance.

7. Conclusions

CRC is one of the most common malignant tumors in humans, and the survival rate remains low (1). Treatment resistance in CRC remains an unsolved problem (17). Generally, the chemical resistance mechanism of CRC is closely associated with CSCs, ncRNAs and the TME (19-22). Wnt/β-catenin signaling maintains the natural chemical resistance of CSCs and improves drug resistance via the promotion of ABC transporter and glycolysis in CSCs cells (25,119). The interaction between Wnt/β-catenin signaling and ncRNAs regulates the cell cycle and the expression of cancer-related genes (26,131,132). The TME enhances Wnt/β-catenin

signaling activity (150). Wnt/β-catenin signaling also mediates tumor immune escape in the TME (151). Therefore, examining the role of Wnt/β-catenin signaling in depth has great potential for therapeutic intervention. More studies should focus on the mechanism of CRC resistance, and robust preclinical drug testing of Wnt inhibitors as a single drug or in combination with CRC is required.

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Authors' contributions

GXZ, ZZS, LC and WJD collected the related literature and drafted the manuscript. QFY and DG participated in the design of the review and drafted the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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