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

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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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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 1) (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
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.

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.

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

| Author, year       | Gene | Function | Type of cancer                                                                 | (Refs.) |
|--------------------|------|----------|----------------------------------------------------------------------------------|---------|
| He et al, 2004     | Wnt1 | GOF      | Non-small-cell lung, prostate, CRC, gastric and ovarian cancer                    | (38-42) |
| Chen et al, 2004; Babaei et al, 2019 |      |          |                                                                                  |         |
| Jia et al, 2017; Bodnar et al, 2014 |      |          |                                                                                  |         |
| 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 | Wnt3 | GOF      | Lung, CRC and gastric cancer                                                     | (45-47) |
| Nie et al, 2019    | Wnt3a| LOF      | B cell precursor acute lymphoblastic leukemia, multiple melanoma and alveolar rhabdomyosarcoma | (48-50) |
| Thiago et al, 2010 |      |          |                                                                                  |         |
| Zimmerman et al, 2013 |      |          |                                                                                  |         |
| Annavarapu et al, 2013 |      |          |                                                                                  |         |
| Fox et al, 2013; Wang et al, 2014 | Wnt3a| GOF      | Malignant mesothelioma, breast and pancreatic cancer                             | (51-53) |
| Akaboshi et al, 2009 |      |          |                                                                                  |         |
| Zhao et al, 2019   | Wnt4 | GOF      | Cervical cancer                                                                  | (54)    |
| McDonald et al, 2009; Li et al, 2010 | Wnt5a| LOF      | Prostate and breast cancer, neuroblastoma, leukemia, squamous cell carcinoma of the esophagus, CRC and thyroid cancer | (55-59) |
| Ying et al, 2008   |      |          |                                                                                  |         |
| Kremeneskaja et al, 2005 |      |          |                                                                                  |         |
| Thiele et al, 2016; Kurayoshi et al, 2006 |      |          |                                                                                  |         |
| Kurayoshi et al, 2006 | Wnt5a| GOF      | Prostate, gastric, pancreatic, ovarian and non-small-cell lung cancer            | (59-62) |
| Kurayoshi et al, 2006; Huang et al, 2005 |      |          |                                                                                  |         |
| Bo et al, 2013     | Wnt5b| GOF      | Acute lymphoblastic leukemia                                                     | (63)    |
| Navarrete-Meneses et al, 2017 |      |          |                                                                                  |         |
| Stewart et al, 2014 | Wnt7a| LOF      | Non-small cell lung cancer, CRC, pancreatic and gastric cancer                   | (64,65) |
| Huang et al, 2015; Kirikoshi et al, 2002 | Wnt7b| GOF      | Breast cancer, adenocarcinoma and embryonal tumor                               | (43,65,66) |
| Vesel et al, 2017  |      |          |                                                                                  |         |
| Li et al, 2019; Li et al, 2017; Hsu et al, 2012 | Wnt10a| GOF      | CRC, ovarian cancer, renal cell carcinoma, esophageal and gastric cancer and papillary thyroid carcinoma | (67-71) |
| Kirikoshi et al, 2001; Dong et al, 2017 |      |          |                                                                                  |         |
| Wend et al, 2013; Chen et al, 2013 | Wnt10b| GOF      | Triple-negative breast and endometrial cancer and gastric carcinogenesis         | (72-74) |
| Saitoh et al, 2001 |      |          |                                                                                  |         |
| 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.
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 G₀ 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 potential channel short transient receptor potential channel 5 (TRPC5)-induces an increase in [Ca2+], 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 chemosensitivity 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 ornament 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 MDR1-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
The 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 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

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.
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 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
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 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.

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 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.

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Competing interests

The authors declare that they have no competing interests.

References

1. Keum N and Giovannucci E: Global burden of colorectal cancer: Emerging trends, risk factors and prevention strategies. Nat Rev Gastroenterol Hepatol 16: 713-732, 2019.

2. Rawp L, Sunkara T and Barsouk A: Epidemiology of colorectal cancer: Incidence, mortality, survival, and risk factors. Prz Gastroenterol 14: 89-103, 2019.

3. Arnold M, Sierra MS, Laversanne M, Soerjomataram I, Jemal A and Bray F: Global patterns and trends in colorectal cancer incidence and mortality. Gut 66: 683-691, 2017.

4. Marmol I, Sanchez-de-Diego C, Pradilla Diate A, Cerrada E and Rodriguez Yoldi MJ: Colorectal carcinoma: A general overview and future perspectives in colorectal cancer. Int J Mol Sci 18: 197, 2017.

5. Calvert PM and Fracht H: The genetics of colorectal cancer. Ann Intern Med 137: 603-612, 2002.

6. Angarita FA, Feinberg AE, Feinberg SM, Riddell RH and McCart JA: Management of complex polyps of the colon and rectum. Int J Colorectal Dis 33: 115-129, 2018.

7. Blank A, Roberts DE II, Dawson H, Zloke I and Lugli A: Tumor heterogeneity in primary colorectal cancer and corresponding metastases. Does the apple fall far from the tree? Front Med (Lausanne) 5: 234, 2018.

8. Dahmus JD, Kotler DL, Kastenberg DM and Kistler CA: The gut microbiome and colorectal cancer: A review of bacterial pathogenesis. J Gastrointest Oncol 9: 769-777, 2018.

9. Jayasekara H, English DR, Haydon A, Hodge J, Lynch BM, Rossett C, Williamson EI, Clendenning M, Southey MC, Jenkins MA, et al: Associations of alcohol intake, smoking, physical activity and obesity with survival following colorectal cancer diagnosis by stage, anatomic site and tumor molecular subtype. Int J Cancer 142: 238-250, 2018.

10. Mehta A and Patel BM: Therapeutic opportunities in colon cancer: Focus on phosphodiesterase inhibitors. Life Sci 230: 150-161, 2019.

11. Salonga D, Danenberg KD, Johnson M, Metzger R, Groschen S, Tsao-Wei DD, Lenz HJ, Leichman CG, Leichman L, Diasio RB and Danenberg PV: Colorectal tumors responding to 5-fluorouracil have low gene expression levels of dihydropyrimidine dehydrogenase, thymidylate synthase, and thymidine phosphorylase. Clin Cancer Res 6: 1322-1327, 2000.

12. Showalter SL, Showalter TN, Witkiewicz A, Havens R, Kennedy EP, Hucl T, Kern SE, Yeo CJ and Brody JR: Evaluating the drug-target relationship between thymidylate synthase expression and tumor response to 5-fluorouracil. Is it time to move forward? Cancer Biol Ther 7: 986-994, 2008.

13. Yaffe P, Osipov A, Tan C, Tuli R and Hendifar A: Review of systemic therapies for locally advanced and metastatic rectal cancer. J Gastrointest Oncol 6: 185-200, 2015.

14. Cunningham D, Humblet Y, Siena S, Khayat D, Bleiberg H, Santoro A, Bets D, Mueser M, Harstrick A, Verslype C, et al: Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. N Engl J Med 351: 337-345, 2004.

15. Van Cutsem E, Peeters M, Siena S, Humblet Y, Hendiliza A, Neyns B, Canon JL, Van Laethem JL, Maurel J, Richardson G, et al: Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer. J Clin Oncol 25: 1658-1664, 2007.

16. Hu T, Li Z, Gao CY and Cho CH: Mechanisms of drug resistance in colon cancer and its therapeutic strategies. World J Gastroenterol 22: 6876-6889, 2016.

17. Li YJ, Lei YH, Yao N, Wang CR, Hu N, Ye WC, Zhang DM and Chen ZS: Autophagy and multidrug resistance in cancer. Chin J Cancer 36: 52, 2017.

18. Thomas H and Coley HM: Overcoming multidrug resistance in cancer: An update on the clinical strategy of inhibiting p-glycoprotein. Cancer Control 10: 159-165, 2003.

19. Tredan O, Galmarini CM, Patel K and Tannock IF: Drug resistance and the solid tumor microenvironment. J Natl Cancer Inst 99: 1441-1454, 2007.

20. Wang MY, Qiu YH, Cai ML, Zhang CH, Wang XW, Liu H, Chen Y, Zhao WL, Liu JB and Shao RG: Role and molecular mechanism of stem cells in colorectal cancer initiation. J Drug Target 28: 1-10, 2020.

21. Liu X, Fu Q, Du Y, Yang Y and Cho WC: MicroRNA as regulators of cancer stem cells and chemoresistance in colorectal cancer. Curr Cancer Drug Targets 16: 738-754, 2016.

22. Fanale D, Barraco N, Listi A, Bazan V and Russo A: Non-coding RNAs functioning in colorectal cancer stem cells. Adv Exp Med Biol 937: 93-108, 2016.

23. Rahmani F, Avan A, Hashemly SM and Hassanian SM: Role of Wnt/beta-catenin signaling regulatory microRNAs in the pathogenesis of colorectal cancer. J Cell Physiol 233: 811-817, 2018.

24. Das PK, Islam F and Lam AK: The roles of cancer stem cells and therapy resistance in colorectal carcinoma. Cells 9: 1392, 2020.

25. Chikazawa N, Tanaka H, Tasaka T, Nakamura M, Tanaka M, Onishi H and Katano M: Inhibition of Wnt signaling pathway: Evidence for the existence of a Wnt/beta-catenin signaling in cisplatin-resistant colorectal cancer cells. Biomed Pharmacother 150: 150-161, 2019.

26. Shi L, Xi J, Xu X, Peng B and Zhang B: MiR-148a suppressed cell viability and migration via targeting WNT10b and modulating β-catenin signaling in cisplatin-resistant colorectal cancer cells. Biomed Pharmacother 109: 902-909, 2019.

27. Hu YB, Yan C, Mu L, Mi YL, Zhao H, Hu H, Li XL, Tao DD, Wu YQ, Gong JP and Qin JC: Exosomal Wnt-induced dedifferentiation of colorectal cancer cells contributes to chemotherapy resistance. Oncogene 38: 1951-1963, 2019.

28. Nusse R and Varmus HE: Many tumors induced by the mouse mammary tumor virus contain a provirus integrated in the same region of the host genome. Cell 31: 99-109, 1982.
Gene expression - Epigenetic profiling of MUTYH, KLF6, β-catenin and SNAIL expression in melanoma cells treated with TGFβ. PLoS One 8: e69593, 2013.

Zhou ET al: Wnt/β-catenin SIGNALLING IS THE TARGET OF DRUG RESISTANCE IN COLORECTAL CANCER.
et al: Secreted AGR2 promotes invasion of colorectal cancer cells. J Cell Biochem 119: 5913-5920, 2018.

Eidenaite E and Laurinavicius A: Significance of Notch and Wnt pathway in CD133-positive colon cancer stem-like cells. Chin J Cancer 29: 810-815, 2010.

Vaish V, Kim J and Shim M: Jagged-2 (JAG2) enhances Wnt signaling in colorectal cancer cell line HCT116. J Cell Biochem 119: 5913-5920, 2018.

Oncotarget 8: 53262-53275, 2017.

Toyama T, Lee HC, Koga H, Wands JR and Kim M: Noncanonical Wnt11 inhibits hepatocellular carcinoma cell proliferation and migration. Mol Cancer Res 28: 254-265, 2020.

Yin P, Wang W, Zhang Z, Bai Y, Gao J and Zhao C: Wnt signaling in human and mouse breast cancer. Focusing on Wnt ligands, receptors and antagonists. Cancer Sci 109: 3368-3375, 2018.

Barker N, van Es JH, Kuipers J, Kujala P, van den Born M, Cojzins M, Hagebarth A, Korving J, Begthel H, Peters PJ and Clevers H: Identification of stem cells in small intestine and colon by marker gene Lgr5, Nature 441: 108-112, 2006.

He X, Semenov M, Tamaoki K and Zeng X: LDL receptor-related proteins 5 and 6 in Wnt/beta-catenin signaling: Arrows point the way. Development 131: 1663-1677, 2004.

Bilec J, Huang YL, Davidson G, Zimmermann T, Cruciat CM, Bienz M and Niehrs C: Wnt induces LRPS signaling and promotes dishevelled-dependent LRPs phosphorylation. Science 316: 1619-1622, 2007.

Zarkou V, Galaras A, Giakountis A and Hatzis P: Crosstalk mechanisms between the WNT signaling pathway and long non-coding RNAs. Noncoding RNA Res 3: 42-53, 2018.

Hammond WS, Swaika A and Moody K: Pharmacologic resistance in colorectal cancer: A review. Ther Adv Med Oncol 8: 57-84, 2016.

Gheirad F, Bakhshandeh B, Teimoori-Toolabi L, Mehtara A, Ghadir M and Zeinali S: Noncanonical Wnt signaling in colorectal cancer cells treated with lapatinib as a common chemotherapeutic drug. Anticancer Drugs 25: 908-916, 2014.

Kobayashi S, Yamada-Oka H, Suzuki M, Natori O, Kato A, Matsubara K, Jau Chen Y, Yamazaki M, Funahashi S, Yoshida K, et al: LGR5-positive colon cancer stem cells interconvert with drug-resistant LGR5-negative cells and are capable of tumor reconstitution. Stem Cells 30: 2631-2644, 2012.

Dahal Laminche B, Jung SY, Yun J, Kang S, Kim DY, Laminiche S, Kim YJ, Park JH, Jang WB, Ji ST, et al: AGR2 is a target of canonical Wnt/beta-catenin signaling and is important for stemness maintenance in colorectal cancer stem cells. Biochem Biophys Res Commun 515: 600-606, 2019.

Li YS, Hsa HC, Tseng KC, Chen HC and Shen CJ: Lgr5 promotes cancer stemness and confers chemoresistance through ABCB1 in colorectal cancer. Biomed Pharmacother 67: 791-799, 2013.

Zhan T, Ambrosi G, Wandmacher AM, Rauscher B, Betje J, Rindtorff N, Haussler RS, Hinsenkamp I, Bamberg L, Hessling B, et al: MEK inhibitors activate Wnt signaling and induce stem cell plasticity in colorectal cancer. Nat Commun 10: 2197, 2019.

Wu W, Cao J, Ji Z, Wang J and Ding H: Co-expression of Lgr5 and CCK4 characterizes cancer stem-like cells of colorectal cancer. Oncotarget 7: 81144-81155, 2016.

Kobayashi S, Yamada-Oka H, Suzuki M, Natori O, Kato A, Matsubara K, Jau Chen Y, Yamazaki M, Funahashi S, Yoshida K, et al: LGR5-positive colon cancer stem cells interconvert with drug-resistant LGR5-negative cells and are capable of tumor reconstitution. Stem Cells 30: 2631-2644, 2012.

Zarin A, Iranshahi A, Matecki S, Casalino L, Sanz M, Aliyu R, et al: Targeting bispicin 4-Acetamidoquinol of noncanonical Wnt signaling in colorectal cancer organoids. J Immunother Cancer 7: 101, 2019.

Chang TC, Yeh CT, Abeady BO, Lin YC, Deng L, Rao YK, Huang CC, Lee WH, Wu AT, Hsiao M, et al: A noncanonical Wnt signaling axis links EMT and tumour microenvironment to promote colorectal cancer stem cells and chemoresistance. Oncogenesis 8: 13, 2019.

Prieiti-Vila M, Takahashi R, Usuba W, Kohama I and Ochiya T: Drug resistance driven by cancer stem cells and their niche. Int J Cancer 138: 2574, 2014.

Li L and Xie T: Stem cell niche: Structure and function. Annu Rev Cell Dev Biol 21: 605-631, 2005.

Liu H, Zhang W, Jia Y, Yu Q, Grau GE, Leng P, Ran Y, Yang Z, Deng H and Lou J: Single-cell clones of liver cancer stem cells have the potential of differentiating into different types of tumor cells. J Cell Death Dis 10: 137, 2016.

Daverey A, Drain AP and Kidambi S: Physical intimacy of breast cancer cells with mesenchymal stem cells elicits trastuzumab resistance through src activation. Sci Rep 5: 13744, 2015.

Kim JY, Lee HY, Park KK, Choi YK, Nam JS and Hong IS: CWP232228 targets liver cancer stem cells through Wnt/beta-catenin signaling: A novel therapeutic approach for liver cancer treatment. Oncoarget 7: 20395-20409, 2016.

Fei X, Robine S, Louvard D and Huelsken J: Wnt/beta-catenin is essential for intestinal homeostasis and maintenance of intestinal stem cells. Mol Cell 58: 755-759, 2015.
in colorectal cancer inhibits Stat3-mediated tumor growth and Moll UM: Therapeutic ablation of gain-of-function mutant p53. Bohnenberger H, Cetecì F, Greten FR, Dobbelstein M and Schulz-Heddergott R, Stark N, Edmunds SJ, Li J, Conradi LC, axis. Biochem Biophys Res Commun 482: 22‑27, 2017.

Song C, Lu P, Sun G, Yang L, Wang Z and Wang Z: miR‑34a and apoptosis and weakening of ADM drug resistance. Eur Rev Med Pharmacol Sci 50: e12341, 2017.

Cao J, Wang H, Liu W, Zhang H, Chen N, Li XL, Zhou J, Chen ZR and Liu S: miR‑506 enhances the sensitivity of human colorectal cancer cells. Biochem Pharmacol 85: 1257‑1268, 2013.

Zhou H, Lin C, Zhang Y, Zhang C, Zhang P, Xie X and Xu X: Tumor microenvironment and cancer therapy resistance. Cancer Lett 380: 205‑215, 2016.

Zhu AD, Diao LT, Xu H, Xiao ZD, Li JH, Zhou H and Qu LH: β‑Catenin/LEFI transactivates the miR‑371‑373 cluster that modulates the Wnt/β‑catenin-signaling pathway. OncoTargets Ther 10: 2969‑2983, 2017.

Wang LQ, Yu P, Li B, Guo YH, Liang ZR, Zheng LL, Yang JH, Xu H, Liu S, Zheng LS, et al: miR‑372 and miR‑373 enhance the stemness of colorectal cancer cells by repressing differentiation signaling pathways. Mol Oncol 12: 1949‑1964, 2018.

Han P, Li JW, Zhang BM, Lv JC, Li YM, Gu XY, Yu ZW, Jia YH, Bai XF, Li JF, et al: the InclRNA CRNDE promotes colorectal cancer cell proliferation and chemoresistance via miR‑181a‑5p‑mediated regulation of Wnt/β‑catenin signaling. Mol Cancer 16: 9, 2017.

Xiao Z, Qu Z, Chen Z, Fang Z, Zhou K, Huang Z, Guo X and Zhang Y: LncRNA HOTAIR is a prognostic biomarker for the proliferation and chemoresistance of colorectal cancer via MiR‑203a‑3p‑mediated Wnt/β‑catenin signaling pathway. Cell Physiol Biochem 46: 1275‑1285, 2018.

Wu KF, Liang WC, Feng L, Pang JX, Waye MM, Zhang JF and Fu WM: H19 mediates methotrexate resistance in colorectal cancer through activating Wnt/β‑catenin pathway. Exp Cell Res 350: 312‑317, 2017.

Deng X, Ruan H, Zhang X, Xu X, Zhu Y, Peng H, Zhang X, Kong F and Guan M: Long noncoding RNA CCAL transferred from fibroblasts by exosomes promotes chemoresistance of colorectal cancer cells. Int J Cancer 146: 1700‑1716, 2020.

Ma Y, Yang Y, Wang F, Moyer MP, Wei Q, Zhang Y, Yang Z, Liu W, Zhang H, Chen N, et al: Long non‑coding RNA CCAL regulates colorectal cancer progression by activating Wnt/β‑catenin signalling pathway via suppression of activator protein 2a. Gut 65: 1494‑1504, 2016.

Harahan D and Coussens LM: Accessories to the crime: Functions of cells recruited to the tumor microenvironment. Cancer Cell 21: 309‑322, 2012.

Sun Y: Tumor microenvironment and cancer therapy resistance. Cancer Lett 380: 205‑215, 2016.

Castellone MD, Teramoto H, Williams BO, Druey KM and Gutkind JS: Prostaglandin E2 promotes colon cancer cell growth through a Gs‑axin‑beta‑catenin signalling axis. Science 310: 1504‑1510, 2005.

Yang L, Lin C and Liu ZR: P68 RNA helicase mediates PDGF‑induced epithelial mesenchymal transition by displacing Axin from beta‑catenin. Cell 127: 139‑155, 2006.

Gupta GP and Massague J: Cancer metastasis: Building a framework. Cell 127: 679‑695, 2006.

Gross JC, Chaudhary V, Bartscherer K and Boutros M: Active Wnt proteins are secreted on exosomes. Nat Cell Biol 14: 1030‑1045, 2012.

Hu JL, Wang W, Lan XL, Zeng ZC, Liang YS, Yan YR, Song FY, Wang FF, Zhu XH, Liao WJ, et al: CAFs secreted exosomes promote metastasis and chemoresistance by enhancing cell stemness and epithelial‑mesenchymal transition in colorectal cancer. Mol Cancer 18: 91, 2019.

Huang Z, Chang W, Yuan J, Han Y, Tan X, Luo Y, Cai H, Liu Y, Gao X, et al: Periostin expression in intra‑tumoral stromal cells is prognostic and predictive for colorectal carcinoma via creating a cancer‑supportive niche. Oncotarget 7: 798‑813, 2016.

Sun Y, Campisi J, Higano C, Beer TM, Porter P, Coleman I, Trim M and Nebuloni PS: Treatment‑induced damage to the tumor microenvironment promotes prostate cancer therapy resistance through WNT16B. Nat Med 18: 1359‑1368, 2012.
159. Sun Y, Zhu D, Chen F, Qian M, Wei H, Chen W and Xu J: SFRP2 augments WNT16B signaling to promote therapeutic resistance in the damaged tumor microenvironment. Oncogene 35: 4321-4334, 2016.

160. Izumi D, Toden S, Ureta E, Ishimoto T, Baba H and Goel A: TIAM1 promotes chemoresistance and tumor invasiveness in colorectal cancer. Cell Death Dis 10: 267, 2019.

161. Takada K, Zhu D, Bird GH, Sukhdeo K, Zhao JJ, Mani M, Lemieux M, Carrasco DE, Ryan J, Horst D, et al.: Targeted disruption of the BCL9/β-catenin complex inhibits oncogenic Wnt signaling. Sci Transl Med 4: 148ra17, 2012.

162. Tan Z, Huang Q, Zang J, Teng SF, Chen TR, Wei HF, Song DW, Liu TL, Yang XH, Fu CG, et al.: HIF-1α activates hypoxia-induced BCL-9 expression in human colorectal cancer cells. Oncotarget 8: 25885-25896, 2017.

163. Li et al: Application of PD-1 blockade in cancer immunotherapy. Comput Struct Biotechnol J 17: 661-674, 2019.

164. Yaghoubi N, Soltani A, Ghazvini K, Hassanian SM and Hashemy S: PD-1/PD-L1‑dependent immune response in colorectal cancer. Biomed Pharmacother 110: 312-318, 2019.

165. Banjaran B: PD‑1/PD‑L1‑dependent immune response in colorectal cancer. Biomed Pharmacother 110: 312-318, 2019.

166. Zhao Q, Zhuang K, Han K, Tang H, Wang Y, Si W and Yang Z: Silencing DVL3 defeats MTX resistance and attenuates stemness via Notch signaling pathway in colorectal cancer. Pathol Res Pract 216: 152964, 2020.

167. Zhang F, Sun H, Zhang S, Yang X, Zhang G and Su T: Overexpression of PER3 inhibits self-renewal capability and chemoresistance of colorectal cancer stem-like cells via inhibition of notch and β-catenin signaling. Oncol Res 25: 709-719, 2017.