REVIEW

Tumor microenvironment involvement in colorectal cancer progression *via* Wnt/β-catenin pathway: Providing understanding of the complex mechanisms of chemoresistance

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Abstract

Colorectal cancer (CRC) continues to be one of the main causes of death from cancer because patients progress unfavorably due to resistance to current therapies. Dysregulation of the Wnt/β-catenin pathway plays a fundamental role in the genesis and progression of several types of cancer, including CRC. In many subtypes of CRC, hyperactivation of the β-catenin pathway is associated with mutations of the *adenomatous polyposis coli* gene. However, it can also be associated with other causes. In recent years, studies of the tumor microenvironment (TME) have demonstrated its importance in the development and progression of CRC. In this tumor nest, several cell types, structures, and biomolecules interact with neoplastic cells to pave the way for the spread of the disease. Cross-communications between tumor cells and the TME are then established primarily through paracrine factors, which trigger the activation of numerous signaling pathways. Crucial advances in the field of oncology have been made in the last decade. This Minireview aims to actualize what is known about the central role of the Wnt/β-catenin pathway in CRC chemoresistance and aggressiveness, focusing on cross-communication between CRC cells and the TME. Through this analysis, our main objective was to increase the understanding of this complex disease considering a more global context. Since many treatments for advanced CRC fail due to mechanisms involving chemoresistance, the data here exposed and analyzed are of great interest for the development of novel and effective therapies.

Key Words: Colorectal cancer; β-catenin pathway; Tumor stroma; Tumor microenvironment factors; Cancer progression; Drug resistance

Core Tip: Currently, there is a high probability of failure in treatments for the advanced stages of colorectal cancer (CRC). For this reason, it is necessary to obtain a better understanding of CRC biology in a more global context for the future design of novel therapeutic approaches. The effects of the Wnt/β-catenin signaling pathway and the tumor microenvironment (TME) on the progression and chemoresistance of this disease were separately described in several review articles. Therefore, herein we comprehensively analyze the complex mechanisms of CRC chemoresistance triggered by TME factors that impact Wnt/β-catenin signaling.

INTRODUCTION

Colorectal cancer (CRC) is the third most frequent malignant disease worldwide in both men and women[1,2]. Data provided by the World Cancer Research Fund International indicate that CRC incidence is growing, and the prevalence of this pathology is expected to increase by 60% in the next 15 years[3]. Among all cancer-induced deaths, the ones associated with CRC reach values of 8%-9%[4,5]. These statistics rely mainly on the fact that 20% of patients show metastasis (stage IV) at the time of diagnosis and the overall survival in these patients is low due to failure in the treatments[5,6]. To improve the response of these patients to therapy, it is necessary to expand the knowledge about the mechanisms that play a critical role in the development, progression and chemoresistance of CRC.

In 2015, Guinney *et al*[7] proposed a classification of colorectal tumors based on four consensus molecular subtypes (CMSs). Groups were defined according to certain parameters such as clinical, genetic and molecular characteristics (Figure 1): The CMS1 group, also designated microsatellite instability immune, is characterized by high microsatellite instability and immune response. The canonical subtype (CMS2) represents 37% of cases and presents hyperactivation of the Wnt and Myc signaling pathways. The CMS3 (metabolic subtype) is characterized by a marked dysregulation of metabolic pathways. Finally, the CMS4 (mesenchymal subtype) group exhibits hyperactivation of the transforming growth factor-β (TGF-β) pathway and a marked switch from the epithelial to mesenchymal transition (EMT)[7,8]. Remarkably, 90% of CRC cases present with aberrant activation of the canonical Wnt/β-catenin signaling pathway[9-11]. This pathway is strictly regulated in physiological conditions and modulates fetal development and homeostasis in adult tissues[11]. Briefly, in the absence of Wnt ligand, β-catenin is continuously phosphorylated in the cytoplasm by a destruction complex comprised of adenomatous polyposis coli (APC), axis inhibition protein (Axin), glycogen synthase kinase 3 (GSK3), and casein kinase 1. Once phosphorylated, β-catenin is ubiquitinated and degraded by the proteasome. When Wnt ligand binds to its receptor, the destruction of β-catenin stops, so this protein accumulates in the cytosol and then translocates to the nucleus. Finally, β-catenin binds to transcription factors from the T-cell factor/lymphoid enhancer factor (TCF/LEF) family and promotes the transcription of several genes[12]. There are several published research as well as review articles on the involvement of the Wnt/β-catenin pathway in CRC development, progression, and chemoresistance[10,13,14]. Furthermore, this pathway became an unquestionable target for novel therapies for CRC. Despite this, to date, there are no approved treatments or clinical trials for CRC based on targeting the Wnt/β-catenin pathway[15].

As extensively described in the open literature, hyperactivation of the Wnt/β-catenin pathway in CRC is directly associated with intrinsic causes such as mutations in the *APC* gene. This results in the nuclear accumulation of β-catenin and the induction of Wnt target genes that promote tumor progression[16]. In this contribution, we intend to analyze how Wnt/β-catenin aberrant activation can be induced or exacerbated by external causes.

In the last decade, the tumor microenvironment (TME) or tumor stroma has become relevant in the progression of CRC[17]. The TME is a niche composed of the extracellular matrix (ECM), a great variety of modified stromal cells and aberrant vasculature[9]. Intercellular communications between the tumor cells and the TME are mainly established through paracrine signaling[9,18]. These communications and factors are extrinsic and may directly affect CRC progression through the Wnt/β-catenin pathway. In this way, a wide range of novel therapeutic targets appears, expanding the possibilities of achieving effective treatments for CRC.
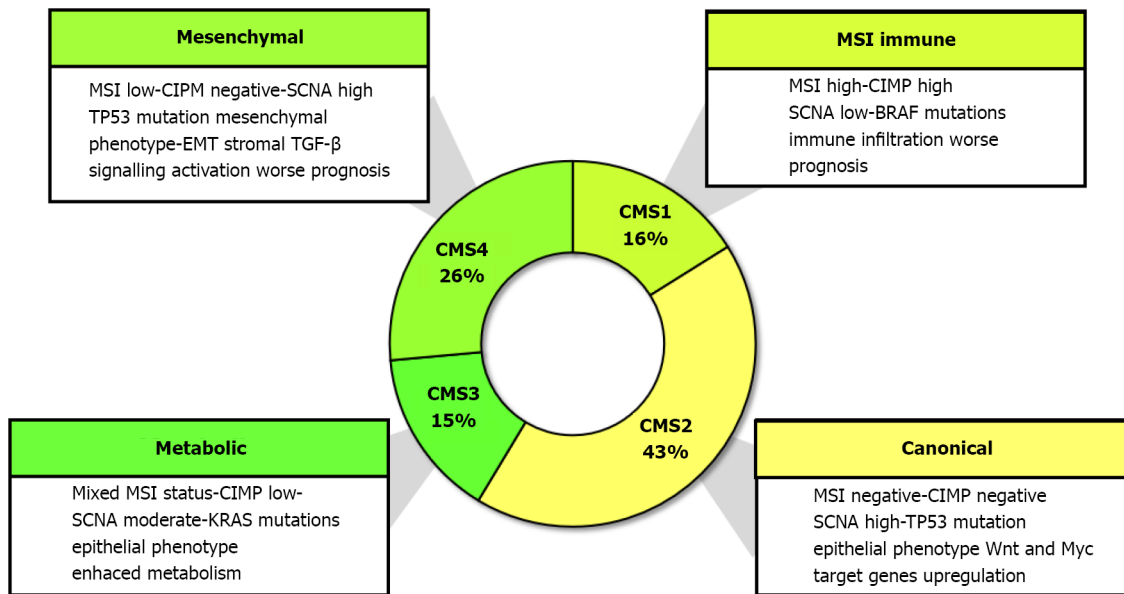
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Figure 1 Consensus molecular subtypes classification for colorectal tumors. BRAF: B-Raf proto-oncogene; CIMP: CpG island methylator phenotype; CNAs: Copy number alterations; EMT: Epithelial to mesenchymal transition; KRAS: Kirsten rat sarcoma 2 viral oncogene homolog; MSI: Microsatellite instability; TGF-β: Transforming growth factor-β; TP53: Tumor protein 53.

This work analyzed the available literature regarding the biomolecules associated with the TME that can modulate the Wnt/β-catenin signaling pathway in CRC cells, which allows a better understanding of the biological causes of the high morbidity and mortality of this pathology in a global context. Although antecedents of this particular analysis are registered in 2008[19], the enormous amount of information collected in recent years results in the emergence of new biomolecules, structures, and even processes related to the TME and the CRC cells that were previously unknown or unrelated. The comprehension of this information enables countless new possibilities for the development of new therapies for CRC.

DYNAMICS ESTABLISHED BETWEEN THE TME AND CRC CELLS

During CRC genesis, the TME and its associated signaling play a key role in tumor fate, since they facilitate the proliferation, invasion, metastasis, and chemoresistance processes. Specifically, the TME is composed of ECM proteins, mesenchymal stem cells, fibroblasts, cancer-associated fibroblasts (CAFs), endothelial cells (ECs), and tumor-infiltrating immune cells, with the last group comprising tumor-associated macrophages (TAMs), tumor-associated neutrophils, natural killer (NK) cells, regulatory T cells, myeloid-derived suppressor cells, and cytotoxic T lymphocytes (also known as CD8+ T cells), among others[5,20].

The TME cells and neoplastic cells continuously secrete and internalize factors that modulate the CRC development and contribute to the maintenance of the tumor ecosystem. These extracellular signals are schematized in Figure 2 and involve soluble proteins, insoluble proteins from the ECM, or compounds of variable nature loaded in vesicles[21]. Table 1 compiles the biomolecules well described in the literature that can be secreted by the TME cells and that allow communication with CRC cells. Some of these factors can travel freely through the tumor stroma space, whereas others are transported through membrane-bound vesicles known as extracellular vesicles (EVs)[22,23]. The EVs structure includes a lipid bilayer composed mainly of ceramide, cholesterol, sphingomyelin, phosphoglycerides, glycosphingolipids, phosphatidyl serine, phosphatidylethanolamine, mannose, N-linked glycans, polylactosamine, and sialic acid[22]. In recent years, EVs have acquired relevance as biological mediators in the communication between the TME and tumor cells. Concerning EVs related to CRC, their loads are considered prognostic factors or indicative of response to therapies. Recent studies have shown that EVs can carry large amounts of biomolecules from the TME cells to cancer cells and vice versa. Usual cargoes include cytokines/chemokines, angiogenic factors, ECM remodeling factors, and nucleic acids such as microRNAs (miRs), long non-coding RNAs (lncRNAs), and circular RNAs (cRNAs)[24-27]. Fluids from CRC patients such as plasma, saliva, and urine contain large amounts of secreted EVs. These molecules can stimulate or inhibit the expression of oncogenes and oncoproteins, thus affecting the phenotype of the neoplastic cells or altering the secretory profile of the TME cells[22,25,28]. Unlike cytokines and growth factors that act in the nearby cells, the EVs can influence both the primary colorectal tumor and

Table 1 Factors secreted by the tumor microenvironment and their role in colorectal cancer progression

Released/secreted components	Source, TME cell	Known effects in CRC	Ref.
Growth factors			
TGF-β	CAFs; TIICs[1]; MSCs[1]	Proliferation on tumor and stromal cells in late stages of tumorigenesis. EMT program and CSC-like traits. Metastasis, vasculogenesis and angiogenesis	[5,21,136]
BMPs	CAFs	Anti-tumor activity. Or pro-tumor activity, induce CSCs phenotype, EMT program and chemoresistance. Differentiation of colon CSCs	[5,137,138]
HGF	CAFs; TIICs; MSCs[1]	Invasion, metastasis and stemness	[21,54,139,140]
VEGF	ECs; CAFs; TIICs	Angiogenesis, invasiveness, metastasis	[104,140,141]
FGF	CAFs; MSCs	CAFs profiles. Tumor growth and metastasis	[142,143]
PDGF	CAFs	Tumor growth and metastasis	[144]
TNF-α	TIICs	Proliferation. Growth arrest and cancer cell death, angiogenesis and metastasis	[141,145]
Cytokines			
IL-1	TIICs	Angiogenesis and metastasis	[141,146]
IL-2	TIICs	Anti-tumor activity	[1,147]
IL-6	TIICs; MSCs; CAFs	Proliferation, angiogenesis and metastasis	[1,141]
IL-8	TIICs; MSCs	Tumor growth, angiogenesis and chemoresistance	[1,148]
IL-17	CAFs; TIICs	Anti-tumor or pro-tumor activity. Invasion and self-renewal of CSCs	[1,104,149]
IL-18	TIICs	Anti-tumor activity	[150]
IL-22	TIICs	Proliferation, invasion and stemness	[1,104]
IL-33	ECs; TIICs	Anti-tumor activity Suppresses tumorigenesis. Or pro-tumor activity. Angiogenesis and metastasis. Tumor growth through immunosuppressive microenvironment favoring	[1,104,151]
CCL2	TIICs; MCS	Tumor progression	[152]
CCL5	TIICs	Tumor progression. Acts on tumor cells and TAMs	[153]
CCL7	CAFs	Proliferation, invasion, and migration	[154]
CXCL12	CAFs; MSCs	Proliferation and invasion	[142,155]
PTHrP	Undefined TME cells	Proliferation, invasion, angiogenesis, migration and chemoresistance	[34,35,66,156,157]
Osteopontin	TIICs	Metastasis, stemness and chemoresistance	[85]
Prostaglandins			
PGs (like PGE2)	CAFs; TIICs; MSCs	Resistance to apoptosis, increased proliferation, angiogenesis and metastasis	[21,32]
Signaling pathways ligands			
NOTCH ligands (Jagged-1; Jagged-2; DLL4)	ECs	CSCs phenotype, EMT program and metastasis	[104,158]
WNT ligands (Wnt2, Wnt5)	CAFs	Invasion, metastasis and angiogenesis	[44,45,54]
Enzymes			
Serine proteinases (like MMPs)	TAMs; TANs	Invasion and angiogenesis	[140,145]
Immunosuppressive enzymes (like iNOS)	TIICs	Tumor progression. Inhibitory effect on the immune system, apoptosis of immune cells	[39]
Receptors			
TLRs	CAFs, ECs	Inflammatory-mediated tumorigenesis	[41,43]
RNA molecules			

miR-92a-3p	CAFs	CSCs phenotype, EMT program and chemoresistance	[24]
lncRNA H19	CAFs	Stemness and chemoresistance	[25]
miR-155	MSCs[1]	Migration	[21,159]
miR-375	MSCs[1]	Chemoresistance	[21,160]
cRNA	CAFs	Tumor progression or anti-tumor activity	[26,27]

[1]Factor's actions demonstrated for colorectal cancer (CRC). Their source from the tumor microenvironment (TME) has been identified for other types of cancer, but not for CRC. BMP: Bone morphogenetic CAFs: Cancer-associated fibroblasts; CCL: C-C motif chemokine ligand; cRNA: Circular RNA; CSCs: Cancer stem cells; CXCL: C-X-C motif chemokine ligand; ECs: Endothelial cells; EMT: Epithelial to mesenchymal transition; FGF: Fibroblast growth factor; HGF: Hepatocyte growth factor; IL: Interleukin; iNOS: Inducible nitric oxide synthase; lncRNA: Long non-coding RNA; miR: MicroRNA; MMPs: Matrix metalloproteinases; MSCs: Mesenchymal stem cells; PDGF: Platelet-derived growth factor; PGs: Prostaglandins; PTHrP: Parathyroid Hormone-related Peptide; TAMs: Tumor-associated macrophages; TANs: Tumor-associated neutrophils; TGF-β: Transforming growth factor-β; TIICs: Tumor-infiltrating immune cells; TLRs: Toll-like receptors; TNF-α: Tumor necrosis factor-α; VEGF: Vascular endothelial growth factor.
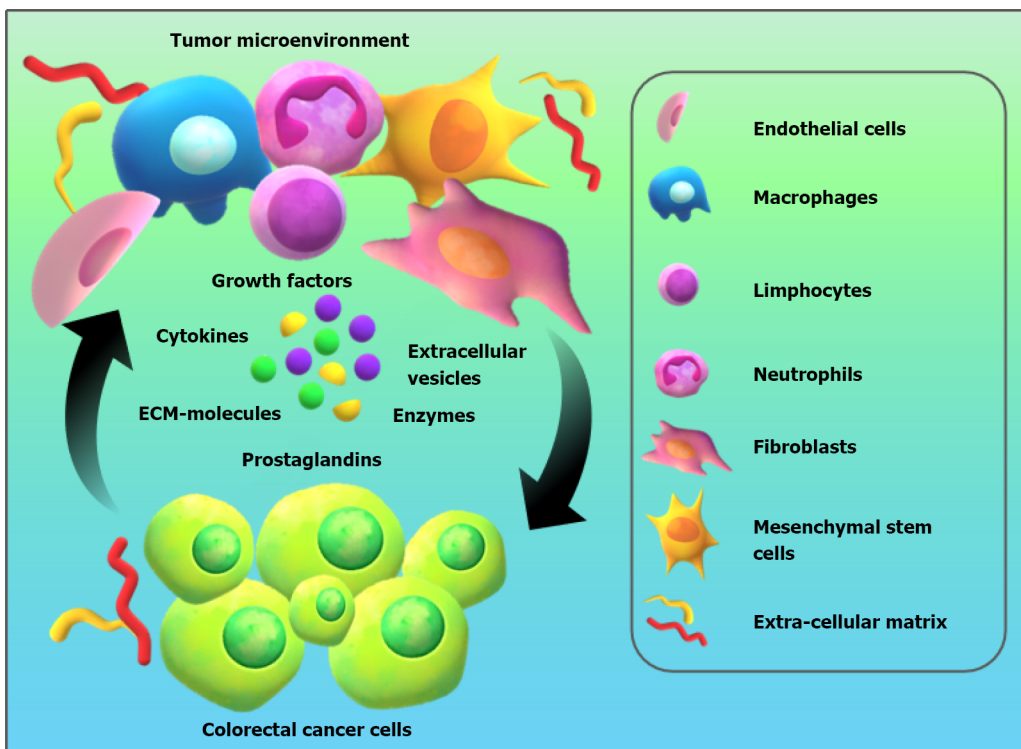
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Figure 2 Extracellular signal molecules secreted by the tumor microenvironment and neoplastic cells. The traffic of soluble and insoluble factors allows crosstalk between tumor cells and their environment modulating colorectal cancer development and progression.

metastatic niche remotely[22,29]. For instance, analysis of the plasma from CRC patients revealed that EVs are directly linked to the establishment of liver proinflammatory phenotype and liver metastasis, with this effect mediated by the modulation of macrophages by EVs[30]. The correlation between CD8+ T cell activation and high EVs concentrations in plasma has also been demonstrated, thus showing the role of EVs in the modulation of the immune response in CRC[31]. In conclusion, EVs have become a new source of therapeutic targets for CRC[22].

On the other hand, the soluble molecules that are directly secreted to the biological fluids exert their actions locally and participate in the communication between the tumor and the microenvironment. These factors are prostaglandins, cytokines, and other paracrine factors, which have distinctive modes of action. Prostaglandins and cytokines act especially as immunomodulators, by promoting or inhibiting the progression of CRC[1,32,33]. Growth factors such as TGF-β, vascular endothelial growth factor (VEGF), and EGF promote the transformation and development of neoplastic cells by inducing proliferation, invasion, and migration responses and also by affecting the TME[21]. In previous works *in vitro* using two CRC cell lines with different grades of aggressiveness, we demonstrated that parathyroid hormone-related peptide (PTHrP) acts as a paracrine factor by inducing the survival, proliferation, migration, cell cycle progression, angiogenesis, and EMT program. Moreover, our *in vivo* studies in CRC

tumor xenografts revealed that the intratumor administration of PTHrP modulates the expression of several tumorigenic markers, which are involved in the same cell responses observed *in vitro*[5,34-37].

Other proteins with different functions were studied in relation to CRC and the TME. In recent years, it has been reported that both neoplastic cells and TME cells can synthesize and secrete enzymes that participate in tumorigenesis. Muñoz-Galván *et al*[38] demonstrated that phospholipase D2 (PLD2) enzyme is overexpressed and secreted by CRC cells. PLD2 in the extracellular space modulates the phenotype and secretory profile of CAFs, thus contributing to promote stemness in tumor cells[38]. Other enzymes such as nitric oxide synthase are capable of inducing immunomodulatory effects[39]. Moreover, enzymes present in the TME, such as metalloproteases, enable the invasion and migration of cancer cells[39]. These enzymes act mainly by altering the structure and function of the ECM, thus allowing the activation of other factors that amplify the pro-tumor signals[40]. Receptor proteins such as Toll-like receptors (TLRs) play a fundamental role in maintaining epithelial barrier homeostasis in the gut and mediating inflammatory and immune responses[41]. TLRs are also expressed in fibroblasts and ECs in the TME and in CRC cells. The dysregulation in TLR pathways is associated with inflammation-driven carcinogenesis[42]. In response to this evidence, currently, there are clinical trials that include TLRs agonists for the treatment of CRC (www.clinicaltrials.gov)[41,43].

The abovementioned factors generally exert their effects by modulating several signaling pathways in the tumor[1,44-46]. In accordance with the focus of this contribution, in the next sections, we further discuss which of these biomolecules participate in aberrant activation of the β-catenin signaling pathway in CRC, and how these findings have provided new opportunities for the development of more efficient therapies.

TME FACTORS AND CONDITIONS THAT MODULATE THE WNT/β-CATENIN PATHWAY IN CRC

It is clear that the signaling triggered by factors that mediate the communication between TME and CRC cells is of great importance. Since Wnt/β-catenin is involved in most of the processes related to CRC genesis and progression[8,47], in this section we focus on the factors from the TME able to modulate this pathway. Figure 3 schematizes the complex interrelationships between the TME and CRC cells that lead to the activation of β-catenin and the consequent effects on disease progression.

Other β-catenin regulation, independently of the destruction complex actions described in the introduction section, involves phosphorylation by other kinases in different amino acids, such as Ser-552 and Ser-675, resulting in the stabilization and nuclear accumulation of this protein[48]. Mutations in the gene that encodes the β-catenin protein (*CTNNB1* gene) will produce structural alterations and its consequent hyperactivation and nuclear accumulation, events directly associated with CRC genesis and progression[7,49]. Voorneveld and collaborators[50] demonstrated that nuclear β-catenin is found predominantly in cells at the invasive front of CRC tumors. Other investigations have proven that the signals that exacerbate aberrant β-catenin function independently of others than those produced by the tumor can come from the TME[44,51].

Activation of the Wnt pathway by TME factors was initially studied a decade ago. Vermeulen and colleagues showed that CAF-derived hepatocyte growth factor (HGF) activates Wnt/β-catenin signaling and subsequently the clonogenicity in cancer stem cells (CSCs) isolated from CRC patients that were transiently transfected with TCF/LEF luciferase reporter vector. Moreover, HGF restored the CSC phenotype in more differentiated tumor cells both *in vitro* and *in vivo*[52]. Essex and collaborators recently replicated these studies, emphasizing the relevance of this pathway and the interaction of tumor cells with their stroma, and in the promotion and development of CRC[53]. As stated in Table 1, various Wnt ligands are secreted mostly by CAFs[44,45,54,55]. A recent study confirmed that Wnt2 acts in an autocrine manner, generating morphogenetic changes in fibroblasts and contributing to the invasive and metastatic capacity of CRC-derived cells[44]. *In vitro* experiments revealed that the treatment of DLD1 and HCT116 cells (both derived from CRC) with conditioned medium obtained from CAFs transfected with small interfering RNA targeting Wnt2, significantly decreased cell invasion and migration[45]. It is of clinical relevance that these ligands are overexpressed in the tumor stroma of CRC patients[45,53]. Moreover, the aberrant expression of Wnt ligand is correlated with a worse prognosis [44]. EVs play a key role in activating Wnt signaling in CRC. On the one hand, EVs can transport mutant β-catenin and activate the Wnt signaling pathway in the recipient cells, thus promoting CRC progression[56]. Regarding the effects of EVs on TME cells, Hu and colleagues demonstrated *in vitro* that fibroblast-derived exosomes (one type of EVs) promote the tumor growth of CSCs upon treatment with 5-fluorouracil (5-FU) or oxaliplatin (OXA)[57]. Further investigations of the same group in subcutaneous xenografts achieved through HT-29 CRC-derived cells and fibroblast co-implantation demonstrated that stromal fibroblasts can secrete exosomes loaded with Wnt ligands. Once these exosomes interact with differentiated CRC cells, Wnt ligands induce the phenotypic reversion of CRC cells to CSCs, which includes features such as the expression of CSCs markers and elevated Wnt activity [57].
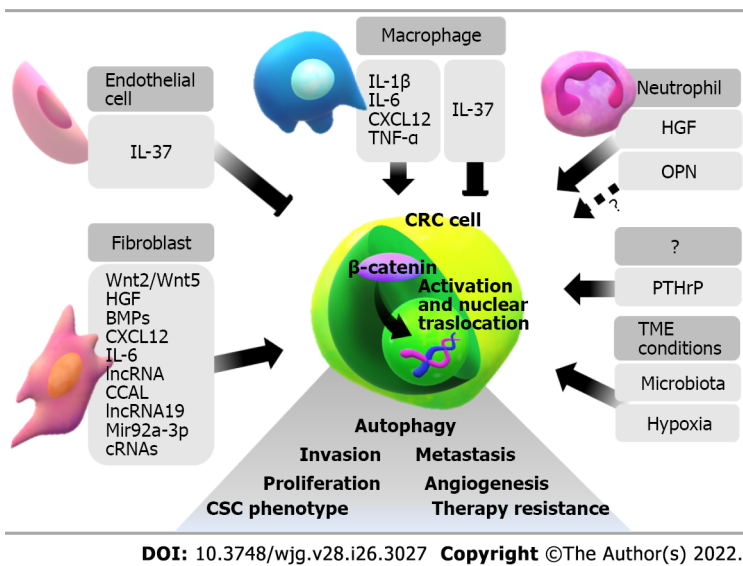
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Figure 3 Influence of tumor microenvironment-derived factors in the activation of β-catenin pathways. Several cytokines, growth factors, and small nuclei acid molecules secreted by stromal cells induce aberrantly activation of β-catenin and its nuclear translocation in colorectal cancer (CRC) cells promoting events associated with an aggressive phenotype of the tumor cells. Il-37 represses the expression of β-catenin and its transcriptional activity. Osteopontin is statistically associated with the expression of β-catenin in CRC and is known to induce its activation in other types of cancer. More studies are necessary to confirm positive feedback between the secretion of this tumor microenvironment (TME) factor and β-catenin signaling pathways in CRC. In addition to these factors, the microbiota and the hypoxia in the TME, also participate in the modulation of β-catenin activation. This figure is original for this work. BMP: Bone morphogenic protein; CCAL: Colorectal cancer-associated lncRNA; cRNA: Circular RNA; CXCL: C-X-C motif chemokine ligand; HGF: Hepatocyte growth factor; IL: Interleukin; lncRNA: Long non-coding RNA; OPN: Osteopontin; PTHrP: Parathyroid Hormone-related Peptide; TNF-α: Tumor necrosis factor-α; Wnt: Wingless protein.

Hypoxia is a prevalent condition in the solid tumor TME, which involves oxygen pressures of less than 5-10 mmHg. The hypoxic TME can deeply influence CRC, and these effects may be mediated by β-catenin. For instance, it was found *in vitro* that Wnt/β-catenin signaling is responsible for the hypoxia-induced self-renewal of colorectal stem cells[58]. Furthermore, Huang and collaborators observed that hypoxic CRC cells can secrete exosomes enriched with Wnt4 Ligands. These exosomes can activate β-catenin signaling in normoxic CRC cells and stimulate prometastatic behaviors such as cell migration and invasion[59]. In another work, the authors demonstrated that Wnt4-loaded exosomes secreted by the tumor cells promoted angiogenesis through the proliferation and migration of ECs. These effects were induced in conditions of hypoxia and mediated by the activation of Wnt/β-catenin signaling[60].

Autophagy is a physiological process through which normal cells degrade intracellular components to maintain cellular homeostasis. It is postulated as an alternative to cell death when the apoptotic machinery fails and is associated with both CRC and the TME, with controversial findings[61-63]. TME hypoxia induces autophagy and also activates several tumor escape mechanisms[62]. Some of the molecular mechanisms involved in the modulation of autophagy are phosphoinositide 3-kinases (PI3K)/protein kinase B (also known as Akt)/mammalian target of rapamycin, TGF-β, Notch, and Wnt/β-catenin signaling[63]. According to evidence, autophagy induced in the early stages of tumor development prevents the infiltration of immune cells as well as tumor cell death. Autophagy can also promote tumor progression in the advanced stages of the disease[63]. On the other hand, it has been reported that the relationship between autophagy and increased lymphocytic infiltration in the TME is mediated by the autophagy-related protein Vps34 in CRC. The modulation of this autophagy-related protein would improve the efficacy of immunotherapies[64]. However, it is still necessary to conduct additional studies on the interrelationship between the Wnt/β-catenin signaling pathway and autophagy, and which TME factors can mediate these events in CRC.

Because about 90% of patients with CRC present with mutations in genes associated with the Wnt pathway[65], more efforts have been made to identify other molecules with the ability to regulate β-catenin. In line with this evidence, our research group also reported interesting results regarding the participation of PTHrP in the activation of signaling pathways associated with β-catenin. Our published data showed that the exposition of cells derived from colorectal adenocarcinoma, to exogenous PTHrP increases β-catenin expression and upregulates cyclin D1 and c-Myc oncogenes with the concomitant cell proliferation induction[66]. Regarding the role of this cytokine in the TME, we demonstrated *in vitro* that tumor conditioned media from PTHrP-exposed CRC cells promotes pro-angiogenic characteristics in the stromal EC line HMEC-1 through VEGF modulation[35]. In addition, we recently found that PTHrP modulates the protein expression and secretion from the HMEC-1 cells of secreted protein acidic and cysteine-rich, a TME factor involved in the EMT program. This event promotes molecular and morphological changes associated with EMT in cells derived from CRC[36]. In this context, we believe that cross-communication may be initially established through overexpression and secretion of PTHrP

by the tumor, which in turn affects the behavior of neoplastic cells and TME cells inducing the subsequent release from them of this cytokine and other factors. More studies are needed to elucidate which stromal cells can secrete PTHrP and participate in the modulation of the β-catenin pathway. Several authors have also described the relationship between PTHrP and activation of the β-catenin signaling pathway in other types of cancer. In prostate cancer-derived cells, PTHrP downregulates the Wnt inhibitor, DKK1, promoting aberrant activation of this pathway[67]. Other research has shown that PTHrP modulates activation of the canonical Wnt/β-catenin signaling in the mammary mesenchyme [68]. Moreover, Johnson and collaborators reported that Wnt activation promotes PTHrP expression in breast and lung tumor cells[69].

Tumor small and long non-coding RNAs are other factors transported by EVs, which are also involved in the modulation of β-catenin signaling. Colorectal cancer-associated lncRNA (CCAL) and H19 (lncRNA19) expressed by CAFs are capable of stimulating aberrant activation of β-catenin in tumor cells[9,25]. Besides, the overexpression of miR-103 and miR-107 has been detected in the plasma and tumor tissue of patients with CRC[70]. In HCT116 and HT29 cell lines, miR-103/107 overexpression enhanced β-catenin activity and its nuclear translocation. These molecules act by inhibiting Axin2, a negative regulator of the Wnt/β-catenin pathway, and in this way, β-catenin is stabilized and its activation is prolonged[70]. Another study showed that miR-92a-3p secreted by CAFs, induces β-catenin nuclear translocation and the expression of target genes related to stemness, the EMT program, and chemoresistance in the human CRC cell lines SW480, SW620, and LOVO. Moreover, the high expression of exosomal miR-92a-3p in serum predicts metastasis and chemotherapy resistance in CRC patients[24]. The overexpression of miR-100, miR-125b, miR-27a, miR-135, and MIR100HG in CRC tumors modulates the canonical Wnt pathway, promoting events such as proliferation and invasion[71,72].

In the last decade, research on small non-coding RNA molecules has focused on cRNAs. Increasing studies have shown that these molecules intervene in the development and progression of various types of tumors including CRC[73]. Results obtained by Zhang *et al*[73] show that circAGFG1 activates the Wnt/β-catenin pathway in SW480 and HCT116 cells promoting the transcription of the CTNNB1 gene. Two years earlier, Fang and his group revealed that circ_100290 promotes CRC progression through activation of the Wnt/β-catenin pathway[74]. Other cRNAs involved in the activation of this signaling pathway in CRC are Hsa_circ_0005075[75], circMTO1[76] and Circ-PRKDC[72]. On the other hand, cRNAs such as circPRKDC and cirITCH act by inhibiting the activity of the β-catenin pathway[77,78]. The action of most of these molecules is mediated by miRNAs[26,79].

HGF and its receptor RTK Met are associated with β-catenin-related pathways in CRC cells, promoting a CSC phenotype, metastasis, and drug resistance[46,51,80,81]. Other factors including tumor necrosis factor-α (TNF-α) also stimulate the main regulatory mechanism of β-catenin activation in CRC cells. Wei and colleagues demonstrated that under TNF-α action, the CSCs derived from the HT29 cell line increase the survival rate and their invasive capacity *via* the Wnt pathway. These actions are mediated by the modulation of β-catenin related proteins expression, such as c-Myc, cyclin D1, E-cadherin, and vimentin, which are cell cycle regulators associated with the stimulation of cell proliferation and/or the progress of the EMT program[82]. Molecules released from tumor cells including PLD2, modify the secretome of CAFs by promoting the release of the following factors: Macrophage migration inhibitory factor (MIF), HGF, and CCL2. The results shown in this article confirm that the treatment of CRC-derived cells (HCT116 and LS180) with these three factors induces the activation of the Wnt/β-catenin signaling pathway. The authors of this work observed a reduction of β-catenin phosphorylation together with an increase in its total expression after treatment with CCL2, HGF, and MIF, as well as a decrease and an increase in the expression of Axin1 and c-Myc, respectively, consistent with Wnt activation. This research also demonstrated that gene transcription induced by the Wnt signaling pathway correlates with high expression of PLD2 and CAFs-derived factors in CRC patients [38].

Osteopontin (OPN) is another factor that plays an important role in the regulatory mechanism of β-catenin. It is a glycoprotein synthesized by a great variety of cells and is overexpressed in CRC. This protein is capable of activating β-catenin *via* Akt and subsequently GSK3β, or by recruiting and activating mitogen-activated protein kinase (MAPK)[83,84]. Youssef and Osman analyzed tumor samples and found an association between the expression of nuclear OPN/β-catenin and markers related to poor prognosis in CRC[85]. In the last decade, an association has also been established between OPN expression and the activation and nuclear translocation of β-catenin in other types of cancer[83,84]. Recent research has shown that this protein is a target gene of the Wnt pathway[86] and in these cases, positive feedback from the system can be generated. Based on the evidence analyzed in the previous lines, positive feedback is highly probable between OPN secretion and the modulation of the Wnt/β-catenin pathway in CRC.

Other cytokines and growth factors released by the TME cells promote activation of the canonical Wnt pathway in cells derived from human CRC[87]. Bone morphogenetic proteins (BMPs) are cytokines closely linked to angiogenesis, EMT program, and induction of CSCs[88]. Voorneveld and colleagues transfected HCT116, HT29, LS174T, RKO, and SW480 cells with the BMPR2 plasmid, increasing BMP signaling. Hyperactivation of this pathway only downregulated Wnt signaling in HCT116 and LS174T cells, both were SMAD4-positive and had wild type p53. In the remaining cell lines, the Wnt pathway was activated by BMP signaling. This work demonstrated that modulation of Wnt/β-catenin signaling

by the BMP pathway is dependent on SMAD4 and p53 status[5,50]. Regarding the role of interleukins (ILs), neoplastic cells promote the release of IL-1β, mainly from TME macrophages. In HCT116 cells, this cytokine induces β-catenin activation and consequently the expression of target genes, through nuclear factor kappa B (NF-KB)/Akt signaling pathway[87,89]. IL-6 secreted by TME cells induces activation of the Wnt/β-catenin pathway through the signal transducer and activator of transcription 3/extracellular signal-related kinase (ERK) pathway favoring the promotion of the aggressive phenotype of SW48 cells [90]. Chemokines such as C-X-C Motif Chemokine Ligand 12 (CXCL12) are overexpressed in CRC. Song *et al*[91] showed that the increased expression of this cytokine and its receptor (CXCR4) in tumor cells induces activation of the canonical Wnt pathway, possibly mediating the processes of proliferation, survival, and invasion[91]. However, not all cytokines act by promoting aberrant activation of the Wnt pathway. IL-37 mainly expressed by TAMs[92] has been observed to inhibit the proliferation, migration, and CSC phenotype by directly repressing the expression of β-catenin and consequently its translocation to the nucleus[49].

Bacteria, fungi, and viruses constitute the microbiota residing within the gastrointestinal tract. However, the gut microbiota and their metabolites can be altered in the TME and directly influence CRC progression[93,94]. Various bacteria have been implicated in these processes by modulating the β-catenin pathway. *Fusobacterium nucleatum* is a CRC inductor and suppressor of NK cell activity[93,95] Recently, it was reported that *F. nucleatum* can stimulate annexin A1 protein, specifically expressed in CRC cells. Then annexin A1 can induce β-catenin nuclear accumulation and finally the exacerbation of CRC cell proliferation[96]. On the opposite side, as extensively analyzed by Li *et al*[93] in their review article, other bacteria could be beneficial for CRC treatment or its prevention. For example, *Lactobacillus* and *Clostridium butyricum* are probiotics that have inhibitory effects on CRC progression *via* modulation of the β-catenin pathway[93]. This background shows that the complex interrelations between tumor cells and their microenvironment (including the microbiota) involve the participation of one of the most outstanding signaling pathways in the promotion and development of CRC, the β-catenin pathway. Therefore, it is important to consider these phenomena in the development of new treatments that focus on inhibiting or silencing the activators/exacerbators of this pathway.

ROLE OF β-CATENIN AND THE TME IN THE CHEMORESISTANCE OF CRC

Among the most used chemotherapeutic drugs, approved as first- and second-line adjuvants in CRC, are 5-FU, irinotecan (CPT-11), OXA, capecitabine, and leucovorin[97,98]. Depending on the CRC subtype, these drugs are also used in combination with monoclonal antibodies, such as bevacizumab or cetuximab[5]. On certain occasions, signs of a poor prognosis appear. Therefore, neoadjuvant or adjuvant chemotherapy must be implemented[99]. Despite this, patients with advanced grades of metastatic disease continue to lag far behind in successful treatment. One of the main causes of failure in treatment is the chemoresistance observed in about half of patients with CRC[99,100]. In this regard, the cell responses that mediate drug resistance are associated with hypoxic conditions, autophagy, induction of the CSC phenotype, and the EMT program[101,102]. At the molecular level, the development of drug-resistant tumors involves alterations of Wnt/β-catenin among other important signaling pathways such as Hedgehog and Notch. It also includes disturbances in the expression of anti-apoptotic proteins, the overexpression of drug transporters of the ATP-binding cassette (ABC) family, increased aldehyde dehydrogenase 1 enzyme activity and also the release of factors from the TME[99, 103]. Regarding the Wnt pathway, its aberrant activation involves induction of the CSC phenotype, the EMT program, the expression of proteins from the ABC family and factors from the TME, all of these events being related to drug resistance[99]. Furthermore, various biological mediators released by stromal cells are capable of inducing chemoresistance through the Wnt/β-catenin pathway in tumor cells[9,25,104]. In this regard, *in vitro* studies made by Hu and colleagues revealed that miR-92a-3p secreted from CAFs activates the Wnt/β-catenin signaling, decreasing the sensitivity to the combination of 5-FU/OXA in SW480, SW620, and Lovo CRC-derived cells[24]. Moreover, *in vivo* studies have demonstrated that exosomes secreted by fibroblasts can load Wnt ligands, thus promoting CSC features and resistance to 5-FU or OXA. On the contrary, the inhibition of Wnt release reverted the observed effects[57]. CAFs are capable of inducing drug resistance by transferring small nucleic acid molecules such as H19 or CCAL lncRNA and activating β-catenin in neighboring cells[25]. H19 lncRNA can also trigger autophagy *via* SIRT1 and consequently induce resistance to 5-FU in CRC cells[105]. Other miRNAs such as miR-27[106], miR-103, and miR-107 decrease the sensitivity of HCT116 cells to 5-FU and OXA, through hyperactivation of the β-catenin pathway[9]. Zhou and colleagues reported that the inhibition of the Wnt/β-catenin signaling pathway by the overexpression of miR-506 decreases the chemoresistance response of HCT116 cells to OXA. The mechanism that explains this effect is that the gene and protein expression of the transporter of the ABC family and multidrug resistance protein 1/P-glycoprotein are blocked[107]. Several cRNAs are also involved in the acquisition of drug resistance by CRC cells through modulation of the β-catenin axis. For instance, circ-PRKDC participates in the development of chemoresistance to 5-FU in SW620 and SW480 cell lines by regulation of miR-375 and the Wnt/β-catenin pathway[77]. These molecules constitute a novel target for the development of

alternative therapies for CRC, given their role in the communication between tumor cells and the TME and their participation in the regulation of Wnt/β-catenin[26,108].

Macrophages also play a crucial role in the development of resistance to drugs. IL-1β released by TAMs activates the canonical Wnt pathway through NF-κB/Akt and subsequently induces the expression of genes associated with chemoresistance. This has been observed in several cell lines derived from CRC such as HCT116, Hke-3, SW480, and RKO[109,110].

In our laboratory, we previously reported that PTHrP, acting as a cytokine, induces chemoresistance to CPT-11 through ERK MAPK and Akt pathways in the CRC cell lines Caco-2 and HCT116[34]. Moreover, as described in previous sections, we also registered nuclear β-catenin nuclear-increased expression after PTHrP treatment in CRC cells[37]. In view of these data, we hypothesize that this protein also participates in the resistance to CPT-11. This is our current research focus.

Growth factors are also involved in the therapy resistance mediated by β-catenin. Activation of the c-MET pathway through HGF signaling is related to drug resistance in many types of tumors[111]. Several works have already shown that HGF is associated with both Met and β-catenin pathways[52, 54]. Studies published by Woo and collaborators showed that this factor is related to resistance to CPT-11 in CRC cells[112]. Since the HGF/Met axis plays an important role in CRC, molecules such as inhibitors, neutralizing antibodies, and antagonists of this pathway have been designed. To date, pre-clinical trials have failed and demonstrated poor efficacy[111,113]. One of the possible causes of the resistance of CRC cells to HGF pathway inhibitors is the activation of the Wnt/β-catenin signaling pathway[113]. All of these data highlight the need for consideration of the mitogenic pathways and paracrine factors released by both the tumor and the TME as targets to revert the chemoresistance.

Li *et al*[114] made a relevant contribution in the field of basic sciences related to CRC therapy and TME cells. They observed that the pharmacological treatment of CAFs inhibits their recruitment and increases the sensitivity of tumor cells to OXA[114]. Chemotherapy combined with treatments that inhibit CAFs recruitment and/or their activity may represent a novel method for the improvement of tumor response to chemotherapy[114]. This area of research is practically vacant and needs to be further explored since other unknown factors derived from TME may be able to stimulate the nuclear translocation of β-catenin and modulate the events related to the chemoresistance of CRC cells.

THE TME AND β-CATENIN PATHWAY: FUTURE PERSPECTIVES FOR CRC MANAGEMENT

In the last decade, therapeutic inhibition of the β-catenin pathway has been considered an invaluable tool for developing new therapy regimens for patients with CRC[115-117]. Despite this, as previously stated, there are still no approved drugs for the treatment of CRC or clinical trials based on the targeting of this signaling pathway[15,117]. For these reasons, comprehension of the regulatory mechanisms of the Wnt/β-catenin signaling pathway will not only expand the knowledge about the pathogenesis and evolution of CRC but also improve the treatment with the implementation of new targeted therapies. Many small molecules with β-catenin inhibitory effects have been developed such as tankyrase inhibitors (TNKSi), R-spondin inhibitors, and porcupine enzyme inhibitors. tankyrases (TNKSs) favor Wnt signaling by inducing Axin degradation. Therefore, TNKSi including XAV939 (XAV), JW55, NVP-TNKS656, and GOO7-LK are effective approaches for inhibiting this pathway in the preclinical stage of validation[118,119]. Moon and collaborators recently discovered that β-catenin expression influences the response of CRC-derived cells to MEK inhibitors, and that TNKSi allows the resistance to this treatment to be exceeded in CRC cell lines with mutant KRAS and PI3K. These results demonstrate the possible efficacy of combined treatments with inhibitors of MEK and β-catenin signaling pathways. However, this kind of therapeutic strategy is not yet in the clinical trial phase[118], and there is even controversy on the implementation of this type of scheme[116]. Drugs that disable enzymes related to Wnt secretion are another possibility to inhibit the Wnt/β-catenin. These compounds are denominated IWP-2, LGK974, or ETC-159 and inhibit porcupine enzyme actions. Some R-spondin inhibitors, such as OMP-131R10 (rosmantuzumab), are also currently under investigation for the treatment of CRC. When this ligand binds to the receptor leucine rich repeat containing G protein-coupled receptor 4 (LGR4) or LGR5, it enhances Wnt signaling, so blocking this point would consequently decrease the transcriptional activity of β-catenin[119].

One of the therapeutic targets that is being studied for CRC treatment is the use of antibodies or small molecules for the inhibition of Wnt ligands, like OMP-54F28, OMP-18R5, and OTSA101[116]; the disruption of the transcriptional activity of β-catenin using small molecules that prevent the binding of this protein with the nuclear transcription factors TCF and LEF, such as LF3 and 2,4-diaminoquinazoline; or pharmacological drugs that stimulate β-catenin proteasomal degradation as MSAB[119, 120].

In addition to the hyper-activating mutations affecting the β-catenin pathway in CRC, as previously mentioned, cross-communication through paracrine signals between tumor cells and TME cells amplify these effects. The Wnt/β-catenin pathway is key for immune cells differentiation and functioning[120], the aberrant activation of this signaling alters the activation and downregulation of the immune

response, especially related to dendritic cells (DCs) and T cells[119]. In the TME, the β-catenin pathway-dependent production of cytokines, such as IL-10, by DCs has been shown to induce immune tolerance through CD4+ and CD8+ T cells[121]. Moreover, it was reported that β-catenin signaling is activated in tumors with an inflammatory microenvironment, immune evasion and poor infiltration of CD8+ T cells [119,122,123]. In CRC, this immune response is favored by the activation of β-catenin, Myc, and RAS[7, 124,125]. Currently known mechanisms that mediate immune exclusion and evasion through the Wnt/β-catenin pathway are: Modulating the production and release of cytokines from DCs and consequently diminishing CD8+ T cells infiltration; stimulating the production and release of soluble factors like Snail and IL-1β from tumor cells and TAMs, respectively; and increasing regulatory T cells survival, which are also effective inhibitors of CD8+ T cells[120,126]. To date, there are some inhibitors related to the immune response that are approved for clinical use, one of them is programmed death-1[127]. However, although immunomodulation can be effective in the treatment of CRC, resistance often occurs. Given that several of these drugs target CD8+ T cells, one of the explanations for the failure of these therapies may be the hyperactivation of the β-catenin pathway in the TME[128]. From this point of view, the current research focuses on the importance of the development of anticancer therapies that target the Wnt/β-catenin pathway as a checkpoint to improve the efficacy of immunotherapies, mainly by restoring T-cell infiltration[119,120,122].

In previous sections, we described the role of several TME-derived factors that activates the β-catenin signaling pathway. Currently, clinical research is aimed at blocking or inhibiting the effects of these molecules on CRC. In our laboratory, we have found that the selective inhibition of the HGF receptor, the RTK Met, suppresses β-catenin phosphorylation at domains that favor its nuclear translocation induced by PTHrP. Concerning this, Rimassa and his research group[129] explored in a clinical phase II study the effect of an oral selective Met inhibitor (tivantinib) and found that, in combination with another drug, at least 10% of patients with CRC respond better to the therapy. This drug is a possible emerging treatment that is already in phase III study in other types of tumors[130]. Another drug that inhibits the activity of the Met receptor by inducing the degradation of β-catenin is celecoxib[116]. However, recent evidence indicates that the combined treatment of celecoxib with the usual chemotherapy did not improve overall survival or progression-free time in patients with CRC[131].

On the other hand, a large number of clinical trials have been developed using cytokine-based immunotherapy for CRC. Different drugs targeting IL, prostaglandins, CXCL, TNF-α and TGF-β superfamily factors are in clinical trials. Although it has not yet been proven that they generate an effect as monotherapy or in combined treatments with commonly used drugs, future expectations are very optimistic[132,133].

Employing non-coding RNA such as miRNAs or cRNAs is a promising solution to overcome CRC drug resistance. It has been seen that miR505, miR199a/b and miR320 decreased sensitivity to cisplatin and OXA by modulating the activity of the Wnt/β-catenin pathway. Others, such as miR30-5p, favor chemosensitivity in CRC cells[134]. In this work, we have also described the role of TME-derived cRNAs in activating the β-catenin signaling pathway and its influence on CRC development and progression. Nevertheless, there is still a lot to explore about its potential role in future therapies for CRC. In this regard, recent research indicates that knockdown circ-PRKDC decreases the resistance of CRC-derived cells to 5-FU by modulating the Wnt/β-catenin pathway[77]. These results could postulate a new strategy to deal with multidrug resistance in CRC. Additionally, Viralippurath and collaborators propose that gene therapy could be aimed at silencing these oncogenic cRNAs or increasing the effects of those molecules that act as tumor suppressors[26]. Despite these findings, to date, there are no available therapies that use these small molecules to evade the strategies of tumor cells against chemotherapeutic drugs. More studies are needed regarding the role of non-coding RNAs in CRC chemoresistance as well as for the development of delivery strategies for these molecules in new targeted therapies. Figure 4 schematizes current studies related to the disruption of the interrelationships between TME and CRC cells that trigger β-catenin activation and are involved in treatment failure.

As previously mentioned, autophagy is a mechanism associated with chemoresistance in CRC[105]. Recent investigations aim to find drugs that help reverse the autophagy process and overcome chemoresistance in CRC[135]. According to Pérez-Plasencia *et al*[62], the involvement of Wnt/β-catenin signaling in the regulation of autophagy was demonstrated in several types of cancer, such as leukemia, hepatocarcinoma, squamous cell carcinoma, lung cancer and prostate cancer[62]. However, it is just a matter of time before the relationship between these two pathways in CRC will be considered crucial for future pharmacological treatments. In their work, the authors postulate several therapeutic approaches based on drugs that are capable of simultaneously disrupting components of β-catenin and autophagy pathways[61].

From what we have analyzed in this work, it is important to highlight that concerning CRC, the achievement of successful future therapies will involve the use of combined pharmacological compounds that inhibit not only the canonical β-catenin signaling pathway but also the TME- derived signaling.
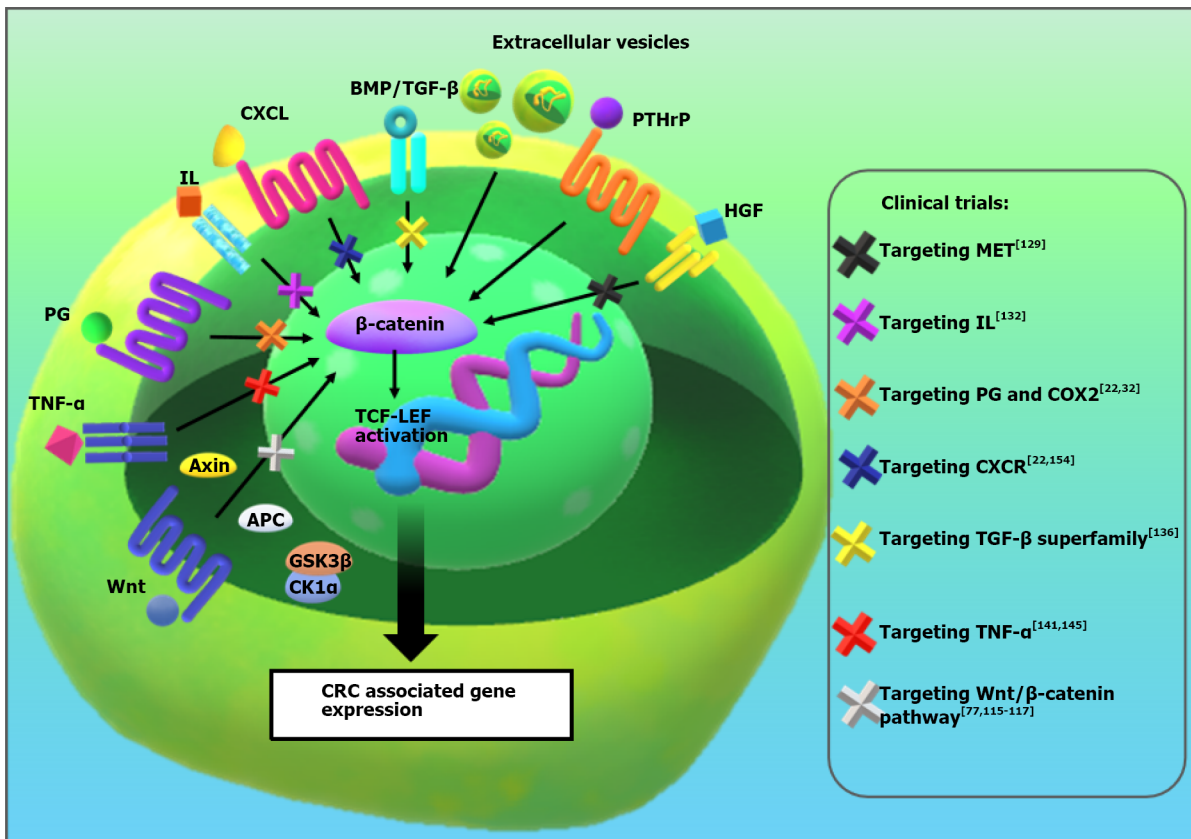
Figure 4 Pharmacological targeting of the tumor microenvironment factors involved in the activation of β-catenin signaling in colorectal cancer. Several therapeutic strategies to block or inhibit the induction of the β-catenin pathway by tumor microenvironment factors in colorectal cancer (CRC) are currently under clinical study. This figure is original for this work. APC: Adenomatous polyposis coli; BMP: Bone morphogenic protein; CK1α: Casein kinase 1 alpha; CXCL: C-X-C motif chemokine ligand; GSK3β: Glycogen Synthase Kinase 3 Beta; HGF: Hepatocyte growth factor; IL: Interleukin; PTHrP: Parathyroid Hormone-related Peptide; PG: prostaglandin; TCF/LEF: T-cell factor/lymphoid enhancer factor; TGF-β: Transforming growth factor-beta; TNF-α: Tumor necrosis factor-α; Wnt: Wingless protein.

CONCLUSION

The cells of the TME are mainly responsible for triggering the mechanisms that determine a worse prognosis of cancer disease. These cells and the biological mediators released in the neoplastic context regulate the expression of ligands and modulate the activity of pro-tumor signaling pathways. TME cells control the fate of the tumor cells through permanent bidirectional communication. It is known that a considerable proportion of CRC patients evolve unfavorably due to chemoresistance. To improve CRC therapies, it is necessary to expand the knowledge about the mechanisms that play a critical role in the development, progression and chemoresistance of CRC.

Given that the factors associated with the TME activate the β-catenin signaling pathway, it will be possible in the future to improve the response of CRC patients to treatment. This goal could be achieved through new therapeutic interventions based on interrupting the crosstalk between the stroma and the tumor that control the β-catenin pathway activation. From the exhaustive search of the bibliography made by the authors of this work, it is concluded that there are multiple vacant areas in the research related to chemoresistance induced by cells from the tumor environment. Even to date, new types of biomarkers are continuously identified and related to a worse prognosis and aggressiveness of CRC. For this reason, it is imperative to strengthen *in vitro* and preclinical studies to support clinical trials in order to achieve novel therapeutic approaches considering the background of each patient and personalized medicine.

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