Exp Oncol 2022
44, 1, 2–6

REVIEWS

Experimental ONCOLOGY

THERAPEUTIC TARGETING OF MOLECULAR PATHWAYS IN COLORECTAL CANCER

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Mutations in tumor suppressor genes, cell signaling, and genes associated with DNA repair lead to onset of colorectal cancer (CRC). Even though most CRC patients get clinical benefits from conventional treatments such as chemotherapy and radiotherapy, treatment success is still not at the desired level despite recent advances in CRC treatments. Therefore, further elucidation of the molecular signaling pathways involved in CRC progression will allow developing targeted therapies. With the detection of signaling pathways that lead to cancer progression and development of the successful treatment methods targeting these pathways, the progression of the disease can be prevented. This review provides an overview of the therapeutic roles of potential molecular targets in recent preclinical and clinical studies in CRC treatment.

***Key Words*: colorectal cancer drugs, molecular targeted therapy, CRC signaling pathways, tumor biomarkers.**

DOI: 10.32471/exp-oncology.2312-8852.vol-44-no-1.17455

Colorectal cancer (CRC) is the most common malignancy in the world. According to estimates by 2030, CRC incidence in the world is expected to increase by 60% with 2.2 million new cases and 1.1 million deaths [1]. Depending on the origin of the mutation, colorectal carcinomas are classified as sporadic and hereditary [2]. The most frequently occurring mutated oncogenes in CRC are *KRAS* and *c-MYC* [3]. *KRAS* is an oncogene responsible for the synthesis of a protein involved in the transmission of mitogenic messages in the cell membrane. Point mutations in *KRAS* are observed in 39–71% of CRC and 42% of adenomatous polyps [4–6].

The following molecular signaling pathways associated with genomic instability have been identified in CRC: chromosomal instability (CIN), microsatellite instability (MSI), and CpG island methylator phenotype pathways [7]. In addition to *KRAS* mutations in CRC, major mutations in the transforming growth factor-β (TGF-β), PIK3CA and TP53 signaling also develop. Single colorectal tumor may contain up to 80 mutated genes [7–8]. These important molecular properties and cell signaling pathways could be the targets in personalized therapies. Moreover, the various strategies such as angiogenesis inhibitors, EGFR-targeted therapy, BRAF mutation-targeted therapies and immunotherapy may be used. In this context, it is quite important that effective and non-toxic targeted therapies based on molecular signaling be discovered [7].

Submitted: September 29, 2021.
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Abbreviations used: APC – adenomatous polyposis coli; CIN – chromosomal instability; CRC – colorectal cancer; EGFR – epidermal growth factor receptor; FZD – Wingless/Int1-Frizzled; MAPK – mitogen-activated protein kinase; MSI – microsatellite instability; PD-1 – programmed cell death-1; PORCN – porcupine-O-acetyltransferase; TGF-β – transforming growth factor-β; TNKS – tankyrase; VEGF – vascular endothelial growth factor.

THERAPEUTIC MOLECULAR TARGETING OF APC

In CRC, specific mutations that stimulate oncogenic signaling occur in CIN tumors (Table 1). One of the most important mutations that cause CIN is adenomatous polyposis coli (*APC*) gene mutations that occur in approximately 80% of CRC, while 5% to 10% have mutational changes in Wnt signaling [5, 9]. The *APC* gene is not only a crucial switch of the Wnt signaling mechanism but also plays a critical role in regulating chromosomal differentiation, cell differentiation, adhesion, migration, and apoptosis. Most general sporadic CRC exhibit unusual activation of the Wnt signaling. The genetic defect of *APC* leads to the activation of the Wnt signaling mechanism being an important initial genetic condition for CRC. *APC* mutations play an important role in the development of both familial adenomatous polyposis (FAP) and sporadic CRC. This resulting loss of function in the *APC* gene triggers a series of molecular-genetic instability and histological changes leading to malignant transformation [10]. As the therapeutic modality for APC targeting, a small molecule called Truncated APC Selective Inhibitor 1 has been shown to inhibit tumor growth in the CRC mouse model with minimal toxicity. The molecule exerts its cytotoxicity independent of Wnt pathway inhibition and does not specifically exert detrimental effects on normal mouse colonic epithelium [11]. Understanding the comprehensive functions of *APC* mutations will shed light on the molecular mechanisms of CRC tumorigenesis and uncover new drug targets that allow developing additional targeted therapeutics for CRC treatment.

THERAPEUTIC MOLECULAR TARGETING OF WNT PATHWAY

Wnt signaling activation is critical in tumor progression. Molecular targets for Wnt signaling inhibition such as porcupine-O-acetyltransferase (PORCN), FZD (Wingless/Int1-Frizzled), Dvl, β-catenin degradation complex,

Table 1. Frequency of genetic mutation in CIN positive CRC [7]

Gene	Chromosomal location	Frequency of mutations (%)	Role of a gene product?
Oncogenes			
KRAS	12p12	~30–50	Cell survival, proliferation and transformation
BRAF	7q34	~40–60	Cell growth, cell division, differentiation, and secretion
CTNNB1	3p22	~4–15	Regulation of Wnt signaling target genes that drive tumor development
PIK3CA	3q26	~20	Cell survival, proliferation
Tumor suppressor genes			
APC	5q21	~30–70	Inhibition of WNT pathway, cytoskeletal regulation
TP53	17p13	~40–50	Apoptosis induction, cell cycle arrest
SMAD4, SMAD2	18q21	~10–20	Intracellular mediators of the TGF-ß signaling
DCC	18q21	~6	Cell surface receptor for netrin-1

nuclear β-catenin, and tankyrase (TNKS) have been identified [11]. Monoclonal antibodies and small-molecule inhibitors have been identified as two therapeutic modalities for targeting Wnt signaling and demonstrated antitumor effects [12]. Several small-molecule inhibitor trials have been conducted in the preclinical and clinical phases of drug research studies, and β-catenin inhibitors PRI-724, CWP232228, and BC2059 that suppress TCF/LEF target genes have been developed [13]. TCF/LEF transcription factors, major endpoint mediators of Wnt/Wingless signaling, are multifunctional proteins that use sequence-specific DNA binding to determine which genes are regulated by Wnt [14]. In previous studies, it was revealed that tumor development was stopped by inhibiting the Wnt signaling pathway, together with the inhibition of the β-catenin/TCF interaction [15]. However, there are two TNKS inhibitors that attenuate Wnt signaling, XAV939 and E7449 [11]. WNT974 and ETC-159 are found as PORCN inhibitors [11]. The small-molecule inhibitor ETC-159 is in phase I clinical trials for the therapy of CRC, while WNT974 is in phase I/II for the treatment of metastatic CRC adenocarcinoma [16–18]. While blocking Wnt pathway via small-molecule inhibitors is a possible therapeutic approach to stop tumor development, further research is required to discover how these inhibitors may also influence other signaling mechanisms in order to decrease toxicity to normal cells [11].

Another way to regulate Wnt signaling is the application of monoclonal antibodies. There are several antibody-based therapies currently under study (Table 2). Phase I clinical trials are ongoing for OMP-18R5, monoclonal antibody, solid tumors targeting the five FZD receptors [19]. Finally, it is in phase I clinical trial for OMP-131R10, an anti-R-spondin 3 antibody for the treatment of solid tumors and metastatic CRC [16]. The application of monoclonal antibodies to target Wnt pathway is promising, but further clinical research is required to determine the clinical importance.

THERAPEUTIC MOLECULAR TARGETING OF TGF-β PATHWAY

In colorectal tumorigenesis, chromosomal changes involving TGF-ß participate in the CIN pathway. Loss

Table 2. Biomarkers of Wnt signaling [20] and Wnt-targeted monoclonal antibodies [21]

Agents of Wnt signaling in CRC under clinical trial			
Molecular signaling mechanism	Agent	Phase	NCT identifier
Wnt/β-catenin signaling	WNT-974	Phase 1/2	NCT02278133
	FOXY-5	Phase 1	NCT02655952
			NCT02020291
			NCT02020291
	LGK-974	Phase 1	NCT01351103
Wnt-targeted monoclonal antibodies under clinical trial			
Target	Agent	Phase	Ref.
R-spondin3	OMP-131R10	Phase I	[15, 22]
FZD10	OTSA101	Phase 1 (terminated)	[15, 23]

of function of *SMAD2* and *SMAD4* tumor suppressor genes inactivates TGF-β signaling mechanism, thereby increasing cell proliferation and escaping apoptosis [9]. In the majority of CRC, activation of MYC, which has an important role in colorectal carcinoma, occurs through inactivation of the TGF-β signaling and/or activation of the Wnt molecular pathway [9].

In CRC, disruptions in TGF-β signaling lead to metastasis and increased tumor growth [24]. For this reason, the TGF-β pathway has become an important molecular pathway for drug development studies. Current candidate anti-TGF-β therapies have focused on the targeting of TGF-β signaling at the ligand-receptor level using monoclonal antibodies or peptides and the use of TGF-β receptor kinase inhibitors [24]. However, the TGF-β pathway is quite complex, with different effects in normal cells and different types of cancer, and paradoxical functions in the immune system modulation and tumor microenvironment. Although TGF-β inhibition has not been used yet in the treatment of CRC, the studies of many candidate molecules are continuing. A list of current TGF-β signaling inhibitors under research can be seen in Table 3 [24].

Table 3. TGF-β receptor and ligand inhibitors under clinical investigation [24–25]

Agent	Target	NCT identifier	Status
TGF-β ligand inhibitors			
Trabedersen	TGF-β2	NCT00844064	Phase I study in CRC completed
FANG vaccine	TGF-β1, TGF-β2	NCT01505166 NCT01453361	Phase II study in CRC ongoing
TGF-β receptor inhibitors			
PF-03446962	TGF-βRI	NCT00557856	Phase I study in CRC completed
		NCT01620970	Phase I study in combination with regorafenib in CRC completed
		NCT02116894	

THERAPEUTIC MOLECULAR TARGETING OF VEGF

Vascular endothelial growth factor (VEGF) is an angiogenic growth factor and the ability of VEGF signaling determines the endothelial cell survival, proliferation, and migration. One study demonstrated that bevacizumab, a VEGF-blocking monoclonal antibody, provided benefit in CRC upon addition to fluorouracil-based combination chemotherapy regimens [26]. Blocking VEGF-A with bevacizumab has proved hopeful in several phase III clinical experiments. Other strategies

for targeting VEGF signaling involve the direct binding of monoclonal antibodies such as ramucirumab to the extracellular domain of the VEGF receptor (VEGFR-2) and the use of tyrosine kinase inhibitors for antiangiogenic effect [26] (Table 4).

Table 4. Agents of VEGFR in CRC under clinical trial

Agent	Target	Phase	NCT identifier
LYN00101	VEGF	Phase 1	NCT03644459
Icrucumab	VEGFR	Phase 2	NCT01111604
Vandetanib	VEGFR/EGFR	Phase 2	NCT00454116
Pazopanib	Pan-VEGFR	Phase 1	NCT00387387

THERAPEUTIC MOLECULAR TARGETING OF RAS PATHWAY

Epidermal growth factor receptor (EGFR), one of the transmembrane receptors, organizes many important cell functions including raising cell proliferation, cell cycle progression, and inhibiting apoptosis by the activation of intracellular signaling including phosphoinositide 3-kinase, mitogen-activated protein kinase (MAPK), and Signal Transducer and Activator of Transcription proteins [27–28]. Various mutations, overexpression or stimulation in MAPK and PI3K signaling pathways, which play an active role in cell proliferation, provide proliferative benefits for tumor cells. The most common mutations affecting MAPK/PIK3 signaling in CRC are *KRAS*, *BRAF* and *PIK3CA* [29]. *KRAS* mutations occur in approximately 40% of CRCs [28, 30]. Especially, abnormal intracellular RAS signaling has various roles within the tumor microenvironment TME. Oncogenic RAS mutations happen in a constitutively initiated state whereby RAS proteins are no longer self-inhibited through normal GTPase activity. Approaches to control mutant RAS signaling require single or dual targeting of RAS itself, the RAS-RAF-MEK-ERK axis, the PI3K-AKT axis (Figure) [31].

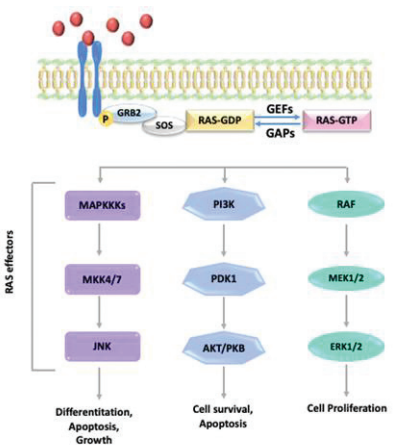

Figure. RAS molecular signaling pathway in cancer. Growth factors binding to their cell surface receptors activate guanine exchange factors (GEF), such as SOS (son of sevenless) that are connected by the adaptor protein GRB2 (growth-factor-receptor bound protein 2). SOS stimulates the release of bound guanosine diphosphate (GDP) from RAS, and it is exchanged for guanosine triphosphate (GTP), pointing to the active RAS-GTP conformation. The guanosine triphosphatase (GTPase)-activating proteins (GAP) can bind to RAS-GTP and stimulate the transformation of RAS-GTP to RAS-GDP, which stops signaling. Mutated RAS is constitutively active in the RAS-GTP conformation. Activated RAS organizes various cellular functions through effectors including MAPK pathway, Raf–MEK–ERK signaling, PI3K molecular pathway

Monoclonal antibodies cetuximab and panitumumab target the EGFR providing an additional clinical therapeutic benefit for CRC patients [32]. Although anti-EGFR monoclonal antibody therapy is used in CRC, mutations in these signaling pathways are resistant to treatment [27]. As with *RAS* and *BRAF* mutations, *PIK3CA* mutations are thought to confer resistance to anti-EGFR treatment. Therefore the molecular properties of EGFR signaling should be investigated in more detail to reveal potential targets for more effective therapy modalities in CRC [29].

THERAPEUTIC MOLECULAR TARGETING OF COX2

Various studies have also shown that COX2 (PTGS2), a molecule produced by prostaglandins that perform a significant function in inflammatory regulation, is overexpressed in CRC cases with *PIK3CA* mutations. For instance, aspirin suppresses COX2 expression and PIK3 signaling pathway. Studies have shown that regular use of aspirin in CRC reduces the risk of overexpression of PTGS2 [33].

THERAPEUTIC MOLECULAR TARGETING OF TP53

TP53, a tumor suppressor gene, is also a cell cycle checkpoint regulatory [7]. With the inactivation of TP53, excessive cell proliferation occurs and tumor progression is ensured. In addition, studies have shown that the transition from adenoma to invasive carcinoma is generally with the inactivation of TP53 [5, 7, 34]. Loss of function of chromosome 17q location where TP53 is localized is a frequent occurrence in colorectal tumors because TP53 operates a significant function in adenocarcinoma [9]. Even though TP53 gene mutations in cancer treatment are still not fully understood, possible TP53-targeted therapies have been proposed both for wild-type and mutant TP53 [35–36]. TP53-based therapies can be grouped according to various treatment strategies. These include restoration of normal p53 function lost by genomic mutation or direct targeting of p53-deficient cells [37–39]. Therefore, molecular characteristics of TP53 gene should be described in detail as potential targets in CRC.

THERAPEUTIC MOLECULAR TARGETING OF PD-1/PD-L1

When PD-L1 (programmed cell death ligand-1) on the surface of tumor cells binds to the programmed cell death-1 (PD-1) receptor on T cells, the resulting inhibitory signal modulates cytotoxic T-cell responses, blocking the antitumor immune response and thus tumor cell death. Blocking PD-1 or PD-L1 with monoclonal antibodies has produced important clinical results in many different types of cancer, such as melanoma, bladder cancer. 60% response rate to the anti-PD-L1 inhibitor pembrolizumab was determined in different CRCs [40]. There are candidate PD-1/PD-L1 molecules whose clinical studies are still ongoing for use in the treatment of CRC. A list of current ap-

proved immunotherapeutics can be seen in Tables 5, 6 below. The use of monoclonal antibodies to target PD-1/PD-L1 is promising, but further clinical research is required to discover clinical importance.

Table 5. Targeted CRC immunotherapy drugs [25]

Approved drug	Target	Reviews of phase III clinical trials leading to approval
Panitumumab	Wild-type KRAS and NRAS	Hocking et al. [41]
Cetuximab	Wild-type KRAS and NRAS	Hoyle et al. [42]
Bevacizumab	Vascular endothelial growth factor (VEGF)	Ilic et al. [43]
Ramucirumab	VEGFR2	Verdaguer et al. [44]
Regorafenib	Dual targeted VEGFR2-tyrosine kinase inhibition	Yoshino et al. [45]
Ziv-Aflibercept	VEGF	Perkins et al. [46]
Pembrolizumab	MSI-H or dMMR	n/a
Nivolumab	PD-1	Rajan et al. [47]

Table 6. Immune checkpoint modulators in CRC under clinical trial [48]

Agent	Target	Phase	NCT identifier
Atezolizumab	PD-1/PD-L1	Phase 3	NCT02912559
JS-001 Toripalimab	PD-1/PD-L1	Phase 1–2	NCT03946917
		Phase 2	NCT04118933
AMP-224	PD-1/PD-L1	Phase 1	NCT02298946
TSR-033	PD-1/PD-L1	Phase 1	NCT03250832
Tremelimumab	CTLA-4	Phase 1/2	NCT03206073

Potential advances in determining the molecular characteristics of CRC will allow finding therapeutic targets for molecularly characterized subtypes. Furthermore, identifying important molecular signaling mechanisms for a particular CRC subtype may provide possible therapeutic strategies that enable better therapeutic approaches. Moreover, cancer immunotherapy is developing as a hopeful strategy for the treatment of various malignancies, including CRC. The complex biological heterogeneity of tumors complicates the implementation of successful treatment. Therefore, it is possible to discover effective molecular biomarkers for CRC and to determine cell signaling mechanisms. Thus, the prognosis of the disease and treatment responses will be better managed, and the potential for personalized treatment will increase [49–50].

In conclusion, although many aspects of molecular classifications of CRC have been identified as potential targets for personalized therapies or prognostic predictors, more information is needed for successful targeted therapy and prognostic procedures in routine clinical application.

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ТЕРАПЕВТИЧНІ МІШЕНІ МОЛЕКУЛЯРНИХ СИГНАЛЬНИХ ШЛЯХІВ У КЛІТИНАХ КОЛОРЕКТАЛЬНОГО РАКУ

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У виникненні злоякісних пухлин, у тому числі колоректального раку, задіяні мутації генів — супресорів пухлинного росту, генів білків сигнальних каскадів та генів, асоційованих з репараціями ДНК. Незважаючи на позитивні клінічні результати застосування хіміотерапії та променевої терапії у хворих на колоректальний рак, результати лікування ще далеко не досягають бажаного рівня. З'ясування молекулярних сигнальних шляхів, задіяних у прогресуванні захворювання, може сприяти розробці нових методів таргетної терапії. В огляді розглянуто потенційні молекулярні мішені, які вивчаються останнім часом у доклінічних та клінічних дослідженнях та можуть знайти своє застосування у лікуванні хворих на колоректальний рак.

Ключові слова: колоректальний рак, молекулярна таргетна терапія, сигнальні шляхи, пухлинні біомаркери.