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REVIEW ARTICLE

Targeting PI3K/AKT/mTOR signaling: A promising therapeutic approach for colorectal cancer

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Abstract

Colorectal cancer is characterized by high prevalence, poor clinical outcomes, and unfavorable prognosis, significantly contributing to human mortality. It is well established that phosphoinositide 3-kinase (PI3K)/protein kinase B (PKB, also known as AKT)/mammalian target of rapamycin (mTOR) signaling pathway plays an important role in the pathogenesis and progression of colorectal cancer. In this review, we examine the role of the PI3K/AKT/mTOR signaling pathway in a variety of cellular processes, including proliferation, autophagy, apoptosis, angiogenesis, and epithelial-mesenchymal transformation in colorectal cancer. Furthermore, the latest advancements in the research on PI3K/AKT/mTOR inhibitors are discussed, offering new insights for targeted therapy in colorectal cancer.

Keywords: Colorectal cancer; PI3K/AKT/mTOR signaling; Inhibitors; Targeted therapy; Research progress

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1. Introduction

The high prevalence of colorectal cancer (CRC) among the human population poses a serious public health concern. According to the 2020 global cancer statistics, CRC is the third most common cancer in terms of diagnosis and the second most fatal cancer.[1] It had been projected that there would be approximately 550,000 new cases of CRC in 2020, resulting in an estimated 290,000 deaths. CRC holds the second highest incidence rate among malignant tumors and the fifth highest mortality rate.[2] There has been an increase in both the prevalence and mortality rates of CRC in recent years, posing substantial risks to society and burdening the economy.[3,4]

The development of CRC is influenced by a multitude of risk factors, which can be primarily classified into two categories: non-modifiable and modifiable risk factors.[5] Non-modifiable risk factors encompass gender, age, race, genetic predispositions,

inflammatory bowel disease, exposure to abdominal radiotherapy, cystic fibrosis, acromegaly, cholecystectomy, and the therapeutic use of androgen derivatives.[6-9] Conversely, modifiable risk factors include obesity, a sedentary lifestyle, smoking, dietary habits, diabetes and insulin resistance, alcohol consumption, and alterations in gut microbiota.[8,10,11]

At present, CRC is primarily managed with surgical intervention or a combination of chemotherapy and radiotherapy. Endoscopic therapy is the primary treatment modality for patients diagnosed with early-stage CRC.[12,13] The cells of CRC exhibit a propensity for lymphatic metastasis, spreading from proximal to distal regions through various lymph nodes, including supracolic, paracolic, mesangial vascular, and mesangial root nodes. Consequently, lymphatic metastasis remains a prevalent contributor to mortality in CRC cases, underscoring the significance of lymph node dissection as a crucial component of surgical intervention for advanced disease.[14] Advancements in medical technology and scientific development have led to the gradual replacement of traditional open surgery with laparoscopic and robotic surgery.[15] While surgery, radiotherapy, and chemotherapy have been shown to increase the survival rates of patients with CRC, the overall efficacy of these treatments remains suboptimal.[16]

The introduction of targeted therapy adds a promising treatment tool to the existing therapeutic armada for CRC.[17] Identifying the pivotal molecules responsible for the regulation of CRC and advancing the development of targeted therapeutic medications are essential components in enhancing the prognosis of CRC. The PI3K/AKT/mTOR signaling is implicated in proliferation, autophagy, and apoptotic processes in colon cancer cells, according to research studies.[18,19] Hence, a comprehensive understanding of the correlation between the PI3K/AKT/mTOR signaling and the pathogenesis of CRC, along with the advancements in research on corresponding inhibitors, is warranted.

2. Components of the PI3K/AKT/mTOR signaling pathway

The PI3K/AKT/mTOR signaling pathway constitutes a critical intracellular regulatory network, comprising pivotal molecules, such as phosphoinositide 3-kinase (PI3K), protein kinase B (PKB, also known as AKT), and mammalian target of rapamycin (mTOR), which are integral to essential physiological processes, including cell proliferation, metabolism, and survival. Moreover, this signaling cascade is crucial for modulating the survival of tumor cells. It has been shown that targeted inhibition of the PI3K/AKT/mTOR pathway can markedly enhance the efficacy of tumor radiotherapy.[20]

The activation of this pathway begins with extracellular stimulation, such as ligands of growth factors, cytokines, and insulin, which bind to receptor tyrosine kinases (RTK) or G protein-coupled receptors (GPCR), triggering downstream cascade reactions. Take RTK as an example: Upon activation, it recruits and activates the p110α catalytic subunit of PI3K. The p110α catalytic subunit works in synergy with the regulatory subunit p85 to phosphorylate phosphatidylinositol 4, 5-bisphosphate (PIP2) on the plasma membrane into phosphatidylinositol 3,4, 5-triphosphate (PIP3).[21] PIP3, as a key second messenger, recruits AKT to the plasma membrane by binding to the pleckstrin homology (PH) domain of AKT.[22] Here, AKT is phosphorylated at the Thr308 and Ser473 sites, respectively, under the action of phosphatidylinositol-dependent protein kinase 1 (PDK1) and mTORC2, achieving complete activation.[23] Meanwhile, the tumor suppressor PTEN can reverse PIP3 to PIP2 through dephosphorylation, negatively regulate the activation of AKT, and maintain the balance of the pathway.[24,25] The activated AKT can further phosphorylate and activate the mTOR complex.

mTOR functions in two complex forms: mTORC1 and mTORC2. mTORC1 is composed of mTOR, Raptor, MLST8, PRAS40, and DEPTOR, and is regulated by multiple factors, such as growth factors, nutrients (such as amino acids), and energy states.[26] Its downstream effect molecules S6K and 4EBP1 affect cell growth by regulating protein synthesis. mTORC2 is composed of mTOR, RICTOR, mLST8, PROTOR1/2, DEPTOR and mSIN1.[27]

It is notable that the abnormal activation of this pathway is closely related to tumorigenesis. Molecular events, such as *RTK* gene mutations, acquired functional mutations of PIK3CA, and loss of PTEN expression can all lead to the continuous activation of the PI3K/AKT/mTOR pathway, promoting the proliferation and survival of tumor cells; therefore, the PI3K/AKT/mTOR pathway is considered a vital component of targeted cancer therapy.

3. Overactivation of the PI3K/AKT/mTOR signaling pathway in CRC cells

The PI3K pathway is activated by RTKs through a multi-step and multi-process manner, as shown in Figure 1. A variety of receptors, including the epidermal growth factor receptor (EGFR), insulin receptor (IR), insulin-like growth factor 1 receptor (IGF1R), cytokine receptors, GPCR, and B cell receptors, can indirectly activate PI3K.[28]

The PI3K-generated PIP3 binds to the PH domains of AKT and PDK1, facilitating their translocation to the

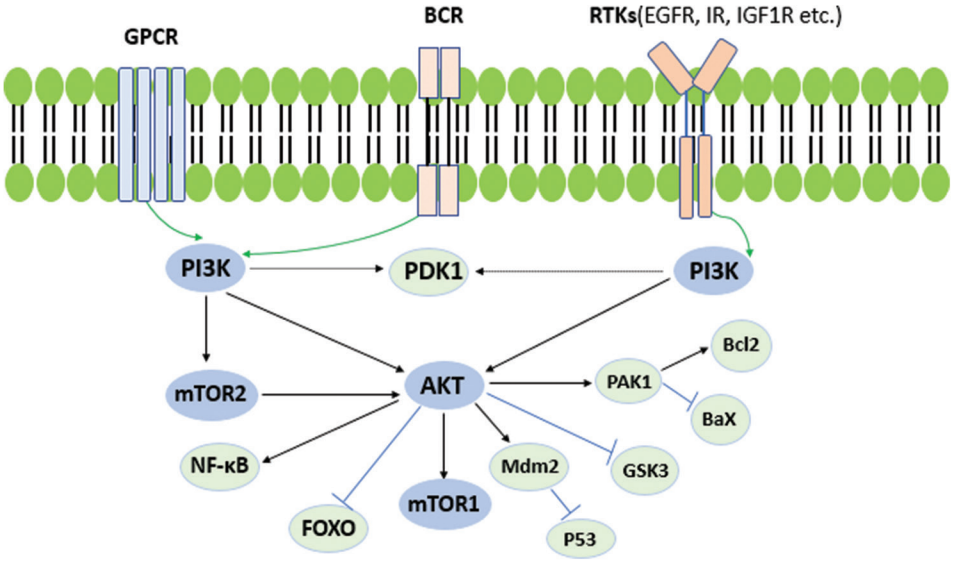

Figure 1. Overactivation of the PI3K/AKT/mTOR signaling pathway in colorectal cancer cells
Abbreviations: PI3K: Phosphoinositide 3-kinase, AKT: Protein kinase B (PKB, also known as AKT); mTOR: Mammalian target of rapamycin.

plasma membrane.[29] Subsequently, PDK1 partially activates AKT, which in turn activates mTORC1, thereby promoting protein synthesis and cell proliferation.[30] The activation of AKT is mediated by phosphorylation by mTORC2. Activation of AKT leads to the specific phosphorylation of downstream substrates, including Bcl2-associated nuclear factor kappa B (NF-κB), mouse double minute 2 homolog (MDM2), forkhead box O (FOXO), and glycogen synthase kinase 3 (GSK3).[31] In CRC cells, hyperactivation of the PI3K/AKT/mTOR signaling pathway affects multiple regulatory processes within CRC cells, including cell proliferation, autophagy, apoptosis, metabolism, protein synthesis, and angiogenesis, as shown in Figure 1.

4. The involvement and functioning of the PI3K/AKT/mTOR signaling pathway in the pathogenesis of CRC

4.1. Cell proliferation

The PI3K/AKT/mTOR signaling pathway is essential in the regulation of cell survival, growth, and proliferation,[32,33] and is frequently dysregulated in human cancer.[34-37] Malkomes *et al.*[38] conducted a study to investigate the impact of targeted AKT inhibition on the proliferation of CRC cells. The usage of MK-2206, a selective AKT inhibitor, led to significantly reduced cell proliferation, particularly in tumor-initiating cells. Furthermore, the capacity of stem cells to generate colonic spheres and initiate tumor growth was significantly diminished.[38] It has been reported that curcumin suppresses the growth of HCT-8 cells by blocking the PI3K/AKT/mTOR signaling pathway, thereby inducing ferroptosis.[39] Huang *et al.*[40] proposed that miR-16-5p inhibited the PI3K/AKT/mTOR pathway by targeting FOXK1, thereby impeding angiogenesis and proliferation in SW620 and HCT8 cells. It has been shown that nuclear casein kinase and cyclin-dependent kinase substrate 1 (NUCKS1), found in the nucleus, are involved in cancer development through activating the PI3K/AKT/mTOR signaling pathway. Cell cycle arrest, proliferation suppression, and apoptosis and autophagy enhancement are observed in CRC cells when the cyclin-dependent kinase substrate 1 is depleted.[41] Research has demonstrated that harakiri (HRK), which exhibits low expression levels in CRC tissues, promotes apoptosis and suppresses proliferation of CRC cells.[42] Similarly, Naringin also inhibited CRC cell proliferation.[43] The findings of Jin *et al.*[44] suggest that elevated expression of serpin peptidase inhibitor clade H member 1 (SERPINH1) may activate the PI3K-AKT-mTOR signaling pathway, thus facilitating the progression of the G1/S phase of the cell cycle. This activation subsequently enhances the proliferation, invasion, and migration of CRC cells.[44]

In recent years, traditional Chinese medicine has assumed an increasingly prominent role in anti-tumor therapies. A study conducted by Qiao *et al.*[45] demonstrates that Buzhong Yiqi Decoction inhibits the proliferation and migration of CRC cells through the suppression of the PI3K/AKT/mTOR signaling pathway.

An increasing body of research indicates that dysbiosis of the intestinal microbiota significantly contributes to the onset and progression of CRC. In a study conducted

by Chen *et al.*,[46] it was demonstrated that *Solobacterium moorei*, a non-spore-forming, Gram-positive anaerobic bacterium, facilitates the proliferation of CRC cells, suppresses apoptosis, and promotes tumor progression through the integrin α2/β1-PI3K-AKT-mTOR-C-myc signaling pathway. These findings suggest that *S. moorei* may serve as a novel target for future prevention, diagnosis, and treatment approaches for CRC.

4.2. Autophagy

During autophagy, autophagosomes, expressed from autophagy-related genes, encapsulate damaged organelles, proteins, and biological macromolecules, subsequently fusing with lysosomes to form autophagolysosomes. Ultimately, the contents of the autophagolysosomes are degraded under acidic conditions; yielding reusable cellular and tissue components.[47] Numerous researchers have investigated the correlation between autophagy and tumorigenesis. Autophagy plays a dual role in tumor growth, either inhibiting or promoting, contingent upon the specific environmental conditions and stages of cancer progression.[48] During the initial phase of tumorigenesis, autophagy functions as a survival pathway and quality control mechanism, serving to impede tumorigenesis and hinder tumor progression. However, as a tumor advances to a more advanced stage, autophagy transitions into a dynamic degradation and circulatory system, thereby supporting tumor survival and proliferation, and enhancing cancer aggressiveness through the facilitation of metastasis.[49] Due to the variability of autophagy's impact on cancer in diverse environments and stages of cancer progression, the modulation of autophagy through inhibitory or promotive strategies can be employed as a targeted approach in the treatment of cancer, contingent upon the specific circumstances.

An increasing body of research has substantiated the close association between the PI3K/AKT/mTOR signaling pathway and the autophagic process in CRC cells.[33,50-65] Researchers found that PH-like domain family A member 2 (PHLDA2) expression is significantly higher in CRC tissues. PHLDA2 inhibition suppresses CRC cell proliferation and PI3K activity, promoting autophagy and inhibiting epithelial-mesenchymal transition (EMT).[51] In a study by Wang *et al.*,[52] the PI3K/AKT/mTOR pathway inhibitor W922 was used in conjunction with the autophagy inhibitor chloroquine to treat HCT116 cells. They found that cell cycle arrest was hindered, and apoptotic cells were significantly increased. In addition, in the xenograft mouse model, W922 significantly inhibited tumor growth while exhibiting low toxicity.[52] A study of 328 human CRC specimens found that G-protein signaling modulator 1 expressed high levels in cancer tissues and was strongly associated with unfavorable outcomes. In a further investigation of the mechanisms of G-protein signaling modulator 1, researchers found that it activates the PI3K/AKT/mTOR pathway, while also suppressing autophagy in these cells.[53] Betulin significantly enhanced autophagy in CT26 and HCT116 cells through the downregulation of PI3K/AKT/mTOR expression.[54] The researchers determined that FAT tumor suppressor homolog 4 (FAT4), which has tumor-inhibitory properties, increases autophagy and suppresses the EMT by modulating PI3K and AKT activity.[55] By modulating autophagy, W922, a novel inhibitor of the PI3K/AKT/mTOR signaling pathway, inhibits the growth of CRC, offering a potential therapeutic strategy. In their study, Li *et al.*[66] identified polyphyllin II, a natural steroid saponin found in *Rhizoma Paridis*, as capable of reducing the levels of phospho-Src, phospho-Janus kinase 2 (p-JAK2), phospho-signal transducer and activator of transcription (p-3STAT3), and STAT3-targeting molecules in CRC cells. Similarly to *in vitro* results, polyphyllin II inhibited xenograft proliferation and induced apoptosis. Chaetocochin J has been shown to stimulate autophagy in CRC cells, a process that is intricately linked to the PI3K/AKT/mTOR signaling pathway.[67] Mahalingam *et al.*[68] conducted a clinical study to evaluate the safety, preliminary efficacy, pharmacokinetics (PKs), and pharmacodynamics (PDs) of a combined treatment regimen involving the autophagy inhibitor hydroxychloroquine and the histone deacetylase inhibitor vorinostat in patients with advanced solid tumors. The study cohort consisted of 27 patients, including 12 individuals diagnosed with CRC, as well as those with renal cancer, ovarian cancer, soft tissue sarcoma, and breast cancer. The treatment protocol involved the oral administration of hydroxychloroquine at escalating doses once daily from day 2 to day 21 for a 21-day cycle, in conjunction with a fixed dose of 400 mg vorinostat once daily from day 1 to day 21. The findings indicated that one patient with renal cell carcinoma exhibited a sustained partial response, while the disease in two patients with CRC remained stable over an extended period. Furthermore, the addition of hydroxychloroquine did not significantly alter the PK profile of vorinostat. The study conducted by Liu *et al.*[69] indicates that ginsenoside Rg1 is capable of inhibiting the expression of phosphorylated Akt (p-Akt), phosphorylated mTOR (p-mTOR), and phosphorylated p70S6K (p-p70S6K) proteins, thereby suppressing autophagy in CRC cells. These findings imply that the anti-colon cancer effects of ginsenoside Rg1 may be associated with the modulation of autophagy, mediated through the inhibition of the AKT/mTOR/p70S6K signaling pathway. Besides, a study by Li *et al.*[70] demonstrated that the expression of methylenetetrahydrofolate dehydrogenase 1 (MTHFD1)

both *in vivo* and *in vitro* can enhance the migration of CRC cells and reduce autophagy in these cells. This effect is closely associated with the PI3K-AKT-mTOR signaling pathway in CRC cells. Conversely, downregulation of MTHFD1 expression leads to an increase in autophagy in CRC cells, while concurrently inhibiting their proliferation, migration, and invasion. It has been shown that the anthraquinone derivative C2 functions as a sensitizer to oxaliplatin (trans-/-diaminocyclohexane oxalatoplatinum), effectively reducing the resistance of HCT116/L-OHP cells to this chemotherapeutic agent.[71] Their findings indicate that anthraquinone derivative C2 can induce autophagy in HCT116/L-OHP cells through modulation of the p53 and PI3K/AKT/mTOR signaling pathways.

Taken together, a variety of compounds, including W922, polyphyllin II, betulin, chaetocochin J, myricetin, pogostone, salidroside, *Celastrus orbiculatus* extract, grape seed procyanidin B2, ethyl acetate extract of *Selaginella doederleinii* Hieron, active fraction of clove, M(4)IDP, ethyl acetate extract of *Halymenia durvillei*, PHLDA2, FAT4, ginsenoside Rg1, and anthraquinone derivative C2, have been identified as potential mediators of colorectal cell autophagy through the PI3K/AKT/mTOR signaling pathway. These findings provide novel evidence and support the notion that modulating the PI3K/AKT/mTOR signaling pathway can serve as a targeted therapeutic approach for CRC. However, the primary limitation of the existing studies in this area is that most of them primarily rely on cytological evidence and animal experiments to verify hypotheses, with a conspicuous lack of reliable human experimental data. This shortcoming undermines the overall persuasiveness of the research findings. Future studies should focus on both animal experiments and clinical trials to explore the specific effects and mechanisms of these compounds.

4.3. Apoptosis

Apoptosis is a cellular process that serves as a mechanism for regulating cell homeostasis through programmed cell death. In healthy tissues, a delicate equilibrium exists between cell proliferation and cell demise, with apoptosis frequently serving as the initiating process for cell death. Apoptosis in CRC cells is influenced by numerous signaling pathways, including the PI3K/AKT/mTOR pathway.[43,47,58,67,72-75]

Lin *et al.* utilized network pharmacological methods and conducted *in vitro* experiments to predict and confirm that Wei-Ton-xin primarily functions in CRC by modulating the activity of PI3K and AKT, as well as mediating endogenous cell apoptosis. Subsequent animal studies also demonstrated the efficacy of Wei-Tongxin as an anti-colon cancer agent *in vivo*.[72] Delicaflavone triggers the oxidative stress-induced apoptosis of cells by activating endoplasmic reticulum stress and mitochondrial pathways, along with suppressing PI3K/AKT/mTOR and renin-angiotensin system (RAS)/extracellular regulated protein kinase (ERK)/mitogen-activated protein kinase (MEK) signaling pathway.[73] FGF14 was found to be downregulated or silenced in all ten CRC cell lines, while being expressed in normal colon tissue and normal colon epithelial cell lines. This suggests that FGF14 may act as a novel tumor suppressor, inducing apoptosis in CRC cells through the mediation of the PI3K/AKT/mTOR pathway.[74] Furthermore, cudraflavone C has been shown to induce apoptosis in CRC cells by inhibiting the PI3K-AKT signaling pathway, subsequently leading to mitochondrial depolarization and activation of the intrinsic caspase pathway.[76] The study conducted by Khan *et al.*[77] demonstrates that fisetin, 5-FU, and their combination are each capable of inducing apoptosis in HCT116 and HT29 colon cancer cell lines. Furthermore, fisetin demonstrates an anti-CRC effect through the inhibition of the PI3K/AKT/mTOR signaling pathway. The concurrent administration of fisetin and 5-FU in treating PIK3CA-mutant CRC has been shown to significantly decrease the number of intestinal tumors.[77] Furthermore, a study conducted by Wang *et al.*[78] demonstrated that while the individual application of KW2478 or DDP effectively inhibits the proliferation of CRC cells, promotes apoptosis, and reduces the expression levels of p-PI3K, p-AKT, and p-mTOR proteins, their combined administration yields even more pronounced effects. Specifically, the combination therapy more effectively impedes CRC cell proliferation, significantly enhances the apoptosis rate, and further downregulates the expression of p-PI3K, p-AKT, and p-mTOR proteins.

CRC cells can be induced to undergo apoptosis by Wei-Tong-Xin, chaetocochin J, delicaflavone, FGF14, Naringin, polyphyllin II, HRK, cudraflavone C, fisetin, *etc.* However, the majority of evidence supporting this effect is derived from pre-clinical investigations, underscoring the need for additional research to elucidate the full extent of their therapeutic potential and underlying mechanisms.

4.4. Angiogenesis

Angiogenesis is a crucial physiological process under normal conditions, facilitating tissue growth, wound healing, and the regulation of the menstrual cycle. Conversely, under abnormal circumstances, angiogenesis serves as a critical mechanism for the proliferation and metastasis of malignant tumors. This is due to the heightened nutritional demands of malignant cells, which

require oxygen, glucose, and growth factors for sustained growth, as well as a sufficient blood supply for optimal circulation. Hence, angiogenesis is a critical factor in facilitating the advancement of tumors and is influenced by various angiogenesis promoters and suppressors within both tumor cells and their surrounding stroma.

The development, advancement, and spread of CRC are significantly influenced by the process of angiogenesis.[79,80] Results from a phase III randomized study conducted at multiple international centers demonstrated that the inhibition of angiogenesis provided significant therapeutic benefits for patients with the metastatic form of CRC in subsequent treatment.[81] There is increasing evidence that angiogenesis may be a pivotal therapeutic target in the treatment of metastatic CRC (mCRC). Signaling pathways involving PI3K, Akt, and mTOR play a crucial role in angiogenesis and metastasis.[82] The PI3K/AKT/mTOR pathway is activated by ESM1, enhancing tumor angiogenesis in CRC cells.[83] An increasing body of research has corroborated the notion that the suppression of the PI3K/AKT/mTOR pathway can impede the angiogenic processes associated with CRC, thereby demonstrating potential efficacy in the therapeutic management of this malignancy. ZDQ-0620, a derivative of 4-aminoquinazoline, functions as a novel pan-PI3K inhibitor and effectively suppresses angiogenesis in CRC cells through the inhibition of the PI3K/AKT/mTOR signaling pathway.[84] MicroRNA-16-5p suppresses angiogenesis in CRC by reducing FOXK1 expression, consequently impeding the PI3K/AKT/mTOR signaling pathway.[40] The Chinese medicinal formulation Chanling Gao appears to enhance overall health indicators and rectify abnormal blood cell counts through modulation of the PI3K/AKT/mTOR signaling pathway. Furthermore, it demonstrates efficacy in inhibiting tumor neovascularization and the expression of associated factors, thereby suppressing tumor growth in nude mice with CRC.[85] A study has demonstrated that proline/arginine-rich end and leucine-rich protein (PRELP), a constituent of the small leucine-rich proteoglycan family, interacts with fibroblast growth factor 1 (FGF1).[86] This interaction diminishes the stability of the FGF1 protein and accelerates its degradation, consequently attenuating the activity of the PI3K/AKT/mTOR signaling pathway. This attenuation ultimately leads to a reduction in tumor angiogenesis and metastasis.

Angiogenesis is dependent on the coordinated regulation of angiogenic promoters and suppressors. Consequently, we propose the utilization of angiogenic suppressors in the initiation, progression, and dissemination of CRC, with particular emphasis on targeting the PI3K/AKT/mTOR signaling pathway.

4.5. EMT

EMT is a biological process characterized by the transdifferentiation of epithelial cells into mesenchymal cells. Upon activation of EMT, the dissolution of tight junctions, disruption of apical polarity, and reorganization of cytoskeletal structure occur in tumor cells. These morphological alterations facilitate cellular migration away from the primary site, invasion of adjacent tissues, metastasis, circulation in the bloodstream, and establishment of metastatic tumors in distant organs.[87,88] The process of EMT plays a significant role in cancer progression by endowing cancer cells with phenotypic traits that are linked to increased aggressiveness.[89-91]

Inosine 5'-monophosphate dehydrogenase type II (IMPDH2) functions as an oncogene in human cancers. Elevated expression levels of IMPDH2 have been associated with tumor cell metastasis, lymphatic vessel invasion, and advanced clinical stages of tumors. Moreover, in CRC patients, high IMPDH2 expression is significantly correlated with reduced survival rates. The overexpression of IMPDH2 can trigger epithelial-mesenchymal transformation by upregulating AKT and PI3K signaling while downregulating mTOR signaling.[92] The kinase superfamily protein KIFC3 is prominently expressed in CRC tissues. Moreover, the activity of PI3K, AKT, and mTOR is regulated by KIFC3 in CRC, resulting in EMT.[93] Tumor suppressor LACTB exhibits decreased expression in CRC tissues. LACTB modulates the function of PIK3R3, influences the abundance of PI3K, facilitates autophagy through the PI3K/AKT/mTOR signaling cascade, and impedes EMT and cellular proliferation.[94]

5. Efficacy of PI3K/AKT/mTOR inhibitors for CRC management

The PI3K/AKT/mTOR signaling pathway plays a crucial role in various cellular processes, including cell survival, proliferation, apoptosis, autophagy, and growth. In CRC patients, aberrant activation of the PI3K/AKT/mTOR signaling pathway is frequently observed. Therefore, targeting the PI3K/AKT/mTOR signaling pathway has emerged as a promising therapeutic strategy for cancer treatment. Several drugs targeting the PI3K/AKT/mTOR signaling pathway (*i.e.*, inhibitors) have been developed and are currently being used for the treatment of CRC. These inhibitors can be broadly categorized into four classes: pan-PI3K inhibitors, Akt inhibitors, mTOR inhibitors, and dual PI3K-mTOR inhibitors. Table 1 provides a comprehensive overview of the utilization and research status of PI3K/AKT/mTOR signaling pathway inhibitors.

Table 1. Research advancements regarding the efficacy of PI3K/AKT/mTOR inhibitors for the management of CRC

Category	Inhibitor name	Application/Status in CRC	References
PI3K inhibitors	Alpelisib	FDA-approved for CRC treatment (pan-PI3K, Class I)	95,100
	Duvelisib	FDA-approved for CRC (pan-PI3K)	96
	Umbralisib	FDA-approved for CRC (pan-PI3K)	97
	Idelalisib	FDA-approved for CRC (pan-PI3K)	98
	Copanlisib	FDA-approved for CRC (pan-PI3K)	99
	ZDQ-0620	Preclinical: Induces apoptosis, as well as inhibits growth/metastasis and angiogenesis in CRC cells	84
	Buparlisib (BKM120)	• Monotherapy: Well-tolerated at 100 mg/day (Phase I) • Combination with panitumumab: Poor efficacy in wild-type-KRAS CRC • Combination with mFOLFOX6: Tolerable at 40 mg/day (phase I)	101-103,108
	Pictilisib (GDC-0941)	Phase I: Well-tolerated in CRC patients	104
	AZD8186	Preclinical: Safe/Tolerable as monotherapy+abiraterone/prednisone; antitumor effects in CRC	106
	TAK-117 (MLN1117/INK1117)	Phase I: Well-tolerated as monotherapy but limited efficacy; requires combination therapy	107
AKT inhibitors	MK-2206	• Monotherapy: Reduces tumor growth in IGF1R-dependent CRC • Combination with lapatinib: Tolerable but severe toxicity (diarrhea/rash) • Combination with selumetinib: No efficacy as shown in the phase II trial	109-112
mTOR inhibitors	Rapamycin/ Temsirolimus	• Preclinical: Inhibits metastasis; enhances oxaliplatin sensitivity • Phase II: No significant benefit in advanced CRC	114,115,121
	Everolimus	Phase II: Well-tolerated but limited efficacy in advanced CRC; synergistic with bevacizumab in refractory CRC	121,122
	Rapalink-1	Preclinical: Dual mTORC1/2 inhibition; suppresses HT-29 xenografts	118
	Torin-1	Preclinical: Inhibits proliferation/angiogenesis in mCRC cells	120
Dual PI3K/mTOR inhibitors	NVP-BEZ 235 (Dactolisib)	Preclinical: Induces apoptosis/autophagy; discontinued due to poor tolerability and efficacy	128,130
	GDC-0980 (Apitolisib)	Phase I: Well-tolerated in CRC patients (30 mg/day)	131
	Gedatolisib	Phase II: Response rate 5%, clinical benefit 16%, PFS 2.8 months	131
	PF-04691502	Discontinued due to poor tolerability; no established MTD	132

Abbreviations: AKT: Protein kinase B; CRC: Colorectal cancer; FDA: Food and Drug Administration; IGF1R: Insulin-like growth factor 1 receptor; mCRC: Metastatic colorectal cancer; MTD: Maximum tolerated dose; mTOR: Mammalian target of rapamycin; PFS: Progression-free survival; PI3K: Phosphoinositide 3-kinase.

5.1. PI3K inhibitors

The pivotal role of PI3K in promoting the survival, angiogenesis, and metastasis of CRC cells underscores the potential benefit of inhibiting or downregulating PI3K expression. The U.S. Food and Drug Administration has approved several PI3K inhibitors for cancer treatment, including alpelisib,[95] duvelisib,[96] umbralisib,[97] idelalisib,[98] and copanlisib.[99] These inhibitors can be categorized based on the subtypes of class IA PI3Ks they target, including pan-PI3K inhibitor options, such as buparisib, ZDQ-0620, and pictilisib, as well as other specific alternatives, such as taselisib and alpelisib.[100]

Qin *et al.*[84] introduced a new pan-PI3K inhibitor, specifically the 4-amino-quinazoline derivative ZDQ-0620. In addition to triggering apoptosis, ZDQ-0620 inhibited the growth, movement, and infiltration of CRC cells and hindered angiogenesis. The pan-class I PI3K inhibitor, buparlisib (BKM120), has demonstrated anticancer efficacy in various pre-clinical cancer models. Buparlisib exerts its inhibitory effects on the proliferation of CRC cells through covalent modification of tyrosine-802 residues, resulting in the inactivation of PI3K.[101] Goodwin *et al.*[102] conducted a clinical trial to ascertain the recommended phase II dose (RP2D) and the response rate of EGFR inhibition in combination with BKM120 for the treatment of advanced CRC. The study population comprised patients with chemotherapy-refractory wild-type-KRAS CRC, all of whom were naïve to the EGFR inhibition therapy. The findings indicated that the RP2D was established as panitumumab at 6 mg/kg administered intravenously every two weeks, in conjunction with BKM120 at a dosage

of 60 mg for five out of seven days per week. The observed toxicities included fatigue, rash, and mucositis. In this cohort, which was not selected based on biomarkers, there was minimal evidence of therapeutic activity.[102] The initial phase I clinical trial of buparlisib in human subjects with advanced solid tumors, which included 31 CRC patients and 21 breast cancer patients, demonstrated that buparlisib was well-tolerated at a dosage of 100 mg/day and exhibited preliminary antitumor efficacy in individuals with advanced cancer.[103] On the contrary, the combination of BKM120 and panitumumab in wild-type-KRAS patients with advanced CRC has demonstrated a lack of anti-cancer efficacy.[102] In a subsequent phase I clinical trial, Sarker *et al.*[104] recruited a cohort of 60 patients with tumors, 16 of whom had CRC, to assess the preliminary clinical efficacy of GDC-0941 (pictilisib) in a human dose-escalation study. The findings indicated that pictilisib exhibited favorable tolerability. AZD8186 is an inhibitor of PI3Kβ, demonstrating minimal activity toward PI3Kδ and exhibiting selectivity against PI3Kα and γ.[105] AZD8186 demonstrated safety and tolerability as a monotherapy, as well as in combination with abiraterone acetate/prednisone or vistusertib.[106] Initial findings suggest that AZD8186 exhibits potential antitumor effects in individuals diagnosed with CRC,[106] indicating the need for further investigation in subsequent studies focusing on PI3Kβ pathway-dependent cancers. Juric *et al.*[107] conducted a study to assess the safety, maximum tolerated dose, PKs, PDs, and initial antitumor effects of the investigational PI3Kα-selective inhibitor TAK-117 (MLN1117/INK1117) in CRC patients. The findings suggest that while intermittent dosing of TAK-117 is well-tolerated, its effectiveness as a monotherapy for tumor treatment is limited. Thus, additional investigation into combination therapy for advanced solid tumors is recommended.[107] In a phase I clinical trial conducted by McRee *et al.*[108] investigating the combination of BKM120 with the mFOLFOX6 regimen (comprising 5-fluorouracil/leucovorin [5-FU/LV] and oxaliplatin), a cohort of 17 patients received BKM120 treatment, including 5 individuals diagnosed with CRC. The findings indicate that the maximum tolerated dose of BKM120, when administered in conjunction with mFOLFOX6, is 40 mg per day, which is significantly lower than the standalone dose of 100 mg per day. This suggests that the combination is both effective and tolerable, whether used as monotherapy or in conjunction with other chemotherapeutic agents. Nonetheless, it is noteworthy that in patients with refractory solid tumors, the toxicity profile of the BKM120 and mFOLFOX6 combination is more pronounced compared to the administration of PI3K inhibitors alone or chemotherapy as the primary treatment modality.

In summary, while the majority of PI3K inhibitors have demonstrated certain effects in *in vitro* studies, animal models, and clinical trials, the prevailing evidence suggests that their efficacy is often enhanced when used in combination with other anti-tumor agents rather than as monotherapies. Nonetheless, not all PI3K inhibitors have exhibited significant anti-tumor activity. For instance, the combination of BKM120 and panitumumab in wild-type-KRAS patients with advanced CRC has shown limited anti-cancer efficacy. Conversely, the combination of BKM120 with 5-FU/LV and oxaliplatin has yielded more favorable outcomes, potentially due to individual patient variability and the specific drug regimens employed.

5.2. AKT inhibitors

Similarly, the suppression of AKT activity demonstrates beneficial outcomes in the management of CRC.[109] Agarwal *et al.*[109] elucidated the mechanism by which the Akt kinase inhibitor MK-2206 induces cell death in IGF1R-dependent colon cancer cells, which leads to the upregulation of PI3K/AKT signaling in response to IGF1R activation, and demonstrated that the administration of MK-2206 resulted in a notable reduction in tumor growth and enhanced cell death in CRC. Further, MK-2206 is well tolerated when combined with carboplatin and chemotherapy agents, such as paclitaxel, docetaxel, or erlotinib.[110] In a phase I clinical trial investigating the use of the AKT inhibitor MK-2206 in combination with lapatinib for the treatment of advanced HER2-positive breast cancer, the findings indicated a significant reduction in carcinoembryonic antigen levels in one participant with CRC.[111] In addition, the combination of MK-2206 and lapatinib was found to be tolerable at doses exceeding those of the individual bioactive drugs. However, the combination therapy was associated with relatively strong toxicity, including severe diarrhea and rash, though these adverse effects remained within a medically manageable range. Consequently, the combination of MK-2206 and lapatinib appeared to be a promising therapeutic strategy. Contrarily, the combination of MK-2206 and selumetinib (a MEK inhibitor) failed to achieve the intended level of targeted inhibition in mCRC during the phase II clinical trial. Despite robust pre-clinical evidence supporting the antitumor efficacy of MK-2206, no clinical response was observed in phase II trials.[112] One possible explanation is that the toxicity of MK-2206 combined with selumetinib exceeds that of either drug individually, putting a limit on the achievable dosage for clinical treatment.

5.3. mTOR inhibitors

There are three distinct generations of mTOR inhibitors, in addition to those derived from natural products.[113]

The initial wave of mTOR inhibitors predominantly consists of rapamycin (also referred to as sirolimus) and its derivatives, exemplified by drugs, such as temsirolimus and everolimus.[114,115] The derivatives of rapamycin exhibit enhanced water solubility and stability compared to rapamycin; however, they are susceptible to degradation upon oral administration. The second-generation mTOR inhibitors primarily consist of ATP-competitive inhibitors, such as pyrazolopyrimidines, pyridinopyrimidines, thienopyrimidines, triazines, and benzalididone.[116,117] Rapalink-1, which is a third-generation mTOR inhibitor, is developed through the integration of rapamycin and MLN018 (an mTOR kinase inhibitor) within a single molecule. This design allows for the simultaneous targeting of two sites on the mTOR enzyme, resulting in enhanced inhibition of mTOR activity and effective suppression of cell proliferation, as well as induction of autophagy.[118] On the other hand, natural product-derived mTOR inhibitors predominantly include curcumin, resveratrol, and sulforaphane.

mTOR inhibitors have been the subject of numerous studies in both fundamental research and clinical trials, with findings indicating a significant enhancement in the anti-tumor efficacy of various drugs following their combination with mTOR inhibitors. The suppression of mTOR activity by Raptor and Rictor has been shown to decrease the metastatic potential of CRC. Moreover, inhibition of mTORC1 and mTORC2 shifted phenotypic switches from stroma to epithelium, increasing oxaliplatin susceptibility in CRC.[119] The mTOR inhibitor torin-1 demonstrates inhibitory effects on the proliferation and viability of mCRC cells, concomitant with a reduction in angiogenesis.[120]

Numerous clinical trials have explored the effectiveness of rapamycin and its derivatives in managing mCRC. Findings indicated that the use of everolimus, an mTORC1 inhibitor, at a dosage of 70 mg/week or 10 mg/day in CRC patients was generally well-tolerated, yet did not yield significant benefits for individuals with advanced mCRC.[121] It may be necessary to explore higher doses of everolimus or to investigate its potential synergistic effects with other therapeutic agents in future research. The findings of a phase II clinical trial evaluating the combination of bevacizumab and everolimus demonstrated acceptable tolerability and modest efficacy in individuals with refractory mCRC.[122] The combination of oral tivozanib and evolimus demonstrates favorable tolerability, as evidenced by the maintenance of stable disease in 50% of patients with refractory mCRC.[123] Patients with refractory mCRC who receive oral tivozanib and evolimus have demonstrated favorable tolerability, as evidenced by the maintenance of stable disease in 50% of patients.[124] The results indicated that the combination of evolimus with mFOLFOX-6 + bevacizumab was well-tolerated and showed promising efficacy in patients with mCRC, especially those with PTEN deficiency, achieving an 86% response rate.[125] Therefore, further research is needed to determine what role rapamycin and its derivatives play and how they work in the treatment of mCRC.

At present, no mTOR inhibitors are approved for the treatment of CRC. Nevertheless, the promising efficacy of dual mTORC1/2 kinase inhibitors against CRC is noteworthy. It was determined that INK-128, a newly developed ATP-competitive kinase inhibitor targeting mTOR, effectively inhibits the activation of mTORC1 and mTORC2 in both primary and transformed CRC cells, leading to growth inhibition and apoptosis induction. In animal experiments, it was discovered that daily oral administration of INK-128 effectively suppressed the growth of HT-29 xenografts in mice.[126] Moreover, it is essential to conduct additional research in future clinical trials and explore combination treatment regimens to further investigate the efficacy of the mTORC1/2 inhibitor TAK-228 in overcoming resistance to evolimus and inducing a therapeutic response in PIK3CA-mutant CRC.[127] Despite the promising results of the pre-clinical studies mentioned above, the findings may not necessarily apply directly to humans. These experimental findings pertain to pre-clinical studies and may yield disparate outcomes when extrapolated from cell and animal experiments to human subjects. Nevertheless, the potential for the development of novel ATP-competitive mTOR kinase inhibitors as primary or adjunctive therapies for CRC is promising, underscoring the importance of conducting clinical trials and exploring combination treatment strategies involving these inhibitors.

In summary, mTORC1 inhibitors, such as rapamycin and everolimus primarily inhibit mTORC1 activity without affecting mTORC2, potentially leading to decreased feedback inhibition of AKT by mTORC2 and subsequently promoting tumor cell survival and drug resistance. This limitation may compromise the anti-tumor efficacy of rapamycin. In contrast to rapamycin, ATP-competitive mTOR inhibitors capable of inhibiting both mTORC1 and mTORC2 can achieve effective compensation for the limited feedback inhibition of AKT by mTORC2, with comparable effects observed with dual PI3K/mTOR inhibitors. Hence, it is theoretically postulated that ATP-competitive mTOR inhibitors and dual PI3K/mTOR inhibitors have the potential to augment the anti-cancer efficacy and mitigate drug resistance arising from the limited feedback inhibition of AKT by mTORC2.

5.4. Dual inhibitors of PI3K/mTOR

The PI3K/mTOR dual inhibitor functions by simultaneously inhibiting the activity of both mTOR and PI3K.

NVP-BEZ 235, also known as dactolisib, inhibits the proliferation and migration of HT-29 cells, induces apoptosis and autophagy, and inhibits tumor growth.[128] The combination of diosmin with BEZ-235 notably suppressed the proliferation of HCT-116 cells in CRC.[129] The results indicated that the clinical efficacy of dactolisib either as monotherapy or combination therapy did not meet the anticipated levels. in addition, the PK profile exhibited low to moderate variability, with significant gastrointestinal adverse reactions observed at high doses. Consequently, the development of this drug for oncology indications was discontinued.[130] The phase I clinical trial of GDC-0980 (also referred to as apitolisib) in patients with advanced tumors, which included 24 CRC patients (10%), involved oral administration of 30 mg of apitolisib once daily. The findings indicated that the treatment was well-tolerated by patients and demonstrated sustained anti-tumor efficacy.[131] The combination of gedatolisib and irinotecan resulted in a favorable response rate and clinical benefit in approximately 5% and 16% of CRC patients, respectively, with a progression-free survival of 2.8 months. Conversely, the dual PI3K/mTOR inhibitor PF-04691502 was pre-maturely discontinued due to poor tolerability, and the maximum tolerated dose was not established. In contrast, PF-04691502, another dual PI3K/mTOR inhibitor, was pre-maturely discontinued due to poor tolerability, with the maximum tolerated dose remaining undetermined.[132]

Radiation sensitivity of tumor cells is also enhanced by PI3K/mTOR inhibitors. Clinical trials of individual inhibitors or their combinations have produced varying results, especially in early-stage CRC. It has been demonstrated in pre-clinical studies that regulating PI3K, AKT and mTOR pathway activity can radiosensitize different types of cancer cells.[133,134] The effects of radiotherapy on CRC cells can be enhanced by administering dactolisib before radiotherapy, based on findings from both laboratory studies and animal experiments.[135] Nevertheless, the tolerance of dual PI3K/mTOR inhibitors in tumor patients remains unclear. Future studies on CRC should focus on the therapeutic effect of dual inhibitors of PI3K/mTOR.

6. Summary and future prospects

Modulation of the PI3K/AKT/mTOR signaling pathway can impact various cellular processes in CRC cells, including proliferation, autophagy, apoptosis, angiogenesis, and EMT, thereby influencing the pathogenesis and progression of CRC, as well as patient prognosis.

It has been identified that modulation of the PI3K/AKT/mTOR signaling pathway can serve as a therapeutic approach in CRC, and various inhibitors targeting this pathway are being tested in pre-clinical and clinical trials. Despite this, only a limited number of inhibitors have been sanctioned for clinical use in the treatment of CRC, with the predominant issue being the adverse effects associated with these drugs. Furthermore, the lack of specificity in inhibitors is a significant contributor to their toxicity. Pan-PI3K inhibitors demonstrate general efficacy but are associated with notable toxicity. Conversely, more selective PI3K inhibitors, exemplified by alpelisib, exhibit enhanced efficacy in individuals with *PIK3CA* mutations and demonstrate reduced toxicity. Moreover, the present body of research on PI3K/AKT/mTOR inhibitors remains predominantly confined to *in vitro* cellular experiments and studies in animal models. Consequently, the extrapolation of these experimental findings to human subjects is significantly constrained, necessitating further validation through clinical trials. At present, while certain clinical trials involving PI3K/AKT/mTOR inhibitors have incorporated individuals diagnosed with CRC, there exists a dearth of research examining the effectiveness of these inhibitors specifically in CRC patients.

Despite findings from research on PI3K/AKT/mTOR signaling pathway in CRC, further investigations on numerous areas are still warranted. For instance, studies on targeted therapy employing inhibitors directed at this pathway to enhance clinical efficacy, minimize adverse reactions, and enhance survival rates should deserve more of our attention.

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Conflict of interest

The authors declare no conflict of interest.

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