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TOPIC HIGHLIGHT

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Targeting mTOR network in colorectal cancer therapy

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Abstract

The mechanistic target of rapamycin (mTOR) integrates growth factor signals with cellular nutrient and energy levels and coordinates cell growth, proliferation and survival. A regulatory network with multiple feedback loops has evolved to ensure the exquisite regulation of cell growth and division. Colorectal cancer is the most intensively studied cancer because of its high incidence and mortality rate. Multiple genetic alterations are involved in colorectal carcinogenesis, including oncogenic Ras activation, phosphatidylinositol 3-kinase pathway hyperactivation, *p*53 mutation, and dysregulation of wnt pathway. Many oncogenic pathways activate the mTOR pathway. mTOR has emerged as an effective target for colorectal cancer therapy. *In vitro* and preclinical studies targeting the mTOR pathway for colorectal cancer chemotherapy have provided promising perspectives. However, the overall objective response rates in major solid tumors achieved with single-agent rapalog therapy have been modest, especially in advanced metastatic colorectal cancer. Combination regimens of mTOR inhibitor with agents such as cytotoxic chemotherapy, inhibitors of vascular endothelial growth factor, epidermal growth factor receptor and Mitogen-activated protein kinase kinase (MEK) inhibitors are being intensively studied and appear to be promising. Further understanding of the molecular mechanism in mTOR signaling network is needed to develop optimized therapeutic regimens. In this paper, oncogenic gene alterations in colorectal cancer, as well as their interaction with the mTOR pathway, are systematically summarized. The most recent preclinical and clinical anticancer therapeutic endeavors are reviewed. New players in mTOR signaling pathway, such as nonsteroidal anti-inflammatory drug and metformin with therapeutic potentials are also discussed here.

Key words: Mechanistic target of rapamycin pathway; Colorectal cancer; Mechanistic target of rapamycin inhibitor; Chemotherapy; Drug resistance

Core tip: Mechanistic target of rapamycin (mTOR) pathway serves as a central regulating axis that coordinates cell growth and proliferation. Single-agent mTOR inhibition therapy, however, has provided only limited therapeutic efficacy towards colorectal cancer. Blocking compensatory pathways and multiple feedback loops is considered the challenge. Combination regimens are being intensively tested in clinic. This review summarizes extensive studies describing crosstalk between mTOR pathway and major oncogenic pathways contributing to colorectal cancer development and novel combinational strategies targeting the mTOR pathway in treating colorectal cancer are also introduced.

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INTRODUCTION

The signaling pathway of mechanistic target of rapamycin (mTOR), regulates cell growth and proliferation largely by promoting key anabolic processes, by sensing nutrition levels and growth factors, as well as various environmental cues[1,2]. The mTOR pathway is conserved in organisms from yeast to human. The central protein, mTOR, is an atypical serine/threonine protein kinase that belongs to the phosphoinositide 3-kinase (PI3K)-related kinase family. mTOR interacts with several proteins to form two distinct complexes, known as mTOR complex 1 (mTORC1) and complex 2 (mTORC2). Both complexes share a DEP domain-containing mTOR-interacting protein (DEPTOR), a mammalian lethal with sec-13 protein 8 (mLST8, also known as GbL)[3] and Tti1/Tel2[4]. Regulatory-associated protein of mammalian target of rapamycin (raptor)[5] and proline-rich Akt substrate 40 kDa (PRAS40)[6] are unique to mTORC1 and rapamycin-insensitive companion of mTOR (rictor)[7], mammalian stress-activated MAP kinase-interacting protein 1 (mSin1)[8] and protein observed with rictor 1 and 2 (protor1/2)[9] are specific to mTORC2. mTOR is the target of rapamycin (or sirolimus), but only mTORC1 is sensitive to rapamycin inhibition upon FKBP12-rapamycin binding[10]. Rapamycin also inhibits the mTORC1 downstream targets differently[11]. mTORC1 plays a pivotal role in regulating protein and nucleotide synthesis by signaling through its main effectors, p70 ribosomal S6 kinase 1 (S6K1) and eIF4E binding protein 1 (4E-BP1). S6 ribosomal protein, a component of the 40S ribosomal subunit, is the best characterized S6K1 substrate and a major effector of cell growth. Phosphorylated 4E-BP1 binds to eukaryotic translation initiation factor 4E (eIF4E), which is an important component of the pre-initiation eIF4F complex and prevents the complex from binding with the 5' end cap structure on messenger RNAs of proteins essential for the cell cycle progression, functioning as a rate-limiting factor in cap-dependent translation initiation. mTORC1 promotes *de novo* lipid synthesis by regulating Lipin-1 and SREBP1/2, and it promotes energy metabolism by positively regulating cellular metabolism and ATP production through activation of HIF1α and suppresses autophagy through ULK1 (unc-51-like kinase 1) and Atg13 (mammalian autophagy-related gene 13). mTORC2 phosphorylates protein kinase B (Akt/PKB), serum- and glucocorticoid-induced protein kinase 1 (SGK1), and protein kinase C-α (PKCα), regulating cell survival, metabolism, and cytoskeletal organization[12]. Multiple feedback loop mechanisms add to the complexity of the mTOR signaling pathway[13].

mTORC1 integrates intracellular and extracellular signals--growth factors, stress, energy status, oxygen, and amino acids--mainly through the TSC1-TSC2 (hamartin-tuberin) complex. The TSC1/2 complex functions as a GAP (GTPase-activating protein) for the Ras homolog enriched in brain (Rheb), of which the GTP-bound form activates mTORC1. The TSC1/2 complex relays signals from upstream regulators that sense environmental growth signals and nutrition levels. TSC1 protects TSC2 from ubiquitin degradation[14]. In response to growth signals, multiple effectors phosphorylate TSC2, including Akt, extracellular-signal-regulated kinase1/2 (ERK1/2), and ribosomal S6 kinase (RSK1), thereby promoting mTOR signaling activation.

The TSC1/2 complex also responds to diverse stress signals. Upon hypoxia or low ATP state, adenosine monophosphate-activated protein kinase (AMPK) phosphorylates TSC2 and enhances its GAP activity toward Rheb[15]. Mitogen-activated protein kinase kinase kinase kinase 3 (MAP4K3)[16], mammalian vacuolar protein sorting 34 homolog (hVPS34)[17] and inositol polyphosphate monokinase (IPMK)[18] are reported as amino acid sensing proteins. However, our understanding of the mechanisms by which mTOR senses amino acids through the v-ATPase (vacuolar H^+-ATPase)-Ragulator (LAMTOR1-3)-Rag GTPase complex has evolved greatly in recent years. Four Rag proteins, RagA to RagD, form heterodimers: RagA with RagB, and RagC with RagD. When RagA/B is bound to GTP, RagC/D is bound to GDP, and vice versa. Amino acids promote GTP loading of RagA/B, thus enabling the heterodimer to interact with raptor. Ragulator binds with Rag GTPases and translocates to the lysosome surface, where mTORC1 interacts with GTP bound Rheb. v-ATPase locates on the lysosomal membrane interacts with Ragulator to relay the amino acid level signals from the lysosomal lumen[19-22].

KEY COLORECTAL CARCINOGENESIS PATHWAYS AND THEIR INTERACTION WITH THE mTOR PATHWAY

Colorectal cancer (CRC) is the third most common cancer worldwide, with more than one million cases annually. CRC caused almost 0.7 million death in 2012 globally[23]. It is the second most deadly cancer among adults in the United States[24]. In approximately 75% of cases, the cancer are confined within the wall of the colon (stage Ⅰ and Ⅱ), or only spreads to regional lymph nodes (stage Ⅲ). These stages of cancer are mostly curable by surgical excision combined with chemotherapy. However, in about 20% of cases, the tumors metastasize to distant sites and are usually inoperable and incurable, with only a 12% 5-year relative survival rate[25,26]. Approximately 75%-80% of colorectal tumors develop in a sporadic manner[27]. An over-simplified model that generalizes the genetic cause of colorectal carcinogenesis is one where microsatellite instability (MSI) contributes to 85% of CRC, while the remaining 15% arise from chromosomal instability (CIN). However, some studies have shown that the MSI and CIN pathways are not mutually exclusive in CRC and considerable crosstalk exists between various pathways[28]. The "canonical" colorectal carcinogenesis model, that the carcinomas arise from pre-existing adenomas, was proposed in 1990 by Fearon and Vogelstein[29]. This

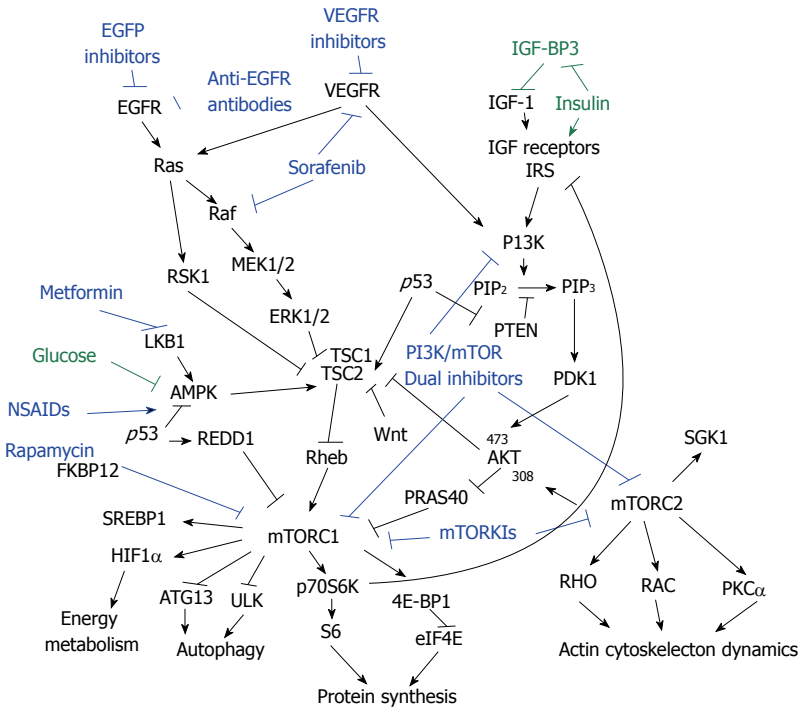

Figure 1 Crosstalk between mechanistic target of rapamycin signaling pathway and colorectal oncogenic pathways. PI3K/AKT and Ras/MAPK pathways are the major upstream mediators of mechanistic target of rapamycin (mTOR) signaling pathway in colorectal cancer. Therapeutic efforts for colorectal cancer targeting mTOR signaling include Rapamycin (or Rapalogs) inhibition as well as mTOR kinase inhibition, plus in combination with blockage of growth factor receptors, and components in upstream pathways such as Raf and PI3K, *etc.* New players regulating the mTOR pathway such as non-steroidal anti-inflammatory drug (NSAIDs) and metformin merit further investigation. IGF: Insulin like growth factor; SGK1: Serum- and glucocorticoid-induced protein kinase; PRAS40: Proline-rich Akt substrate 40 kDa; TSC1: Tuberous sclerosis-1; TSC2: Tuberous sclerosis-2; AMPK: Adenosine monophosphate-activated protein kinase; eIF4E: Eukaryotic translation initiation factor 4E; RSK1: Ribosomal S6 kinase.

model describes approximately 80%-90% of CRC and it is still accepted, despite a large body of new information on CRC that has emerged during the last two decades. In this model, the accumulation of genetic alterations, such as APC, *p*53, DCC, and K-ras, enable colorectal carcinogenesis, as well as histological malignancy progression[27].

Many of the genetic pathways involved lie upstream of mTOR, and the oncogenes affected elicit part of their oncogenic effect through the mTOR signaling pathway[30]. The interaction between mTOR signaling and other important pathways involved in colorectal carcinogenesis are reviewed here (Figure 1).

Wingless/wnt pathway

Aberrant crypt foci (ACF) is considered the first identifiable precursor lesion in colorectal tissue[31]. ACF derives from epithelial cells in the lining of the colon and rectum and can develop into adenomatous polyps, which could potentially progress to adenocarcinoma[32]. Adenomatous polyposis coli (APC) tumor suppressor gene normally suppresses the Wnt pathway by actively degrading β-catenin and inhibits its nuclear localization[33]. A close link between β-catenin signaling and the regulation of VEGF-A expression was observed in human CRC, indicating the role of β-catenin in CRC angiogenesis[34]. β-catenin was also shown to induce cyclin D1 in CRC cells, which contributes to neoplastic transformation[35]. Aberrant, mutant APC or APC loss can cause constitutive activation of the Wnt pathway, which is considered the initiating event in colorectal cancer. APC mutation can cause more than 100 adenomatous polyps[36-38]. The Wnt signaling pathway stimulates the TSC-mTOR pathway[39]. mTOR signaling, as well as the mTOR protein level, was observed to be elevated in $Apc^{\Delta 716}$ mice. Inhibition of the mTORC1 pathway by treating the APC mutant mice with RAD001 (everolimus) was reported to suppress intestinal polyp formation and reduce the mortality of the animals[15,39].

PI3K/AKT pathways

Nutrient signals act mostly through insulin or insulin-like growth factor (IGF) signaling pathways. Growth factors-receptors, such as epidermal growth factor receptor (EGFR), platelet-derived growth factor receptor (PDGFR), insulin like growth factor-1 receptor (IGF-1R), and cell adhesion molecules, such as integrin and G-protein-coupled receptors, activate the PI3K pathway to promote cell survival, proliferation and cell growth[40]. The activated receptor tyrosine kinases interact with PI3K, where class I PI3K family members convert phosphatidylinositol 4,5-bisphosphate (PIP_2) to phosphatidylinositol 3,4,5-trisphosphate (PIP_3), hence activating phosphoinositide-dependent kinase-1 (PDK1) and mTORC2. Specifically, phosphatase and tensin homolog (PTEN) reverses this process by dephosphorylating PIP_3 to PIP_2. IGF-BP3 binds to IGF-1 and prevents

over activation of IGF-1/AKT signaling. It is currently believed that PDK1 phosphorylates AKT on Thr308, whereas mTORC2 phosphorylates AKT at Ser473. Double phosphorylation fully activates AKT activity[41]. Hyperactivation of the PI3K/AKT pathway is associated with malignant behavior, including proliferation, adherence, transformation, and survival[42-45]. PI3K/PTEN/AKT pathway mutations are found in a large number of CRC cell lines[46-49]. The PIK3CA mutation is found in 15% of metastatic colorectal cancer (mCRC)[50]. Germline PTEN ablation is associated with Cowden syndrome, which can cause an increased lifetime risk for CRC[51,52]. Elevated protein levels of PI3K subunit p85α and AKT1/2, and phosphorylation levels of $mTOR^{Ser2448}$ and phosphor-$p70S6K^{Thr389}$ have been observed in CRC patients. Notably, p85α expression was considerably higher in stage Ⅳ tumors than in earlier stages[46]. Analyzing the mechanism of GP130-mediated mTORC1 activation in mice revealed a requirement for JAK and PI3K activity in the activation of mTORC1, leading to colorectal tumorigenesis[53]. mTOR inhibition abolishes S6K phosphorylation and relieves the feedback suppression on RTK, leading to PI3K activation and, eventually, to AKT activation[54,55].

p53 pathway

*p*53 is considered the "guardian of the genome". *p*53 mediates diverse stress signals, such as DNA damage, energy and metabolic stress, hypoxia, oxidative stress, oncogene stress and ribosomal dysfunction. Functioning as a transcription factor, *p*53 regulates its downstream factors to elicit its tumor suppressive functions, which include cell cycle arrest, senescence, DNA repair, and programmed cell death[56]. Under normal conditions, *p*53 inhibits the mTOR pathway by multiple routes. De-regulation of the *p*53 pathway by either mutation of the TP53 gene or by 17p chromosomal deletion is thought to be the second key step in tumorigenesis of CRC, marking the transition from adenoma to carcinoma[26,57]. *p*53 closely monitors the IGF-1/AKT pathways, which is an upstream regulation pathway of mTOR[58,59]. *p*53 induces IGF-BP3 to inhibit mitogenic signaling[60] and directly regulates the transcription of PTEN[61]. In addition, *p*53 induces Sestrin1/2 upon DNA damage and oxidative stress, which negatively regulates mTOR through activation of AMPK and TSC2 phosphorylation[62]. Furthermore, in colorectal cancer cell lines, *p*53 can suppress mTOR activity by regulating AMPK-β1 and TSC2 directly. Notably, the increased mRNA level of TSC2 by γ-irradiation-induced *p*53 activation can be cell type specific. However, data showed that *p*53-dependent induction of TSC2 exists in HCT116 cells and mouse colon tissue[63,64]. REDD1 is another *p*53 target gene that regulates the mTOR pathway[65]. REDD1 is regulated by reactive oxygen species (ROS) and oxidative stress. REDD1 is necessary for hypoxia induced TSC1/2 activation[66].

RAS/RAF/MITOGEN-ACTIVATED PROTEIN KINASE PATHWAY

Ras is the first identified oncogene and the most frequently mutated gene in human malignancy. Ras is a small GTPase that relays signals from a subset of growth factors responsive RTK to its effector pathways, which are responsible for growth, migration, adhesion, cytoskeletal integrity, survival and differentiation. The three true Ras proteins in the RAS family that have been most studied are H-Ras, N-Ras and K-RAS[67]. The *K-RAS* gene is the most mutated RAS pathway member in CRC, with a 35%-45% mutation rate in mCRC, compared with BRAF 8% and NRAS 4%[50]. K-RAS mutation is thought to be a relatively early event that correlates histologically with early to late adenomas. N-RAS mutations are also observed in a small percentage of CRC[31]. The major Ras downstream pathway is the Raf-mitogen-activated protein (MAP) kinase kinase-MAP kinase signal transduction pathway. Ras also indirectly signals to mTOR through its other effector pathway, the PI3K/AKT pathway[68,69]. The p44/42 mitogen-activated protein kinase pathway (MAPK)-ERK1/2 directly phosphorylates and inactivates TSC2[70,71]. ERK phosphorylates ribosomal protein S6, a direct effector of S6K1, stimulating cap-dependent translation[72,73]. The MAPK-activated kinase and RSK interact with and phosphorylate TSC2 at Ser-1798, thus inhibiting the tumor suppressor function of the TSC1/2 complex, resulting in increased mTOR signaling to S6K1[74].

Autophagy

It is well established that mTORC1 negatively regulates autophagy. Atg1/ULK1 are central components in autophagy, and ULK1 as a direct target of TORC1[75]. On the other hand, the role of autophagy in cancer, including colorectal cancer, can be complicated. Autophagy can contribute to cell death during chemotherapy, but could also serve as a survival mechanism for cancer cells. In fact, its function may vary in different types of tumors, as well as for various stages of cancer[76-78]. Autophagy is also reported to contribute to cancer cachexia. High level of HMGB1 was detected in the serum of CRC patients, and was associated with colorectal cancer progression. HMGBI was shown to induce autophagy in muscle tissue by reducing mTOR phosphorylation in tumors bearing mice, therefore increasing plasma free amino acid levels, providing energy source to the cancer cells[79].

Other mechanisms

The mTOR signaling pathway may have a direct effect on carcinogenesis. Elevated mTOR mRNA and protein levels, as well as Raptor and Rictor levels, are observed in CRC patient tissues. Furthermore, a good correlation between a higher malignancy stage and higher expression level was observed[80,81] mTORC1/2 are critical for CRC

metastases *via* RhoA and Rac1 signaling[81]. Using a genetically engineered mouse model, mTOR was proposed to contribute to tumorigenesis by causing chromosomal instability[82,83].

COLORECTAL CANCER THERAPIES TARGETING THE mTOR PATHWAY

mTOR has a central role in the regulatory network sensing nutrition and growth signals, coordinating cell growth and proliferation. It has long been proposed that mTOR inhibitors may be efficacious for treating and preventing tumor progression[84-86], particularly in CRCs[87]. Tremendous efforts have been made to develop potent and effective molecules to target the mTOR pathway[88]. Efforts on targeting the mTOR pathway for CRC treatment have been reviewed extensively in previously published reviews[89,90].

Nowadays, CRC chemotherapy consists mainly of oral fluoropyrimidines, with the addition of irinotecan and oxaliplatin. The emergence of targeted monoclonal antibodies (Mabs), such as bevacizumab (Bev) (anti-VEFG-A), cetuximab and panitumumab (anti-EGFR), has provided more treatment options to extend survival and improve clinical outcomes in mCRC[91,92]. However, less than 20% of patients with mCRC respond to clinically available targeted drugs when used as monotherapy[50]. This also suggests that a better understanding of the in depth molecular alterations in CRC is needed to discover more precise and effective therapeutic targets for those CRC cases that do not respond well to current treatment paradigms.

First generation of mTOR inhibitors-rapamycin and rapalogs

Rapamycin is the first discovered natural inhibitor of mTOR. The antitumor effect of rapamycin in colorectal cancer has been demonstrated *in vitro* and in various mouse models[39,53,93] Rapamycin inhibits mTORC1 with high specificity; however, its hydrophobicity and poor bioavailability has made it a less than optimal antitumor agent. Rapalogs, such as temsirolimus (CCI-779), everolimus (RAD001), and ridaforolimus (AP-23573, deforolimus) confer better potency, pharmacokinetic profiles and clinical activity than rapamycin, and are thus being used in the clinic or in developing treatments for many types of cancer, mostly solid tumors[90]. Temsirolimus and everolimus are approved for treating metastatic renal cell carcinoma and pancreatic neuroendocrine tumors. Everolimus is also approved for breast cancer therapy. However, multiple clinical trials have failed to demonstrate meaningful efficacy of everolimus in the treatment of CRC in the single agent setting[94,95]. Moreover, Rapalogs used alone are thought to be cytostatic in most tumor types and primarily stabilize clinical disease[83,86]. Deregulation of the PI3K and K-Ras signaling pathways determines therapeutic response to everolimus[96]. The central role of the PI3K/mTOR pathway in cancer biology suggests that other drug combinations showing mTOR inhibition merit evaluation. Combinational regimens consisting of Rapalogs and other antitumor agents have shown promising results[97].

Both preclinical data and clinical trials have demonstrated that combined VEGF and mTOR inhibition has greater anti-angiogenic and anti-tumor activity than either monotherapy. Bevacizumab and everolimus combined therapy was well tolerated, with prolonged stable disease in patients with refractory, metastatic colorectal cancer[98,99]. Reported side effects included risks related to mucosal damage and/or impaired wound healing[100]. The addition of a chemotherapy agent, such as doxorubicin, is also in development for advanced cancer therapy. Molecular analyses revealed an association between tumor response and a PIK3CA mutation and/or PTEN loss/mutation, suggesting further evaluation in patients with PI3K pathway dysregulation[100]. Using a xenograph tumor model, Lapatinib was shown to reduce tumor volume synergistically with everolimus, by reducing P-glycoprotein (P-gp) efflux of everolimus through inhibition of P-gp. This provided a new lead towards new chemotherapy in mCRC harboring K-RAS mutations[101]. The mosaic mutations in various oncogenic/tumor suppressive genes downstream of EGFRs undermines the therapeutic response of the anti-EGFR antibodies. K-RAS and BRAF mutations are associated with poor prognosis in CRC[102]. Temsirolimus has limited efficacy in chemotherapy-resistant K-RAS mutant disease, and K-RAS mutation is a negative predictive prognostic factor during mCRC treatment with anti-EGFR compounds[95,103]. Sorafenib, which is a multikinase inhibitor of Ras/MAPK signaling targeting Raf, also inhibits growth factor receptors, such as VEGFR and PDGFR. Sorafenib has been shown to enhance the therapeutic efficacy of rapamycin in CRC carrying oncogenic K-RAS and PIK3CA, in preclinical settings[104].

In a subgroup analysis of the Phase Ⅲ trial, the combination of everolimus and octreotide LAR demonstrated a significant prolonged median progression-free survival (PFS) in patients with advanced colorectal neuroendocrine tumors[105]. Everolimus combined with irinotecan proved to be well tolerated in a phase I study as second-line therapy in mCRC; however, an *in vitro* study showed an additive effect in HT29 tumor xenografts, but not in HCT116, which both harbor BRAF/PIK3CA mutations[106].

Second generation of mTOR inhibitors-Dual PI3K/mTOR inhibitors and mTOR kinase inhibitors

Isolated inhibition of mTORC1 by rapamycin or Rapalogs proved that they were only partial inhibitors of mTORC1 and they do not have a meaningful contribution clinically in a single agent setting. Moreover, because of the release of feedback inhibition of AKT from S6K1 inhibition, a pro-survival effect derives from induced AKT activity. Inhibitors that block both the PI3K

signaling pathway and mTORC1/2 have been developed and have shown greater anticancer effects than Rapalogs[107-111]. Dual PI3K/mTOR inhibitors are less likely to induce drug resistance than single-kinase inhibitors. mTOR specific kinase inhibitors are expected to inhibit mTORC1 and mTORC2 simultaneously, although inhibiting mTORC1 may cause mTORC2 upstream AKT activation. Many dual PI3K/mTOR inhibitors and mTOR kinase inhibitors are under preclinical study and some have entered the clinical phase[88].

Resistance arises from simultaneous mutation in parallel pathways related to the mTOR pathway. Preclinical and clinical studies indicate that PIK3CA mutation in the absence of KRAS mutation is a predictive marker for the response to PI3K and mTOR inhibitors[109,112]. However, CRC with the KRAS activation mutation is frequently observed, and it commonly coexists with PIK3CA mutations. Coexisting mutations of KRAS, BRAF and PIK3CA attenuate sensitivity to PI3K/mTOR inhibition in CRC cell lines[113,114]. Partial mTOR inhibition from rapamycin and mTOR kinase inhibitors indicates the existence of an unknown 4E-BP1 kinase that is potentially responsible for resistance in CRC[115]. The combination of a MEK inhibitor and PI3K/mTOR inhibitor was thus proposed to overcome the intrinsic resistance to MEK inhibition in CRCs[116,117]. Concomitant BRAF and PI3K/mTOR inhibition has been shown to be required for treatment of BRafV600E CRC[118].

Others

Non-steroidal anti-inflammatory drugs, including aspirin and selective cyclooxygenase-2 (COX-2) inhibitors, have been investigated for protection against CRC development[119]. Aspirin was reported to lower the risk of, and improve the survival from, colorectal cancer[120,121]. PIK3CA mutation in colorectal cancer may serve as a predictive molecular biomarker for adjuvant aspirin therapy[122]. A study showed that aspirin reduced mTOR signaling by activating AMPK; suppressed autophagy by mTOR inhibition may contribute to the antitumor effect of aspirin[123]. Indomethacin and nimesulide are also reported to reduce mTOR signaling and suppress CRC growth *via* a COX-2 independent pathway. These studies unveiled a novel mechanism through which COX-2 inhibitors exert their anticancer effects, as well showing protective effects against development of CRC, further emphasizing the validity of targeting mTOR signaling in anticancer therapy[124]. Additive antitumor effects with low carbohydrate diets were observed with the mTOR inhibitor CCI-779 and, especially, with the COX-2 inhibitor Celebrex[125].

A meta-analysis showed that diabetes mellitus increased risk of developing CRC[126], while metformin therapy appears to be associated with a significantly lower risk of colorectal cancer in patients with type 2 diabetes[127,128]. Metformin regulates glucose homeostasis by inhibiting liver glucose production and increasing muscle glucose uptake. A preclinical study showed that metformin inhibits insulin-independent growth and xenograft tumor growth of cells carrying the gain-of-function H1047R mutation of the *PI3KCA* gene, which has been shown to form diet restricted-refractory xenotumors[129], suggesting that metformin was not a *bona fide* diet restriction mimetic[130]. In both chemical carcinogen-induced and APC mutant colorectal carcinogenesis murine models, metformin activated AMPK and inhibited the mTOR/S6K1 pathway, leading to suppressed colonic epithelial proliferation and reduced colonic polyp formation[131,132]. These data suggest that metformin might be a safe and promising candidate for the chemoprevention of CRC.

Tandutinib inhibits several receptor tyrosine kinases, including the Fms-like tyrosine kinase 3 receptor, platelet-derived growth factor receptor (PDGFR), and c-Kit receptor tyrosine kinase. Tandutinib inhibits the Akt/mTOR signaling pathway to inhibit CRC growth[133].

Curcumin, derived from the tropical plant *Curcuma longa*, has a long history in traditional Asian medicine. The preventive and therapeutic properties of curcumin are associated with its antioxidant, anti-inflammatory, and anticancer properties. Curcumin regulates the expression of inflammatory cytokines, growth factors, growth factor receptors, enzymes, adhesion molecules, apoptosis related proteins, and cell cycle proteins. Curcumin modulates the activity of several transcription factors and their signaling pathways[134]. The antitumor effect of curcumin towards CRC was mediated by modulation of Akt/mTOR signaling[135]. Another natural product, pomegranate polyphenolics, was shown to suppress azoxymethane-induced colorectal aberrant crypt foci and inflammation, possibly by suppressing the miR-126/VCAM-1 and miR-126/PI3K/AKT/mTOR pathways[136].

PERSPECTIVE

Epidemiological studies indicate that lifestyle factors throughout life influence CRC incidence and prognosis[137]. For example, a large waist circumference and body mass index has been associated with CRC risk[138,139]. A plausible mechanism was proposed that ample nutrition factors such as amino acids, insulin, glucose and IGF-1 circulating in the body, constantly activates the mTOR pathway. Another study showed that hyperinsulinemia decreases IGFBP3 and consequently increases circulating IGF-1 and diabetes, both of which increase the risk of CRC[140]. CRC is a multifactorial disease. A new model: convergence of hormones, inflammation, and energy-related factors (CHIEF), proposes that various environmental agents (commensal bacteria, dietary antigens, mucosal irritants and pathogens) activate a basal, repetitive, mild subclinical inflammation, while additionally estrogen, androgens and insulin levels provoke the inflammation, which influences the CRC risk[141]. mTOR appears to be in the hub of this network. The concept of the CHIEF model agrees with the contemporary therapeutic trend, recognizing multiple parallel pathways, and suggesting that combined inhibition of multiple pathways would provide more comprehensive tumor suppression

efficacy, with a better chance of overcoming resistance.

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