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The mTOR pathway in obesity driven gastrointestinal cancers: Potential targets and clinical trials

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ABSTRACT

The mechanistic target of rapamycin (mTOR) is a crucial point of convergence between growth factor signalling, metabolism, nutrient status and cellular proliferation. The mTOR pathway is heavily implicated in the progression of many cancers and is emerging as an important driver of gastrointestinal (GI) malignancies. Due to its central role in adapting metabolism to environmental conditions, mTOR signalling is also believed to be critical in the development of obesity. Recent research has delineated that excessive nutrient intake can promote signalling through the mTOR pathway and possibly evoke changes to cellular metabolism that could accelerate obesity related cancers. Acting through its two effector complexes mTORC1 and mTORC2, mTOR dictates the transcription of genes important in glycolysis, lipogenesis, protein translation and synthesis and has recently been defined as a central mediator of the Warburg effect in cancer cells. Activation of the mTOR pathway is involved in both the pathogenesis of GI malignancies and development of resistance to conventional chemotherapy and radiotherapy. The use of mTOR inhibitors is a promising therapeutic option in many GI malignancies, with greatest clinical efficacy seen in combination regimens. Recent research has also provided insight into crosstalk between mTOR and other pathways which could potentially expand the list of therapeutic targets in the mTOR pathway. Here we review the available strategies for targeting the mTOR pathway in GI cancers. We discuss current clinical trials of both established and novel mTOR inhibitors, with particular focus on combinations of these drugs with conventional chemotherapy, radiotherapy and targeted therapies.

Contents

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1. Introduction

The mechanistic target of rapamycin (mTOR) is an evolutionarily conserved serine/threonine protein kinase belonging to the phosphatidylinositol-3 kinase (PI3K) related kinase superfamily [1]. It acts as a cardinal regulator of metabolism, energy homeostasis and nutritional status of the cell as well as coordinating signalling from growth factors such as mitogens, cytokines and hormones. mTOR exists as the catalytic core of its two known signalling complexes, mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2), which are each comprised of distinct substrates and carry out different cellular functions [2]. mTORC1 is characterised by its exclusive partner raptor (regulatory-associated protein of mTOR) [3] whereas mTORC2 is defined by its exclusive partner rictor (rapamycin-insensitive companion of mTOR) [4].

mTORC1 function is inherently dependent on amino acid levels as depletion of amino acids past a certain threshold renders mTORC1 completely refractory to all other signals and inputs, which prevents the cell engaging in energy costly anabolic processes when sufficient nutrients are not available [5]. This prevents the cell engaging in energy costly anabolic processes when sufficient nutrients are unavailable [6]. Upstream activation of mTORC1 is primarily mediated through activation of the GTPase Rheb (Ras homolog enriched in brain) by growth factors (eg. insulin, insulin-like growth factor 1 (IGF-1)) and amino acid dependent (specifically leucine [7]) translocation of inactive mTORC1 from the cytoplasm to the lysosomal membrane via the Ragulator–Rag complex [8] (Fig. 1). The main substrates phosphorylated by activation of mTORC1 are ribosomal protein S6 kinases (S6K) and the eukaryotic initiation factor 4E (eIF4E) binding proteins 1–3 (4EBP1-3), which drive cell proliferation, growth and cap-dependent protein synthesis [9]. mTORC1 signalling also promotes lipid synthesis [10], nucleotide synthesis [2] and suppresses autophagy [11]. In this respect mTORC1 is often described as a central driver of anabolic processes and an inhibitor of catabolic processes [12]. Additionally recent research has defined the role of mTORC1 signalling in angiogenesis whereby mTORC1 acts as the integration point of metabolic signals and signalling from vascular endothelial growth factor A (VEGF-A) [13]. mTORC1 has been shown to regulate HIF-1a expression and drives VEGF-A expression through activation of STAT3, 4E-BP1 and S6K1 all working in conjunction to drive angiogenesis under hypoxia [14]. mTORC2 has not been as thoroughly studied as its counterpart mTORC1, however it is known to phosphorylate Akt, protein kinase C (PKC), and SGK1 (serum and glucocorticoid-induced protein kinase) [15]. Therefore its role is seen to be more related to modulation of metabolism and cell survival through up regulation of Akt. While the upstream regulators of mTORC2 remain to be fully elucidated, it is known to involve association with ribosomes in a PI3K-dependent manner and phosphorylation of Akt [16].

2. mTOR and obesity

Because the mTOR pathway is so central to the assimilation of signalling from growth factors, hormones and nutrients with cell growth and metabolism, there has been substantial research implicating it with obesity and cancer [17]. Obesity is a state of systemic chronic inflammation induced by excess adipose tissue accumulation when specific calorific needs exceed energy expenditure [18] and is one of the leading risk factors for development of cancer [19,20]. Current evidence suggests a strong association between incidence of obesity and specific gastrointestinal cancers such as colorectal, gastric, pancreatic and esophageal cancer [21]. It is well established that adipose tissue is an important endocrine organ involved in the production of numerous metabolic and inflammatory mediators such as free fatty acids, chemokines and adipocytokines [22,23]. Adipose-associated polypeptides such as leptin, adiponectin, insulin-like growth factors and ghrelin represent potential mechanisms promoting cancer development [24]. For example hyperinsulinemia and insulin resistance frequently occurs in most obese patients and is associated with a worse prognosis in multiple malignancies [25]. Insulin can stimulate the synthesis of IGF-1 [26], which exerts multiple mitogenic effects on cancer cells through activation of numerous signal pathways such as PI3K/Akt, MAPK and STAT3 [18]. These pathways contribute greatly to cancer initiation and progression and can all converge downstream on mTOR [27–29]. A growing body of research is showing that the mTOR pathway is heavily implicated in the initiation and progression of obesity driven gastrointestinal cancers [30]. Equally, increased signalling through mTOR is being implicated in the pathogenesis of obesity [17], and the development of insulin resistance in metabolic syndrome [31]. Both hyperaminoacidemia and postprandial hyperinsulinemia have been shown to increase phosphorylation of S6K and inhibitory insulin substrate-1 [31]. Importantly mTOR signalling is required for adipogenesis as early studies showed that rapamycin inhibited both the proliferation and differentiation of human adipocytes [33]]. Rapamycin was also shown to reduced obesity induced by a high fat diet in mice through long term inhibition of mTORC1 [34], however this effect, while beneficial, progresses to impaired glucose tolerance and insulin resistance [35].

3. mTOR and obesity related gastrointestinal cancers

3.1. Oesophageal cancer

Oesophageal cancer is rapidly increasing in incidence, particularly when compared to other malignancies and is characterised by low survival rates and poor prognosis [36]. Oesophageal adenocarcinoma (OAC) has one of the strongest associations with obesity, specifically visceral (abdominal) obesity, in terms of incidence and pathogenesis [37]. Barrett's oesophagus (BO), a premalignant lesion associated with the development of OAC, is also associated with obesity and concomitant gastro-oesophageal reflux disease (GORD) [38]. This proposed mechanism between BO and visceral obesity is believed to be related, at least in part, to increased acid reflux observed in obese patients [39]. Chronic exposure to bile acid and gastric reflux initiates the inflammatory processes crucial in the progression from BO to OAC, and this can activate mTOR through stimulation of IKKβ/TSC1 signalling in BO associated OAC [40]. Treatment of oesophageal cancer cells with mTOR inhibitors rapamycin and Bay-11-7082 was shown to effectively inhibit bile acid induced cell transformation and proliferation [40].

In a xenograft mouse model of oesophageal cancer both rapamycin induced and siRNA induced inhibition of mTOR were shown to decrease tumour size and mTOR expression [41]. The use of both agents was shown to have a greater anti-tumour effect than either agent alone. In OAC patients, overexpression of phosphorylated mTOR (p-mTOR) is significantly correlated with poorer overall survival [42].

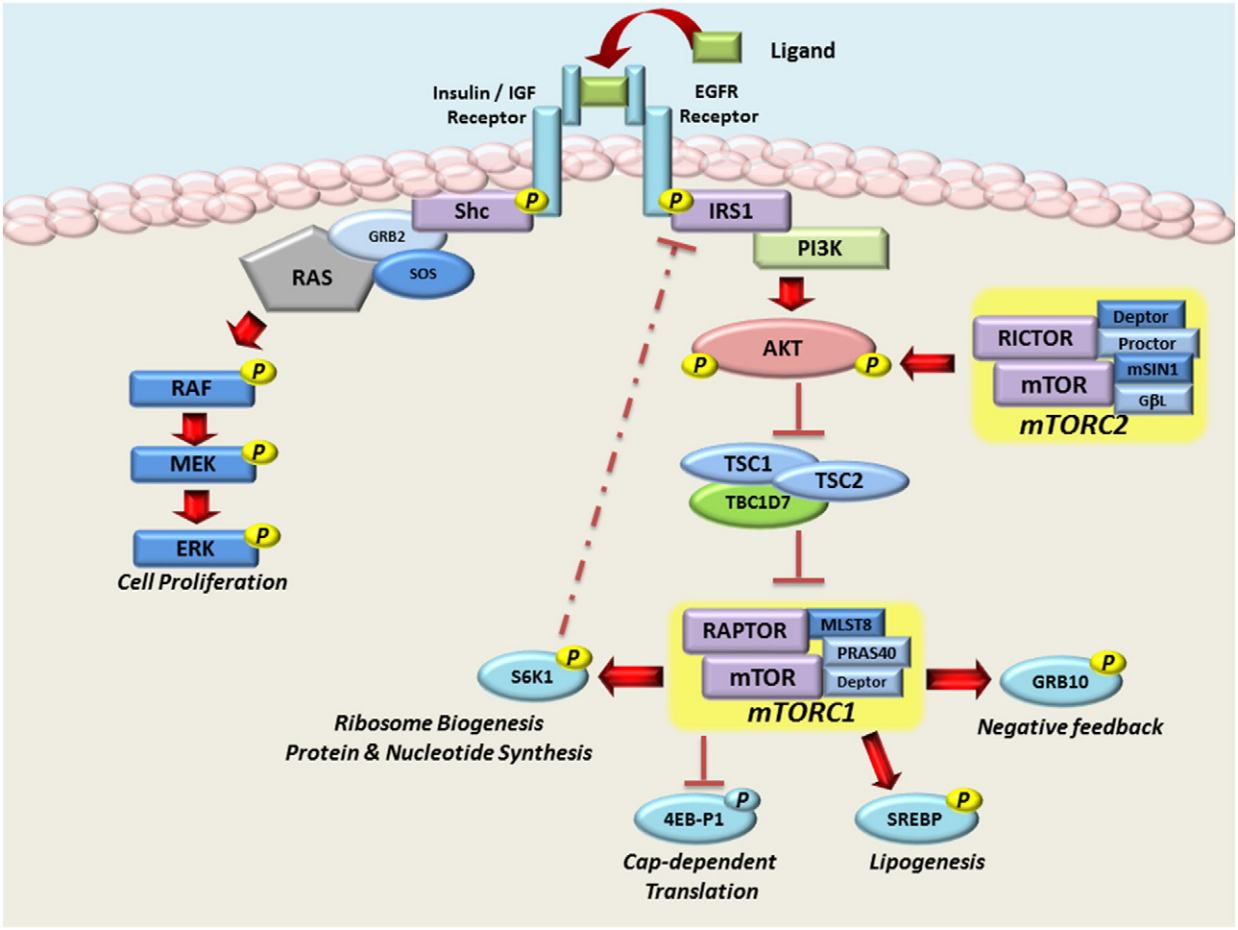

Fig. 1. Schematic representation of the mTOR pathway, it's classical upstream inputs and downstream targets. mTOR exists as two separate signalling complexes which are structurally distinct. mTOR complex 1, which is defined by raptor, receives signalling inputs from amino acids, ATP, insulin, growth factors and hormones, which all culminate in the initiation of multiple downstream signalling pathways. mTORC1 phosphorylates a limited number of known substrates, the principle ones being S6K1, 4EBP1, SREBP and GRB10. Activation of these mTORC1 targets culminates in the up regulation of anabolic processes and the down regulation of catabolic processes and mediates a negative feedback loop towards PI3K via S6K1. mTORC2, while not as throughly studied as mTORC1, is defined by raptor and is activated by PI3K signalling and acts downstream on Akt.

In addition to its importance in OAC, mTOR is shown to be involved in the pathogenesis of oesophageal squamous cell carcinoma (OSCC). Increased expression and activation of mTOR was shown in a study examining mTOR expression in multiple resected OSCC tumours and OSCC cell lines [43]. Down regulation of the tumour suppressor PTEN significantly correlated with up regulation of mTOR in multiple OSCC cell lines [44]. A large patient cohort study of single nucleotide polymorphisms in mTOR revealed certain mTOR genotypes could increase risk of OSCC [32]. Interestingly when stratified by patient BMI there was a greater significant association between three specific mTOR SNPs (rs2295080, rs1057079, and rs1064261) and risk of OSCC in patients with a BMI > 25 [45]. Studies such as these underpin the role of mTOR in the interaction between genetic and environmental risk factors in obesity related oesophageal cancers [46–49].

3.2. Gastric cancer

Obesity has long been a suspected risk factor for gastric cardia adenocarcinoma (GCC) while has been shown to be unrelated to gastric non-cardia adenocarcinoma (GNCC) [50,51]. While data is limited meta-analysis has shown no association between GNCC and obesity and this was not significant when adjusted according to patient sex [52]. A recent meta-analysis from the EPIC cohort showed that obesity as measured by BMI showed no association in terms of risk with GCC or GNCC, however when adjusted for waist circumference there was a higher risk of GCC. Therefore further investigation into the role abdominal obesity and risk of GCC is warranted. There is mounting evidence that the mTOR pathway is deregulated in gastric cancer with specific genetic mutations in the PI3K/Akt/mTOR pathway frequently being observed regardless of GC subtype [53]. IHC analysis of GC patient samples showed that high expression of p-mTOR, specifically in the tumour cell cytoplasm, correlated with tumour stage, metastasis and overall survival [54]. Related studies have reported similar findings of mTOR expression in GCC having a positive correlation with tumour metastasis and invasiveness. One such study determined that mTOR is highly expressed in GCC tumour cells with relatively little expression in the surrounding normal gastric tissue [55]. Mouse studies of mTOR signalling in GC have shown that targeted inhibition of mTOR using everolimus can inhibit cell proliferation, tumour vascularisation [56] and local tumour dissemination [57]. Upstream of mTOR, mutations and amplification of PI3K and Akt respectively are often observed in GC [58] and over activation of PI3K, Akt and eIF-4E were significantly associated with lymph node metastasis [59].

3.3. Hepatocellular carcinoma

While hepatocellular carcinoma (HCC) can arise from a vast myriad of carcinogenic factors both obesity and non-alcoholic fatty liver disease (NAFLD) are established risk factors for the development of HCC [60,61]. Increased levels of both adiponectin and leptin has been observed in patients with cirrhotic HCC and non-cirrhotic HCC [62] and adiponectin level has been found to be predictive of overall survival in HCC patients

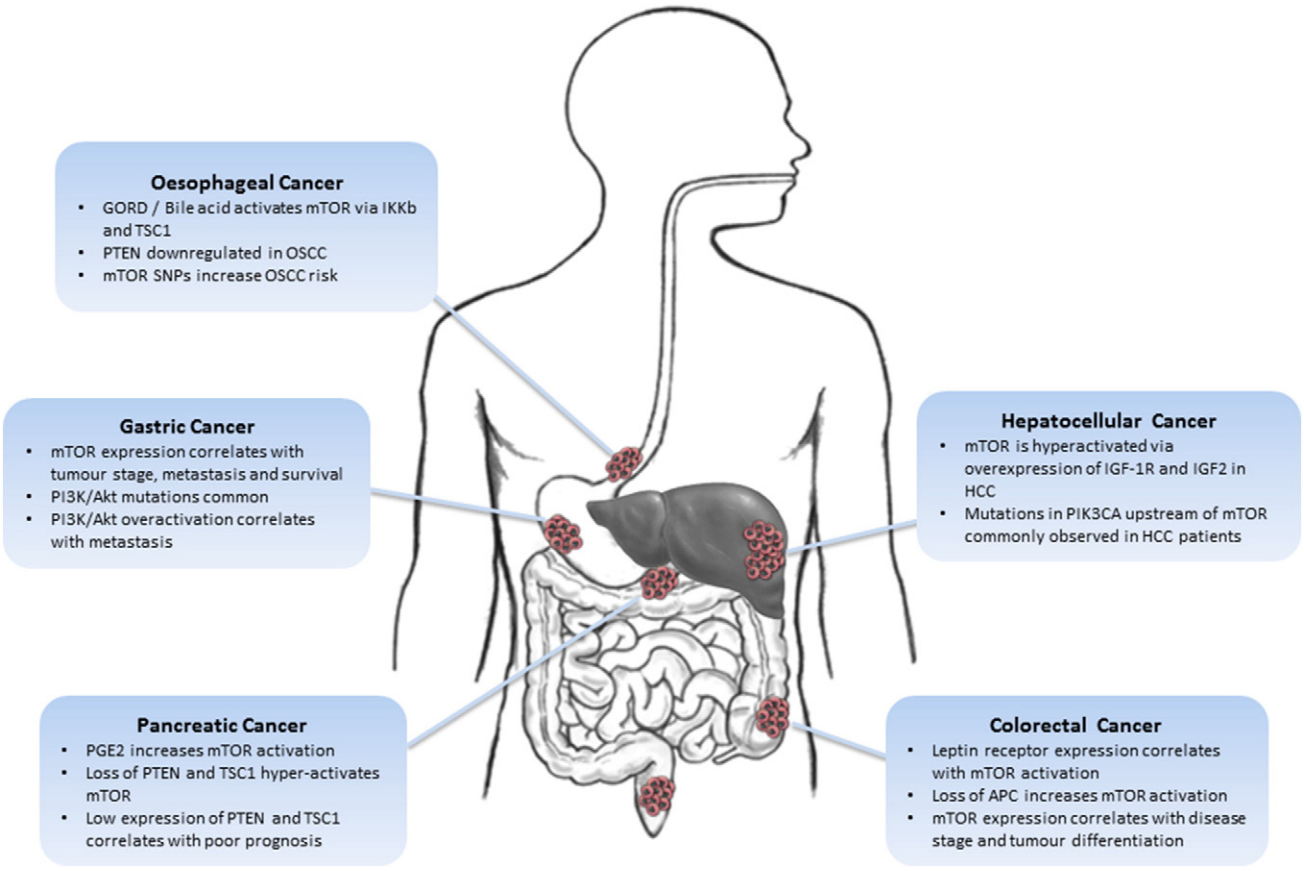

Fig. 2. Summary of the emerging role of the mTOR pathway in obesity related gastrointestinal malignancies. While the direct mechanisms by which the mTOR pathway drives the progression of obesity related GI cancers have yet to be defined, there is substantial emerging evidence the mTOR is heavily implemented in these malignancies.

[63]. Hypoadiponectinaemia can accelerate the formation of HCC [64] and concomitantly, adiponectin inhibits phosphorylation of mTOR and can prevent HCC tumourigenesis in nude mice [65]. Mutations in the mTOR pathway are seldom seen in HCC with mTOR activation in HCC principally being due to upstream ligand dependent receptor activation [66] namely the EGFR, IGF and PTEN signalling pathways [67].

Transcriptomic analysis of patient data sets has similarly revealed HCC subsets that have upstream over-expression of IGF2 and IGF1R in addition to mutations in PIK3CA, culminating in deregulated mTOR signalling [68]. Blockade of mTOR can enhance upstream inhibition of growth factors involved in HCC such as fibroblast growth factor receptor (FGFR). Combined inhibition of both FGFR and mTOR, using FGFR inhibitor BGJ398 and rapamycin, in an orthotropic model of HCC lead to a significant inhibition of tumour growth and prevented recruitment of vascular smooth muscle cells (VSMCs) and hepatic stellate cells (HSCs) into liver tumours [69].

3.4. Pancreatic cancer

While diabetes is a well established risk factor for pancreatic cancer (PC), there hasn't been as clear a delineation between obesity and risk of PC with only a weak association being reported [70] or certainly a non-linear relationship [71]. However recent research has revealed a link between pro-inflammatory eicosanoid prostaglandin E2 (PGE2) signalling and the mTOR pathway in obesity associated pancreatic cancer [72]. PGE2 is an integral effector in the inflammatory milieu seen in obesity and is over activated in the progression of obesity-associated cancers [24]. In multiple pancreatic cell lines treatment with PGE2 resulted in enhanced signalling of the mTOR pathway via increased phosphorylation of S6K1 [72]. It is becoming increasingly evident that the mTOR pathway is intricately involved in the progression of PC with mTOR pathway genes found to be mutated in specific subsets of PC, as multiple mTOR pathway genes are mutated in specific subsets of PC [73]. Tissue microarray analysis revealed down-regulation of two critical upstream regulators of mTOR, TSC2 and PTEN, low expression of which correlated with poorer disease free and overall survival in PC patients [74]]. A recent study of metastatic pancreatic ductal adenocarcinoma (PDAC) revealed a specific disease subset, whereby loss of PTEN or TSC1 haploinsufficieny facilitated development of PDAC through hyper activation of the mTOR pathway [75].

3.5. Colorectal cancer

Colorectal cancer (CRC) is the third most common cancer globally [36] and its incidence is consistently linked to incidence of obesity [76, 71]. Leptin signalling has been shown to be a driving factor in colon cancer cell proliferation and can induce phosphorylation of Akt and mTOR [77]. Expression of the leptin receptor (Ob-R) was strongly correlated with activation of the PI3K/Akt/mTOR pathway and downstream phosphorylation of mTOR [77]. Conversely activation under low adiponectin conditions was found to be a key mechanism in the promotion of proliferation and colorectal carcinogenesis [78].

Genes important to the development of CRC, such as APC, p53 and K-ras, lie upstream of mTOR and can mediate their oncogenic signalling in part through mTOR [79]. APC gene mutations are common in sporadic CRC and mTOR has been found to have a crucial role in APC-deficient colorectal cancer [80]. Loss of the APC gene is pivotal in the pathogenesis of CRC and mTORC1 activity is essential for the proliferation of APC

Table 1
Clinical development of both conventional and novel mTOR inhibitors

Target	Compound (company)	Malignancy	Phase of development
mTORC1	Everolimus (Novartis)	Renal cell carcinoma, subependymal giant cell astrocytoma, pancreatic neuroendocrine tumors, ER + breast cancer (in combination with exemestane)	Approved
	Temsirolimus (Pfizer)	Renal cell carcinoma	Phase II
PI3K/mTOR	BEZ235 (Novartis)	Advanced solid tumors, breast cancer, castration-resistant prostate cancer, renal cell carcinoma, leukemias, pancreatic neuroendocrine tumors, urothelial transitional cell carcinoma	Phase II
	GDC-0980 (Genentech)	Solid cancers, non-Hodgkin lymphoma, breast cancer, prostate cancer	Phase II
	PF-05212384 (Pfizer)	Advanced solid tumors, colorectal cancer, endometrial neoplasms	Phase II
	SAR245409 (XL-765; Sanofi/Exelixis)	Advanced solid tumors, CLL, indolent non-Hodgkin lymphoma, mantle cell lymphoma, ovarian cancer	Phase I
	VS-5584 (Verastem, Inc)	Advanced solid tumours, Relapsed mesothelioma,	Preclinical
	PI-103	Xenograft and in-vivo models	Phase II
mTORC1/2	AZD2014 (AstraZeneca)	Advanced solid tumors, breast cancer, renal cell carcinoma	Phase I/II
	CC-223 (Celgene)	Breast cancer, glioblastoma, hematologic malignancies, liver cancer, NSCLC, neuroendocrine tumors	Phase I
	AZD8055 (AstraZeneca)	Hepatocellular carcinoma, Glioblastoma Mutiforme	Phase I
	INK128 (National Cancer Institute) (NCI)	Recurrent Glioblastoma, Metastatic Anaplastic Thyroid Cancer	Phase I
	MLN0128 (INK128; Intellikine)	Advanced solid tumors, hematologic malignancies	Phase II
	Temsirolimus (Pfizer)	Advanced solid tumors, breast cancer, castration-resistant prostate cancer,[53] renal cell carcinoma, leukemias, pancreatic neuroendocrine tumors, urothelial transitional cell carcinoma	Phase II
	BEZ235 (Novartis)	Solid cancers, non-Hodgkin lymphoma, breast cancer, prostate cancer	Phase II

deficient enterocytes [81]. Using multiple genetic mouse models it was found that APC loss led to increased activity of eukaryotic elongation factor 2 (eEF2) [82], which is required for intestinal cell proliferation. Increased activity of mTORC1 in APC deficient mice could be blocked with rapamycin, and this was effective at suppressing tumour development, and in parallel did not affect normal intestinal proliferation or apoptosis [81].

Examinations of both the mRNA level and protein level of mTOR in CRC revealed a significant relationship between high mTOR expression level and disease stage, lymph node involvement and recurrence [83]. mTOR has also been implemented in CRC metastasis, as elevated mTOR signalling through RhoA and Rac1 regulated epithelial-mesenchymal transition (EMT) and cell motility [84]. CRC metastasis was completely inhibited in vivo upon inhibition of mTOR1 and mTORC2 [85]. Immunohistochemical analysis of mTOR and its downstream effectors p70s6K, and 4EBP1 in human CRC samples showed high activity of the mTOR signalling pathway and that these correlated with depth of CRC infiltration [85].

While our understanding of the mTOR pathway in GI cancers is still in its infancy, research in this area has established a strong enough link to justify targeting mTOR in obesity associated GI cancers (Fig. 2).

4. Targetting the mTOR pathway in clinical trials

4.1. Clinical trials of rapamycin and rapalogs

The discovery of rapamycin (the first mTOR inhibitor) predated the discovery of mTOR itself. Originally approved as an immunosuppressant [86], it was later discovered that rapamycin targeted mTOR and that it had anti-proliferative effects, which resulted in the drug being investigated as an anti-cancer agent [87]. Rapamycin's unfavourable pharmacokinetics limited it's use as a cancer drug which drove the development of the first generation of rapamycin analogs (rapalogs); temsirolimus (CCI-779) [88], everolimus (RADD001) [89], and ridaforolimus (AP23573) [90] (Table 1). Rapamycin acts by irreversibly binding to the FKBP12-rapamycin domain of mTORC1, halting its kinase activity, however it's exact mechanism of action has yet to be fully defined [91]. Rapalogs also inhibit mTORC1 in this manner yet do not strongly inhibit mTORC2 [92]. Rapalogs prevent phosphorylation of two downstream mTORC1 targets, 4E-BP1 and S6K1, which prevent initiation of cap-dependent mRNA translation, thus inhibiting cell proliferation [93] (Fig. 3). Resistance to rapalogs is common due to negative feedback loops that regulate both mTOR and PI3K/Akt signalling [94,95]. Rapalog induced mTORC1 inhibition blocks the S6K-mediated feedback loop, which mitigates hyper activation of PI3K signalling increasing phosphorylation of Akt [95]. Increased activation of Akt can also occur via increased signalling through mTORC2, which occurs through PI3K hyper activation [96]. Recent studies revealed that mTORC1 phosphorylates Growth Factor Receptor Bound Protein 10 (Grb10), causing accumulation of Grb10 and inhibition of PI3K and the MAPK pathway [97]. Thus, over-activation of pathways upstream of mTOR due to the suppression of negative feedback counterbalances the antiproliferative effects of mTORC1 inhibitors. Currently there are over 90 clinical trials examining the therapeutic potential of rapalogs as either single agents or in combination with other therapeutics in GI malignancies, the majority of which are in OAC, GC and CRC (Tables 3, 4 and 5).

Clinical trials with mTORC1 inhibitors, sirolimus and everolimus have confirmed the use of these agents in a narrow range of malignancies [98,89,99–101], however their broad use has yet to be demonstrated clinically. There are currently 8 ongoing clinical trials of everolimus as single agent in gastrointestinal cancers including advanced gastric cancers and oesophageal cancer (Table 2). Recently however, the GRANITE-1 study, a phase III randomised, double blind trial of everolimus in advanced gastric cancer, failed to show an improvement in overall survival compared to best supportive care (BSC) [102]. Everolimus reduced the risk of progression by 34% and the PFS was 1.7 months compared to 1.4 months compared to BSC, indicating that combination of everolimus with other effective targeted therapies or chemotherapeutics may be a more promising strategy [102].

The adverse events profile for everolimus in gastric cancer was consistent with that observed in other trials evaluating everolimus in other cancers. Everolimus was suggested to have clinical activity in a subset of patients in this study and extensive biomarker analysis of the GRANITE-1 study is underway in an effort to identify this subset of GC patients [102].

4.2. Clinical trials of ATP competitive mTOR kinase inhibitors

Following on from the somewhat disappointing clinical efficacy of rapalogs, ATP-competitive mTOR tyrosine kinase inhibitors (TKIs) were developed. These compounds inhibit the catalytic site of the mTOR kinase domain, giving them the advantage of targeting the kinase activity of both mTORC1/2 thus blocking the feedback activation of the PI3K/Akt signalling pathway [103]. This robust inhibition of mTORC2 dependent activation of Akt limits this form of resistance to mTOR inhibitors hopefully enhancing their efficacy. In a preclinical assessment

of the oral mTOR kinase inhibitor OSI-027, this compound was shown to selectively inhibit mTORC1 mediated phosphorylation 4E-BP1 and S6K1 as well as mTORC2 specific activation of Akt in multiple rapamycin sensitive and resistant in-vitro models [104]. Additionally it had superior efficacy compared to rapamycin in multiple colon cancer xenograft models [104]. OSI-027 was brought forward to a phase I clinical trial to assess it's pharmacodynamic profile in a broad range of cancers and achieved substantial clinical effect [105]. However it was poorly tolerated with over a third of patients requiring dose reductions [105] and was discontinued due to lack of clinical efficacy in phase II trials [106].

One promising mTOR TKI, AZD2014, has shown dramatic antiproliferative effects in preclinical studies of breast cancer [107] and HCC [108]. The first clinical trial of AZD2014 examined pharmacokinetics and pharmacodynamics in 56 patients across a range of malignancies [109]. The Mean Tolerated Dose (MTD) was established and there were partial clinical responses seen in both pancreatic and brest cancer patients [109]. Azd2014 has been brought forward to phase II clinical trials in Gastric adenocarcinoma in combination with paclitaxel (NCT02449655). Another similar mTOR TKI, INK128, has shown efficacy in preclinical studies of GI cancers such as PAC [110] and is being examined in phase I studies across a range of malignancies.

4.3. Clinical trials of dual mTOR/ PI3K inhibitors

As mTOR is heavily linked to the PI3K pathway in terms of cancer progression and resistance to mTOR inhibitors, this prompted the development of dual PI3K/mTOR inhibitors, which target the p110α, β, and γ isoforms of PI3K in addition to the catalytic sites of mTORC1/2 [90]. This dual targeted approach attempts to completely shut down the PI3K/Akt/mTOR pathway even in cancers that have over expression of this pathway [111]. In a recent study of CRC, mTORC2 was shown to be over-expressed in CRC cells and down-regulation of mTORC2 reduced proliferation of colon cancer cells and inhibited the formation of tumour xenografts in vivo. Combined inhibition of PI3K and mTORC1/2 by dual mTOR/ PI3K inhibitor NVP-BEZ235 was shown to induce tumour regression in a mouse model of sporadic CRC [112]. Consistent with this, a more recent study also demonstrated the efficacy of NVP-BEZ235 and of an additional catalytic mTOR inhibitor, pp242, in human colon cancer cell line xenografts [113]. In addition to its effect in CRC, NVP-BEZ235 has recently been shown to highly effective in attenuating growth of pancreatic cancer cells and work synergistically with gemcitabine to induce potent cytotoxicity in gemcitabine resistant pancreatic cancer cells [114].

Another highly selective dual mTOR/PI3K inhibitor VS-5584 has been shown to have significant efficacy in a rapalog resistant colorectal cancer xenograft model reducing both tumour growth and the number of functional tumour blood vessels [115]. More pertinent however is the preferential targeting of cancer stem cells (CSCs) by VS-5584, where it has been shown to exert a selective effect on CSCs in a broad range of cell lines, xenograft and patient tumour explant models [116]. VS-5584 has recently been granted orphan status for clinical development in mesothelioma and has entered into a Phase I dose escalation

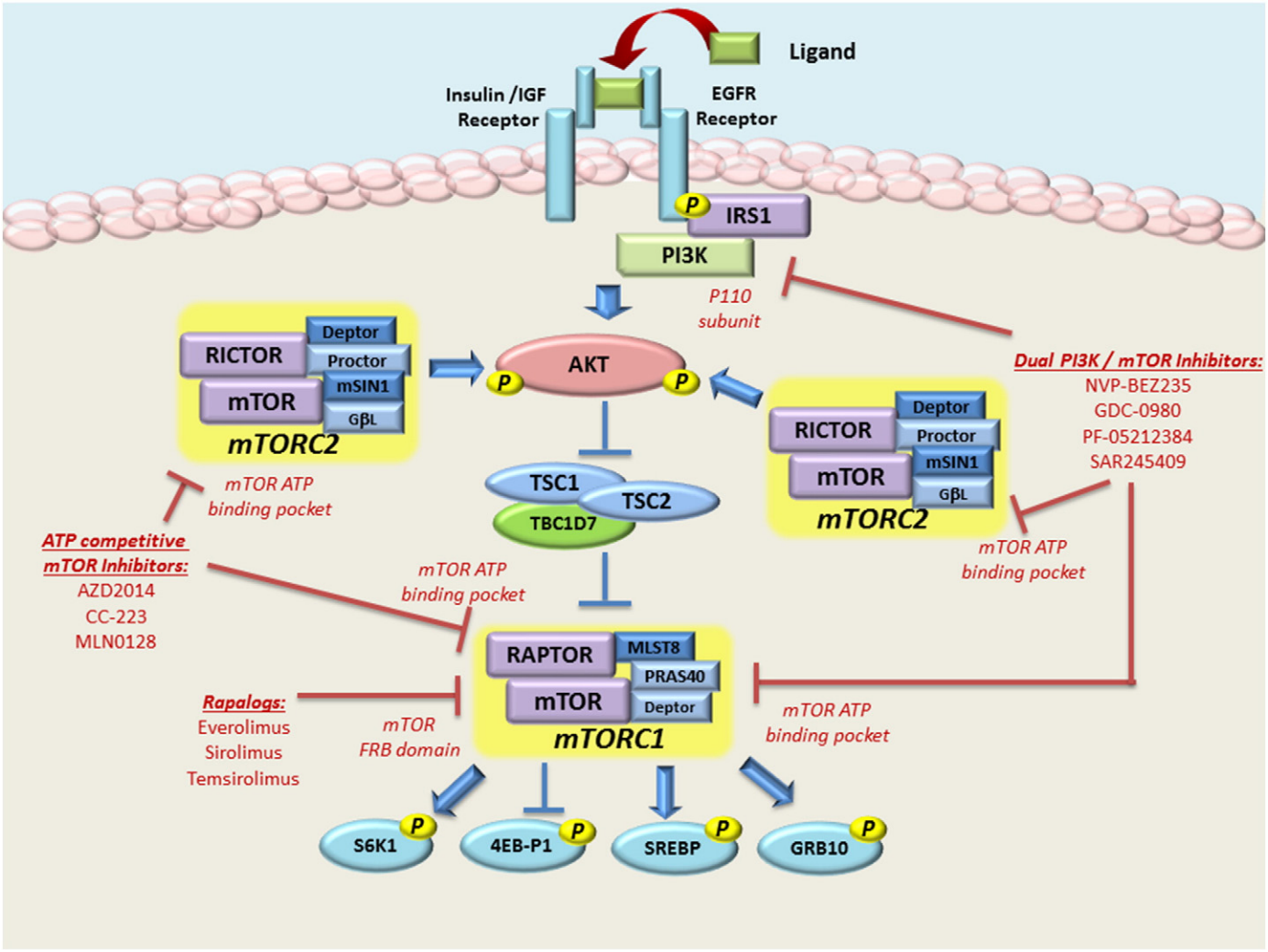

Fig. 3. Targeting the mTOR pathway. Specific target domains of mTOR and PI3K are highlighted at the point of inhibition.

Table 2
Clinical trials of mTOR inhibitors as single agents in GI cancer

mTOR inhibitor	Patients	Phase	Trial number
Everolimus	Gastric cancer	III	NCT00879333
		II	NCT01482299
			NCT00519324
			NCT00729482
	Oesophageal cancer	II	NCT00985192
	Colorectal cancer	II	NCT00419159
			NCT00390364
			NCT00337545
	Hepatocellular carcinoma	II	NCT00516165
	Gastrointestinal neuroendocrine tumors	II	NCT01648465
	Pancreatic neuroendocrine tumors	II	NCT02273752
			NCT005 10068
			NCT02031536
			NCT00409292
Temslrolimus	Metastatic pancreatic cancer	II	NCT00075647
			NCT00093782
Sirolimus	Pancreatic cancer	II	NCT00499486

study in advanced non-hematologic malignancies and lymphoma (NCT01991938).

Several clinical trials are examining the efficacy of dual PI3K/mTOR inhibitors and while there is some encouraging early trial data, there is still evidence that some cancers may be intrinsically resistant to dual inhibition of PI3K/mTOR. A recent screening of multiple cancer cell lines found that KRAS mutations could confer resistance to dual PI3K/mTOR inhibitors [117]. This resistance was specifically linked to changes in the level of phosphorylation of 4E-BP1, and was absent in wild type KRAS tumours or PIK3CA mutated tumours [117]. Studies such as this highlight the need for reliable clinical biomarkers to assess efficacy of mTOR inhibitors.

4.4. Clinical trials of mTOR inhibitors in GI cancers in combination with other therapeutics

Many mTOR inhibitors have only modest clinical activity and rapid development of resistance is common. Consequently clinical trials are largely shifting in favour combining mTOR inhibitors with conventional chemotherapy and radiotherapy to improve outcomes and circumvent resistance. Due to the heterogeneity in mTOR signaling seen across multiple cancer types [59,75] it is critical to assess which subsets of cancer patients will benefit from addition of an mTOR inhibitor to their existing treatment regimens. Combining PI3K/AKT/mTOR pathway inhibitors with chemotherapy and radiotherapy could improve efficacy [114, 118–120] and potentially prevent tumour regrowth between doses of treatment.

Table 3
Clinical trials of mTOR inhibitors in combination with chemotherapy and targeted therapies in Pancreatic cancer.

mTOR inhibitor	Patients	Drug combination	Phase	Trial Number
Everolimus	Pancreatic cancer	gemcltabine	I/II	NCT00560963
		BYL719 and exemestane	I	NCT02077933
	Pancreatic neuroendocrine tumors	5-FU	III	NCT02246127
		Octreotide acetate with or without bevacizumab	II	NCT01229943
		Pasireotide	II	NCT01374451
				NCT00804336
				NCT01263353
		VEGFR/PDGFR dual inhibitor X-82	I/II	NCT01784861
		Temozolomide	I/II	NCT00576680
		Sunitinib	II	NCT02315625
		Octreotide and metformin	I	NCT02294006
	Metastatic pancreatic cancer	Cetuximab and Capecitabine	I/II	NCT01077986
Rapamycin	Pancreatic cancer	Metformin	I/II	NCT02048384
Sirolimus	Metastatic pancreatic cancer	Vismodegib	I	NCT01537107

4.4.1. Clinical trials combining mTOR inhibitors and conventional therapies

Recent studies have demonstrated that dual PI3K/mTOR inhibitors can act as radiosensitisers and augment radiation-induced cytotoxicity in cancer cells. The dual PI3K/mTOR inhibitor BEZ235 was shown to have a synergistic effect with radiation in CRC cells by attenuating double strand break repair and sensitising CRC cells to radiation [121]. The same synergistic effect was seen in vivo where combination of BEZ235 and radiation decreased tumour size greater than either therapy alone. The expression of mTOR, eIF4E, and S6 was also significantly decreased [121], indicating that combined mTOR targeting and radiotherapy could be particularly beneficial.

Preliminary clinical data holds promise that mTOR inhibitors can sensitise cancer cells to conventional chemotherapy. A phase I trial investigating the combination of everolimus and capecitabine showed encouraging results in a broad cohort of cancers, with the combination regime being safe and tolerable [122]. This study demonstrated clinical benefit in 39% of patients, with drug related adverse events being mainly of grade <2, however for future trials it may be advisable to screen patients for alterations in the PI3K/AKT/mTOR pathway as this could result in the greatest clinical benefit.

The combination of an mTOR inhibitor with capecitabine (5-fluorouracil) has demonstrated synergy in preclinical studies and safety in a phase I trial examining combination of everolimus and capecitabine in pancreatic cancer. A recent phase II trial further contested the feasibility and clinical efficacy of this combination in a cohort of pancreatic cancer patients and an acceptable toxicity profile was observed for 5 mg everolimus BID and capecitabine 1000 mg/m^2 for 14 days every 3 weeks [123]. Moderate clinical activity was achieved only in first line pancreatic cancer patients [123].

4.4.2. Clinical trials of mTOR inhibitors and targeted therapies

The use of mTOR inhibitors, to both increase the efficacy and overcome resistance of targeted therapies, has been supported substantially by preclinical data. Ongoing phase I and II trials are examining combinations of mTOR inhibitors and multi-targeted TKIs such as imatinib, neratinib and pazopanib in a broad range of cancers. A phase I trial in gastrointestinal stromal tumours combining everolimus and imatinib in 31 patients with imatinib refractory disease showed disease stabilisation in 8 patients and partial response in 2 patients [124]. This could indicate that mTOR inhibition may be resensitising certain patients to imatinib.

A recent phase I study examined the combination of temsirolimus and neratinib, a pan-human epidermal growth factor (HER) TKI, in 60 patients with advanced solid tumours including colorectal and pancreatic cancer. The combination of neratinib and temsirolimus was tolerable across a range of malignancies with the best overall response including two complete responses, six partial responses and 27 cases of stable disease [125]. Results from this trial indicate that evaluation of this combination in GI cancers with significant HER2 and PI3K/mTOR pathway activation is warranted.

Inhibition of mTOR is known to have a direct anti-angiogenic effect through regulation of HIF-1α [126]. Therefore combinations mTOR inhibitors with anti-angiogenic therapeutics have been put forward as rationale treatment strategies. A phase II trial combining everolimus with the anti-VEGF monoclonal antibody bevacizumab in metastatic colorectal cancer showed encouraging results with minor responses reported in 16% of patients and a further 30% achieving disease stability [127]. This combination was shown to be tolerable and had modest clinical activity however recent phase I trials combining mTOR inhibitors with anti-angiogenic TKIs have shown conflicting results. A phase I study of the combination of temsirolimus and pazopanib (a pan-VEGF receptor

Table 4
Clinical trials of mTOR inhibitors in combination with chemotherapy and targeted therapies in liver cancers.

mTOR inhibitor	Patients	Drug combination	Phase	Trial Number
Everolimus	Hepatocellular carcinoma	Doxorubicin	II	NCT01009801
	Metastatic hepatocellular carcinoma	Bevacizumab	II	NCT00775073
		Pasireotide	II	NCT01488487
		Sorafenib Tosylate	II	NCT01005199
	Unresectable fibrolamellar Hepatocellular carcinoma	Estrogen Deprivation Therapy With Leuprolide + Letrozole	II	NCT01642186
Temsirolimus	Advanced hepatocellular carcinoma	Bevacizumab	II	NCT01010126
		Sorafenib	II	NCT01687673
Sirolimus	Unresectable hepatocellular carcinoma	Bevacizumab	I	NCT00467194

inhibitor) in advanced solid tumours including CRC showed high levels of grade 3 and higher toxicities as doses far less than the approved dose of each drug as a single agent [128]. Overlapping mTOR inhibitor and VEGFR TKI toxicities could account for the unfeasibility of this combination and further research is required to understand these potential interactions and evaluate alternate treatment strategies to circumvent these toxicities.

In spite of certain negative trial results, many pharmaceutical companies are moving forward with trials combining mTOR inhibitors with targeted therapies, as this remains one of the more promising avenues to improve clinical efficacy of available therapeutics and overcome resistance.

Table 5
Clinical trials of mTOR inhibitors in combination with chemotherapy and targeted therapies in Oesophageal, Gastric and Colorectal cancers.

mTOR inhibitor	Patients	Drug combination	Phase	Trial number
Everolimus	Colorectal cancer	Panitumumab & Irinotecan	I/II	NCT01139138
		Cetuximab & Irinotecan	I/II	NCT00522665
			I	NCT00478634
		FOLFOX & Bevacizumab	I/II	NCT01047293
	Metastatic colorectal cancer	Cetuximab	I	NCT01637194
		Bevacizumab	II	NCT00597506
		Cetuximab	II	NCT01387880
		Irinotecan	I	NCT01154335
		OSI-906 & Tivozanib	I/II	NCT01058655
	Oesophageal cancer	Paclitaxel & Carboplatin & Cetuximab	I	NCT01490749
	Gastric cancer	MitomycinC	I	NCT01042782
		Paclitaxel	III	NCT01248403
		LDE225	I	NCT02138929
		Paclitaxel Carboplatin	I/II	NCT01514110
	Imatinib resistant gastrointestinal stromal tumors	Imatinib	I/II	NCT01275222
	Metastatic gastric cancer	Cisplatin; 5-FU;	II	NCT00632268
		Leucovorin & Capecitabine	I/II	NCT01099527
		Fluorouracil & leucovorin calcium & oxaliplatin	I/II	NCT01231399
	Esophageal cancer Gastric cancer Colon cancer	TS-1 & Cisplatin	I	NCT01096199
Temsirolimus	Colorectal cancer	Irinotecan	II	NCT00827684
		Cetuximab	II	NCT00593060

5. Novel pathway crosstalk and potential new targets of the mTOR pathway

Recent studies have uncovered multiple novel upstream regulators of the mTOR pathway highlighting the extensive crosstalk between mTOR and signalling pathways such as Hedgehog, WNT, Notch and Hippo [129]. These “non classical” inputs of the mTOR pathway could reveal promising novel targeting opportunities in GI cancers where this crosstalk is driving tumour progression through the mTOR pathway.

5.1. Hippo pathway

The Hippo pathway controls organ size by promoting apoptosis and inhibiting proliferation through its main downstream effector Yes-associated protein 1 (YAP1) [130]. Yap1 controls the transcription of genes that govern proliferation and induce apoptosis [131]. Coordination between Hippo and mTOR pathways was hypothesised to occur given the function of YAP1 in cell proliferation, which cannot be sustained without coordinate cell growth modulation by mTOR [131]. A recent study has reported a molecular mechanism through which the Hippo pathway can regulate cell growth by modulating mTORC1 and mTORC2 through the positive control of YAP1 [132]. YAP is responsible for the transcription of the microRNA mir-29, which in turn inhibits the translation of PTEN. This down-regulation of PTEN by YAP1 leads to increased PI3K signalling and subsequent increased activation of mTORC1 and mTORC2. This crosstalk is also implemented in the progression of HCC through another key activator of the Hippo pathway, the transcriptional coactivator TAZ. Knockdown of TAZ in HCC cell lines attenuated cancer cell growth via inactivation of the mTOR pathway and expression of TAZ mRNA was associated with HCC tumour size [133].

5.2. Hedgehog pathway

The Hedgehog (HH) pathway is essential for growth and development and is implicated in the pathogenesis of multiple GI cancers. Specifically in oesophageal cancers over activation of the HH pathway correlates with lymph-node metastasis [134,135]. A recent study has revealed crosstalk between the mTOR and Hedgehog pathways in OAC whereby S6K1 phosphorylates the HH transcription factor Gli1 independent of any upstream signalling from the HH pathway [136]. Gli1 is an established oncogene [137] and could be contributing to the development of OAC via the mTOR pathway. Combinations of mTOR inhibitors and HH inhibitors in OAC cells revealed greater growth inhibition than either therapeutic alone [136]. Equally a novel synthetic lethality has been identified in rhabdomyosarcoma, whereby combination treatment with GLI1/2 inhibitor GANT61 and PI3K/mTOR inhibitor PI103 reduced tumour growth in an in vivo model of rhabdomyosarcoma through caspase-dependent apoptosis [138].

5.3. Notch pathway

Notch signalling is an integral pathway to cellular proliferation, differentiation and development [139]. Binding of the cell surface ligands delta and jagged to the notch receptors on an adjacent cell initiates a signal transduction pathway that culminates in the Notch intracellular domain (NCID) translocating to the nucleus and promoting target gene expression. A recent study in rat hepatoma cells showed that activation of mTORC1 by notch signalling promoted hepatic lipogenesis via hyper activation of the key component of mTORC1, raptor [140]. This hyper activation of raptor was independent of an increase in mRNA levels of raptor and shows that notch signalling is capable of promoting mTORC1

signalling via increased interaction of mTOR and raptor as well as increased assembly of mTORC1. However further research is required to define the molecular mechanism by which this hyper activation of Notch signalling increases mTOR-raptor interactions and where along this pathway there are potential targets.

6. Moving forward

Research into the role of the mTOR pathway in cancer is rapidly developing and as a result there has been considerable efforts invested in bringing mTOR targeting agents to the clinic. While rapalogs have high specificity for mTOR, their propensity for the development of resistance means they may only be suited to combination therapy for the majority of cancers.

Dual PI3K/mTOR inhibitors appear to have the widest profile of activity as these have multiple targets in the mTOR pathway however the severity of overlapping toxicities that these agents will have with other tyrosine kinase inhibitors is currently unknown and this may restrict their use with other targeted therapies. Available data on second-generation ATP-competitive mTOR kinase inhibitors demonstrates that their dual targeting of mTORC1 and mTORC2 could overcome issues with resistance to rapalogs and have greater single agent activity. However further genomic profiling of responsive tumours is necessary to be able to implement this in the most clinically relevant way.

While significant progress has been made in the development of new agents to target mTOR, how to best evaluate mTOR inhibitors in the clinical setting remains to be fully elucidated. Therefore there is a pressing need to develop biomarkers able to assess the efficacy and predict the response of mTOR inhibitors in patients. Currently it is possible to monitor activity of mTOR by analysing the phosphorylation status of S6K and 4E-BP1 and some clinical trials have successfully used blood and tumour samples from patients undergoing treatment with mTOR inhibitors to detect a decrease in S6K and 4E-BP1 phosphorylation [141]. However these may not be robust enough to become companion diagnostic tools as 4E-BP1 has been shown to contain rapamycin resistant phosphorylation sites [142]. Development of biomarkers must also address the discord in mTOR expression between primary and metastatic tumours, and considerable intratumoural heterogeneity of mTOR signalling between vascularised and hypoxic regions of tumours.

Furthermore, mTOR inhibitors may bring additional challenges in the clinical setting due to the complexity of their metabolic effects and their immunosuppressive potential especially in light of the fact that rapamycin is approved to prevent allograft rejection. These potential issues need to be clarified in both preclinical and clinical trials as they could greatly influence the cancer patients' course of treatment.

Recent genomic, proteomic and metabolomic studies of mTOR in cell lines have revealed a wealth of information on novel cross talk between mTOR signalling and other pathways in GI cancers with Hippo, Hedgehog and Notch signalling pathways identified as upstream regulators of mTOR pathway [132,136,129]. Further investigation into the multiple pathways that converge on mTOR will reveal valuable information not only on the regulation of mTOR but also may provide new novel targets in this signalling network. Despite the challenges that need to be addressed in further studies on targeting mTOR, this area of research holds great promise in terms of potential clinical benefit and will likely have an important role in the treatment of obesity associated gastrointestinal cancers.

Abbreviations

mTOR	mechanistic target of rapamycin
GI	gastrointestinal
PI3K	phosphatidylinositol-3 kinase
raptor	regulatory-associated protein of mTOR
rictor	rapamycin-insensitive companion of mTOR
Rheb	Ras homolog enriched in brain
IGF-1	insulin-like growth factor 1
eIF4E	eukaryotic, initiation factor 4E
4EBP1-3	4E binding proteins 1–3
S6K	S6 kinases
VEGF-A	vascular endothelial growth factor A
STAT3	signal transducer and activator of transcription 3
PKC	protein kinase C
SGK1	serum and glucocorticoid-induced protein kinase
Akt	protein kinase B
MAPK	mitogen-activated protein kinase
OAC	oesophageal adenocarcinoma
BO	Barrett's oesophagus
GORD	gastro-oesophageal reflux disease
IKKβ	IκB kinase β
TSC1	tuberous sclerosis 1
p-mTOR	phosphorylated mTOR
OSCC	oesophageal squamous cell carcinoma
GCC	gastric cardia adenocarcinoma
GNCC	gastric non-cardia adenocarcinoma
HCC	hepatocellular carcinoma
NAFLD	non-alcoholic fatty liver disease
EGFR	epidermal growth factor receptor
PTEN	phosphatase and tensin homolog
PIK3CA	phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha
FGFR	fibroblast growth factor receptor
VSMCs	vascular smooth muscle cells
HSCs	hepatic stellate cells
PGE2	prostaglandin E2
PC	pancreatic cancer
PDAC	pancreatic ductal adenocarcinoma
CRC	Colorectal cancer
Ob-R	leptin receptor
eEF2	eukaryotic elongation factor 2
EMT	epithelial–mesenchymal transition
Grb10	growth factor receptor bound protein 10
TKIs	tyrosine kinase inhibitors
CSCs	cancer stem cells
BSC	best supportive care
HER	human epidermal growth factor
YAP1	Yes-associated protein 1
HH	hedgehog
NCID	Notch intracellular domain

Conflicts of interest

The authors declare that they have no competing interests.

Transparency Document

The Transparency document associated with this article can be found, in the online version.

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