REVIEW ARTICLE

Targeted therapy of obesity-associated colon cancer

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ABSTRACT

Obesity is increasing worldwide and has become a major health problem. It not only increases the incidence of colon cancer but also leads to poorer prognosis. The mechanisms could be the activation of multiple signaling pathways including PI3K/Akt, MAPK and STAT3 that are induced by increased levels of cancer risk factors in obesity. Activation of these signaling pathways can cause drug resistance to chemotherapeutic agents, leading to poorer treatment outcome. Thus, inhibition of these pathways may increase the therapeutic efficacy of obesity-associated colon cancer. Many small molecule inhibitors have been developed for selection. Inhibition of a single signaling molecule may be not sufficient to reverse the activation of signals in obesity. Dual inhibitors for PI3K and mTOR or dual inhibitors for Akt and MAPK may be more effective. Combinational use of inhibitors could also increase treatment efficacy.

KEY WORDS

Obesity-associated colon cancer; multiple signal pathways; targeted therapy; PI3K/Akt; MAPK; STAT3

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Introduction

Obesity is defined as body mass index (BMI) ≥30 and is now recognised as a major health problem worldwide (1). Epidemiological studies showed that about one third of the population in developed countries is obese (2). Obesity is also increasing in developing countries. For example in China, obesity is increased from 2.6% in a national survey in 2002 to about 5% in a recent survey (3-5). There are more than 20% of obese populations in some cities in China. Although the percentage of obesity in the Chinese population is still lower than that in developed countries, the total number of obese people is high due to a total population of 1.3 billion in China. Obesity can cause many co-morbidities including type 2 diabetes, hypertension, hyperlipidemia, heart disease and cancer. As obesity is difficult to be prevented and treated, its co-morbidities must be well studied so that they can be effectively prevented or treated. It is now clear that obesity can increase the incidence of many cancers including colon cancer and lead to poorer treatment outcome (6-10). This is associated with the altered multiple cancer risk factors in obesity including increased serum levels of insulin, insulin-like growth factor-1 (IGF-1), leptin, Interleukine-6 (IL-6), IL-17, tumo necrosis factor-alpha (TNF-alpha) and decreased serum levels of adiponectin (7,11-13). These altered factors in turn result in the activation of multiple signaling pathways including phosphoinositide 3-kinase/protein kinase B (PI3K/Akt), mitogen-activated protein kinase (MAPK) and signal tranducer and activator of transcription 3 (STAT3) pathways (Figure 1) (14-17). Activation of these signaling pathways is important for the drug resistance to clinical therapy, leading to poorer outcome of treatment (17-19). Thus, inhibition of multiple signaling pathways could improve the treatment efficacy of obesity-associated cancer. The study of obesity-associated cancer is urgent because this disease can result in increased mortality (9,10).

Colorectal cancer is the third most common cancer in males and the second in females worldwide with estimated death number of 608,700 in 2008 (20). It is caused by both environmental factors such as dietary intake and genetic factors such as inherited or somatic gene mutations (21). These factors lead to the activation of several signaling pathways. Several gene mutations are shown to activate survival signaling pathways. Inactivating gene mutation of *Adenomatous polyposis coli (APC)* is most studied in colorectal cancer (21). It can result in the accumulation of beta-catenin in Wnt signaling pathway, which in turn increases transcription of many oncogenes. *KRAS* is activating mutated in about 40% of

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colon cancer which can activate both PI3K and MAPK pathways (22). *PTEN* inactivating mutation and *PIK3CA* activating mutation lead to the activation of the PI3K/Akt pathway (21). Oncogene *CMYC* is activated in 10% of colorectal cancer (23). The carcinogenesis of colon cancer starts from the early lesion of the formation of polyps and some of these polyps develop into adenocarcinoma dependent on the progressive accumulation of mutations in key regulatory genes (24). Inoperable colon cancer requires treatment by chemotherapy. The main chemotherapeutic agents for colon cancer are 5-fluorouracil (5-FU), oxaliplatin and irinotecan. 5-FU inhibits the enzyme thymidylate synthase to affect DNA replication. Oxaliplatin also interferes with DNA replication by covalently binding to DNA to form platinum-DNA adducts. Irrinotecan is semisynthesized from camptothecin and inhibits topoisomerase to prevent DNA from unwinding. The success of treatment will depend on the initial effectiveness of the drugs and reduced drug efficacy is a major problem. The initial response to these drugs is about 50%. The low responses are caused by many factors including increased drug metabolism and transportation out of target cells (25). Obesity is known to impact colon cancer by activation of multiple signaling pathways. As multiple signaling pathways are activated and play important roles in many obesity-associated colon cancers, inhibition of these signaling pathways could increase treatment efficacy (26). This review will summarise the evidence of poorer prognosis of obesity-associated colon cancer and propose treatment strategies for the inhibition of signaling pathways and several novel approaches to improve the treatment of obesity-associated colon cancer

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Obesity and poorer outcome of colon cancer treatment

Epidemiological evidence has shown that the outcome of obesity-associated cancer is much poorer than colon cancer without obesity. Calle demonstrated that obesity increased the mortality of many cancers including colon cancer (27). In an epidemiological study in 39 Asian-Pacific Cohorts, it was also found that obesity increased significantly the risk of mortality from colon cancer (28,29). The study showed that there were 4872 deaths among 401,215 patients within 3 years. The mortality risk is increased in colon cancer in obese patients compared with those with normal weight and the hazard ratio is 1.50 (28).

Laboratory studies have provided supportive evidence for the epidemiological studies. Several studies demonstrated that cancer risk factors, which are increased in obesity, have caused drug resistance and poorer prognosis of obesity-associated colon cancer (6). Addition of insulin into cultured colon cancer cell HT29 resulted in the drug resistance to chemotherapeutic agents oxaliplatin and 5FU (30,31). The drug resistance is mediated at least partially by the activation of the PI3K/Akt pathway. Leptin has been demonstrated to make colon cancer worse by increasing metastasis and drug resistance via multiple signaling pathways (32-37). In colon cancer stem cells, leptin activated both Akt and MAPK pathways (32). This not only increases cell proliferation but also intereferes with the treatment efficacy of 5-FU.

Inhibition of multiple signaling pathways as a strategy for the treatment of obesity-associated colon cancer

As activated multiple signaling pathways in obesity play critical roles in the treatment outcome of obesity-associated colon cancer, reversing these pathways to normal status could increase the treatment efficacy of the disease. Treatment of obesity may be able to make such reverse. However, there is no effective treatment for obesity at present. Therefore, small molecule signaling pathway inhibitors could be chosen for the treatment of obesity-associated colon cancer for targeted therapy (Figure 1, 2). The objectives are to choose the most effective nodes of these signaling pathways for the inhibition and avoid the side-effects as much as possible. Simultaneous inhibition of two or more nodes of these signaling pathways could also be chosen to increase effectiveness.

As colon cancer is a heterogenous disease, the detailed plan for targeted therapy should be worked out dependent on the activation status of signal pathways in an individual patient. The development status of obesity in an individual patient could be assessed for estimation of the activation of multiple signal pathways. Other mutations in an individual patient may also shape the signal pathways in the patient, making it different from others. The actual activities of these signal pathways may be determined for the detailed targeted therapy plan.

Inhibition of the PI3K/Akt pathway

The PI3K/Akt pathway plays a central role in cell proliferation, cell survival, cell growth, cell metabolism, cell motility, angiogenesis and genomic stability. It is activated by receptor tyrosine kinases such as epidermal growth factor receptor (EGFR), platelet derived growth factor receptor, insulin receptor, insulin-like growth factor-1 receptor and regulates a cascade of down-stream targets. Several excellent reviews are available for the details of the pathway (38,39). The pathway is activated in many cancers including colon cancer. Activation of the PI3K/Akt pathway in cancer has been associated with decreased drug efficacy in the treatment and inhibition of the pathway increases the sensitivity of cancer cells to cytotoxic agents (40). Many inhibitors have been developed for

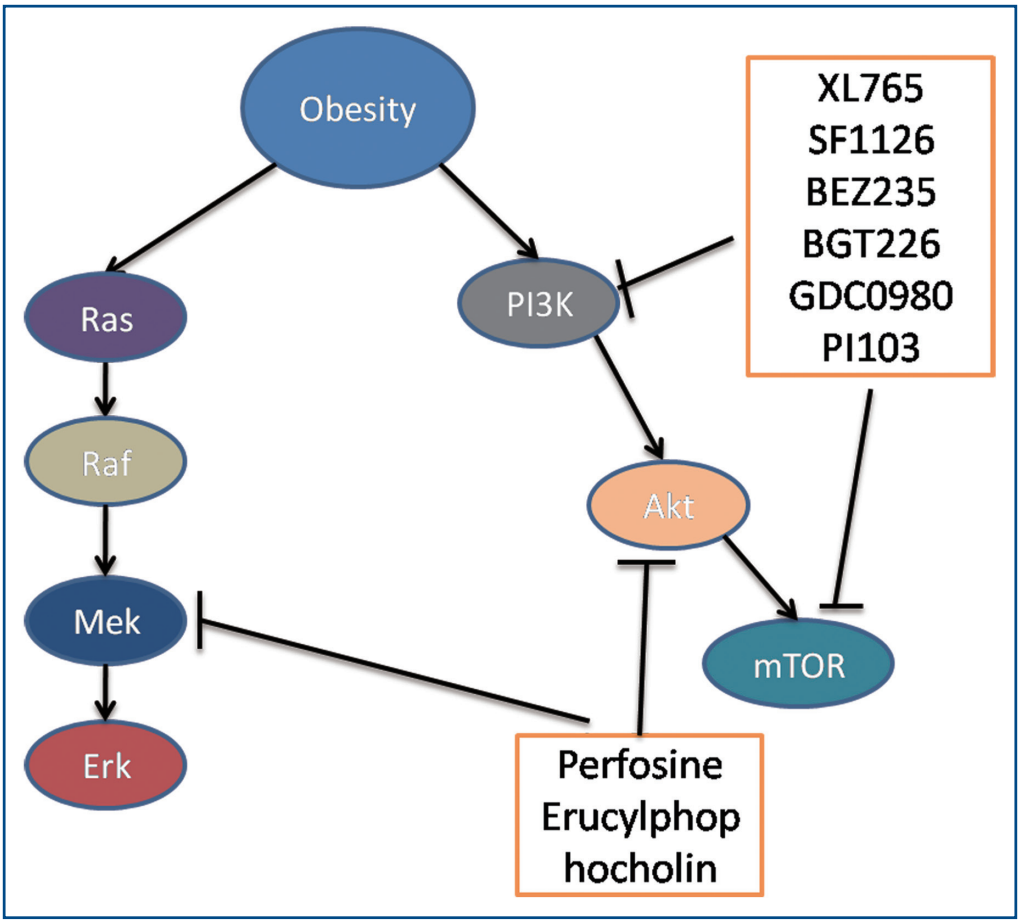

Figure 1. Inhibitors for activated signaling pathways in obesity-associated colon cancer. Many small molecule inhibitors have been developed to inhibit key molecules in PI3K/Akt, MAPK and STAT3 pathways. Some of them are shown in the box. Abbreviation: PI3K: phophoinositide 3-kinase Ras; Akt: protein kinase B; mTORC: mammalian target of rapamycin; Ras: a protein subfamily of small GTPases; Raf: proto-oncogene serine/threonine-protein kinase; Mek: Map kinase kinase; Erk: extracellular signal-regulated kinase STAT3: signal tranducer and activator of transcription 3.

the pathway to target its major components, especially now the dual inhibitors targeting both PI3K and its down-stream target-mammalian target of rapamycin (mTOR) are available. Inhibition of the pathway has been used for the treatment of colon cancer.

In obesity-associated colon cancer, it has been shown that the PI3K/Akt pathway is activated and inhibition of the pathway by specific inhibitors or food restriction reduces the incidence of colon cancer (41-43). In an *in vitro* model, insulin which is increased in obesity was shown to increase drug resistance to 5-FU and oxaliplatin via the activation of the PI3K/Akt pathway. Inhibition of the pathway by Ly294002 restored the colon cancer cell sensitivity to these two chemotherapeutic agents (43). This may be further studied in animal models in order to be used in clinical trials. Therefore PI3K/Akt pathway inhibitors may be useful to improve the therapeutic effectiveness of chemotherapy for obesity-associated colon cancer. These signaling pathway inhibitors are listed in Table 1 and discussed in detail below.

PI3K inhibitors

There are three classes of PI3K but only class I is closely related with cancer (39). Class I PI3K consists of a regulatory unit p85 and a catalytic unit p110. There are 5 isoforms of p85 including p85 alpha, beta, p55 alpha, p55 gamma and p50 alpha. The isoforms of p110 contain p110 alpha, beta, gamma and delta. Several PI3K inhibitors are described below.

PX-866 (Oncothyreon, Seattle, WA, USA)

PX-866 is a pan-isoform PI3K inhibitor derived from

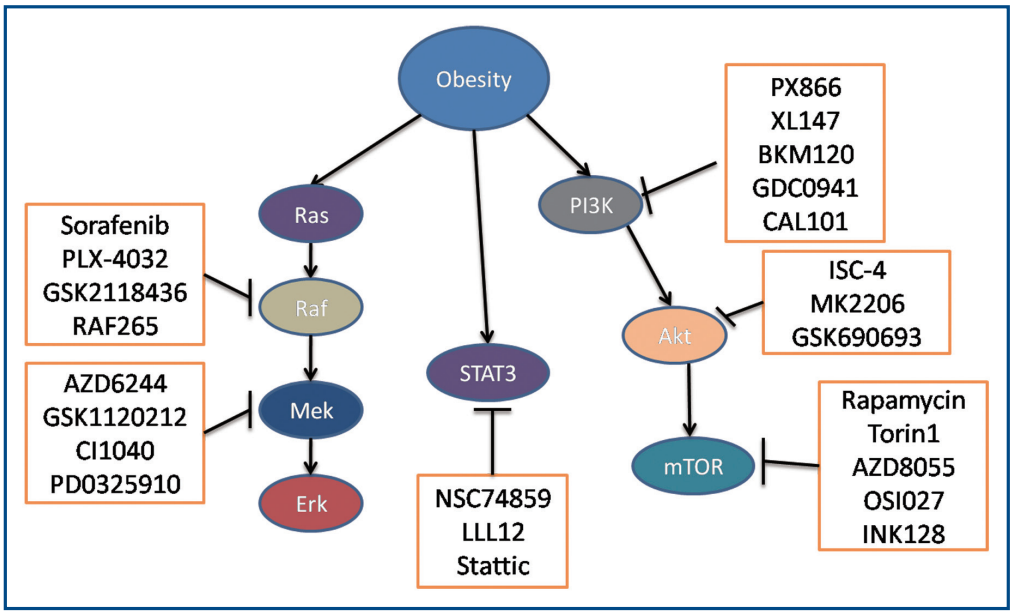

Figure 2. Dual inhibitors for activated signaling pathways in obesity-associated colon cancer. Dual inhibitors can inhibit two key molecules in a single pathway or two pathways. Some samples are shown in box.

Table 1. PI3K/Akt pathway inhibitors.

Signaling molecules	PI3K	Akt	mTOR	PI3K/mTOR
Inhibitors	PX-866, XL147, BKM120, GDC-0941, CAL-101	ISC-4 MK-2206 GSK690693	Rapamycin Torin1 AZD-8055 OSI-027 INK128	XL765, SF1126, BEZ235, BGT226, GDC-0980 PI-103

wortmannin. It has been shown to inhibit PI3K in colon cancer HT29 cells with an IC50 of 0.1 nM (44). In an HT29 xenograft colon cancer mouse model, it inhibited PI3K, as indicated by decreased phosphorylation of Akt (45). One phase I clinical trial in advanced solid tumors for the tolerance study with escalated dosage has completed (NCT00726583) and four phase I and II clinical trials are recruiting participants. The most noted side-effect of PX-866 is hyperglycemia which can be overcome by pioglitazone (46).

XL147 (Sonofi-aventis)

XL147 selectively inhibits class I PI3K isoforms by binding to the isoforms in an ATP-competitive manner. In a phase I clinical trial, XL147 decreased phosphorylation of Akt and its down-steam target S6 in several cancer cell lines, resulting in inhibition of cell growth (47). It was also demonstrated to be effective against tumo growth in the xenograft models of several cancers. In addition, XL147 has an additive effect with chemotherapeutic drugs in breast cancer (47). A problem in using XL147 was subsequent up-regulation of HER3 which attenuated the effect of XL147 (48). In a xenograft model, HER2 and HER3 antagonists were shown to have synergistic effects with XL147. The maximum tolerated dose (MTD) was identified to be 600 mg. At this dose, PI3K was inhibited and prolonged stable diseases have been achieved. The side-effects of XL147 include skin rash, arterial thrombosis, transaminase elevation and hyperglycermia. At present, a phase II clinical trial is recruiting participants (NCT1013324).

BKM120 (Novartis)

BKM120 is a pan-PI3K inhibitor and has been testead in several cancers including melanoma, medulloblastoma and breast cancer (49-51). It was shown to inhibit the growth of melanoma cells and

has asynergistic effect with rapamycin (49). In medulloblastoma, the inhibitor of a protein called G-protein Smoothened (Smo) can cause tumor regression in an animal model (50). However, activation of PI3K/Akt can lead to drug resistance to Smo inhibitors. BKM120 overcome the development of such drug resistance. In ER-positive breast cancers, BKM120 alone can lead to apoptosis under the condition that estrogen is deprived (51). Two clinical trials using BKM120 are currently recruiting (NCT01300962 and NCT01297491).

GDC-0941 (Genentech)

GDC-0941 is a potent inhibitor of the PI3K isoform p110 alpha and has high selectivity against class I PI3K (52). It has been tested in several cancers including breast ovarian, lung and prostate cancer (52-54). In breast cancer, ABT-737 can cause apoptosis but its effect is modest. GDC-0941 has been shown to have strong synergistic cytotoxicity with ABT-737 (54). In an MDA-MB-231 xenograft breast cancer model, their combinational use had also greater effects than one agent alone. Several clinical trials for GDC-0941 are recruiting (www.clinicaltrials.gov).

CAL-101 (Calistoga Phamaceuticals, Inc.)

CAL-101 is the PI3K inhibitor which has been tested in haematological malignancies (55-62). It is a selective inhibitor of p110 delta. Inhibition of the isoform by CAL-101 has been shown to decrease pAkt and its down-stream targets, and cause increased caspase cleavage and apoptosis in B-cell leukemia (60).

Akt inhibitors

Akt, a serine/threonine kinase, is the major mediator of the PI3K and used as an indicator for the activation of the pathway (39). There are three isoforms of Akt; Akt 1, Akt 2 and Akt 3 encoded by three distinct genes located in 14q32, 19q13 and 1q44 respectively (63). All of them include an N-terminal pleckstrin homology (PH) domain, a regulatory hydrophobic C-terminal domain and a central kinase domain. PH interacts with PIP3 and directs Akt to locate to the plasma membrane for phosphorylation by phosphoinositide-dependent kinase 1. The Akt inhibitors were developed recently.

ISI-4

ISC-4 is synthesized from natural product isothiocyanate (64). Isothiocyanate was found to have anti-cancer effect in screening against Akt3. It was further chemically modified to be isoselenoocyanates by increasing alkyl side chains and substituting sulfur with selenium to be more potent. ISC-4, which has four carbon alkyl side chains, was tested to be effective against colon cancer (65). In a mouse model with HT29 colon cancer cell xenografts, ISC-4 increased the effect iveness of 5-FU treatment.

MK-2206 (Merck)

MK-2206 is an allostetic inhibitor of all three Akt isoforms. Preclinical studies showed that it is effective on several cancers. A phase I clinical trial to test MK-2206 in solid cancers has now been conducted (66). In thirty three patients, the agent was given at the doses of 30, 60, 75 and 90 mg on alternative days and the MTD was identified to be 60 mg. At this dose, the phosphoryaltion of Akt at Ser473 was found to be decreased and the tumors were shrinked. The most noted side-effects were skin rash and stomatitis. MK-2206 has synergistic effects with anti-cancer agents erotinib, lapatinib, doxorubincin, camptothecin, gemcitabine, 5-FU, carboplatin and docetaxel (67).

mTOR inhibitors

mTOR, a serine-threonine kinase discovered in 1994, is a major mediator in the PI3K/Akt pathway (68-70). It is also activated by MAPK pathway. mTOR is a 2594 amino acid peptide with a molecular weight of 289 kDa and is included in two mTOR complexes. mTORC1 consists of mTOR, regulatory associated protein of mTOR, mammalian LST8/G protein β-subunit like protein (mLST8GβL), PRAS40 and DEPTOR while mTORC2 contains mTOR, GβL, rapamycin-insensitive companion of mTOR (Rictor), and mammalian stress-activated protein kinase interacting protein 1 (71,72). Both complexies play important roles in colon cancer tumorigenesis and progression (73,74). Traditional inhibitor of mTOR rapamycin can only inhibit mTORC1. New developed mTOR inhibitors torin 1, AZD8055, INK128 and OSI can inhibit both mTORC1 and mTORC2.

Rapamycin (Wyeth)

Rapamycin, a macrolide antibiotic isolated from the soil bacterium Streptomyces hygroscopicus, is used clinically as an immunosuppressive agent in organ transplantation (75). It has been tested to be effective for colon cancer (73,74,76-78). Rapamycin can inhibit mTORC1 and reduce colon cancer cell migration and invasion (74). Rapamycin in combination with irinotecan greatly inhibited mTOR and its down-stream target hypoxia-inducible factor 1 and resulted in greater reduction of tumor volume in a xenograft model compared with single agent (78). *In vitro* experiments, two agents caused massive death of HT29 cells under hypoxic condition. However, HCT116 cells did not respond to

the treatment probably due to the activating mutations of both the PI3K/Akt and Ras/MAPK pathways in the cells.

Torin 1

Torin 1 was discovered by Gray and Sabatini from a biochemical screening for inhibitors of mTOR in a library of heterocyclic compounds (79). It has much broader substrates than rapamycin. Torin 1 can also inhibit mTORC2 as well as rapamycin-resistant phosphorylation of 4EBP1. Therefore, it is more effective than rapamycin in anti-cancer treatment.

AZD8055 (AstraZeneca)

AZD8055 inhibits both mTORC1 and mTORC2 and has been tested both *in vitro* and *in vivo* (80). The IC50 was identified to be 0.8 nM. *In vitro* it inhibited cancer cell proliferation in lung cancer cell lines H838 and A549 with decreased phosphorylation of both mTORC1 and mTORC2 downstream targets such as p70S6K, 4EPB1 and Akt. In animal xenograft models, it led to regression of tumours including colon cancer (80). AZD8055 has also synergistic effect with chemotherapeutic agents and is now in phase I clinical trial (81-83).

OSI-027 (OSI Pharmaceuticals Inc.)

OSI-027 inhibits both mTORC1 and mTORC2 with IC50 22 and 65nM respectively (84,85). Preclinical studies showed it inhibited cancer cell proliferation. It also reduced vascular endothelial growth factor (VEGF) production and vessel sprouting (86). OSI-027 is now in aphase I clinical trial for solid tumors and lymphomas (NCT00698243).

INK-128 (Intellikine)

INK-128, the first compound of Intellikine used for clinical trial, is an orally administered mTOR inhibitor which selectively inhibits mTORC1 and mTORC2. It directly inhibits the mTOR kinase in both complexes with the IC50 1nM. The compound is much more potent than rapamycin. In both *in vitro* and *in vivo* experiments INK-128 was shown to be effective for several cancers indicated by reduced phosphorylation of mTORC1 down-stream targets p70S6K1 and 4EPB1, and mTORC2 down-stream target Akt (87). A phase I clinical trial is employed to test the safety and pharmacokinetics of INK-128 in advanced solid tumors (NCT01058707). Another clinical trial is to test its combinational use with paclitaxel and trastuzumab in HER2 positive breast cancers (NCT01351350).

Dual inhibitors of PI3K and mTOR

XL765

XL765 has been tested in several cancers such as pancreatic cancer and glioblastoma cell lines (88,90). It was shown to increase cytotoxicity in a dose-dependent manner in glioblastoma cell lines with the inhibition of the PI3K/Akt pathway (90). The agent had additive effect with chemotherapeutic agent temozolomide. XL765 was also effective in xenograft models. It was shown to induce higher autophagy. The combination of XL765 with autophagy inhibitor chloroquine produced an synergistic effect (88).

SF1126

SF1126 was developed by Garlich *et al*. from Ly294002 with increased solubility and half-life (91). It has been studied in breast cancer and neuroblastoma (92,93). In HER2 over-expressed breast cancer cells, which are resistant to trastuzumab, SF1126 caused apoptosis, inhibited cell proliferation and colony formation (92). The phosphorylation of Akt was reduced with the increased apoptosis markers caspase 3 activity and PARP protein. In neuroblastoma the compound was shown to cause apoptosis and increase sensitivity to doxorubicin (93). It reduced phophorylation of Akt induced by IGF-1 and disrupted actin cytoskeleton. SF1126 also inhibited tumo growth in an *in vivo* neuroblastoma xenograft model (93).

PI-103 (Astellas Pharma Inc.)

PI-103 acts on PI3K as well as mTORC1 and mTORC2. It has been shown to inhibit cell proliferation of glioma *in vitro* and reduce the size of xenograft gliomas in mice with inhibition of mTOR and PI3K kinases (94-97). It was also effective to several other cancers including colon, prostate, hepatoma, acute myeloid leukemia, neuroblastoma and non-small cell lung cancers (98-104). PI-103 was shown to have synergistic effects with sorafenib, radiotherapy, arsenic disulfide, rapamycin (100,101,105,106). The compound is rapidly metabolized *in vivo*, therefore it is not suitable for clinical use but could be used as a lead compound for further development.

BEZ235 (Novartis)

Bez235 is derived from imidazoquinoline and has been studied in many cancer cell lines including colon cancer (49,107-114). BEZ-235 causes transient PI3K blockage and sustained decreases in mTORC1/mTORC2. *In vitro* experiments, Bez235 decreased

colon cancer cell viability independent of PIK3CA mutations (113). *In vivo*, treatment with Bez235 decreased xenograft colon cancer volume by 43% compared with a 97% growth in the control (113). There were a 56% decrease in cell proliferation and 75% reduction in angiogenesis but no effect on apoptosis. At present there are 7 clinical trials are recruiting for Bez235.

BGT226 (Novartis)

Anti-cancer effect of BGT226 has been tested in breast cancer and in head and neck cancer (51,115). In estrogen positive breast cancer cell lines, BGT226 had synergistic effects with fulvestrant (51). It also inhibited the proliferation of many head and neck cancer cell lines. The signaling pathway analysis showed reduced phosphorylation of Akt at Ser473 and mTOR at Ser2448 by BGT226. The cells were shown to be arrested in G0/G1 phase with decreased number at S phase. In FaDu cancer cell xenograft mouse model, oral administration of BGT226 at dosages of 2.5 and 5 mg/kg for three weeks inhibited the tumour growth by 34.7% and 76.1%, respectively.

GDC-0980 (Genentech Inc.)

GDC-0980 is developed from GDC-0941 with the additional ability to inhibit mTOR by substituting indazole with aminopyrimidine (116). It is effective against many cancer cell lines but less effective against the cells with activated MAPK pathway (116,117). Oral administration of a low dose of GDC-0980 (1 mg/kg) inhibited tumo growth in a xenograft model (116). It is now in phase I clinical trial.

MAPK pathway inhibitors

MAPK is a mitogenic pathway and plays a key role in cell proliferation and survival and responss to diverse mitogens such as EGFR, erbB2, PDGFR and environmental stresses (118-121). MAPK is activated in many cancers and promotes cancer cell proliferation and decreases apoptosis. Inhibition of the pathway has been shown to be effective to inhibit cancer cell growth. As this pathway has been demonstrated to be activated in obesity-associated colon cancer, its inhibition may be effective for the treatment of the disease (26,43). The details of the pathway has been reviewed else where (120,122). Some inhibitors of the MAPK pathway are listed in Table 2 and described below.

Sorafenib (Bay 43-9006, Nexavar)

Sorafenib, the first RAF inhibitor for clinical trial, was initially developed for the inhibition of RAF and was later found to also inhibit PDGFR, VEGFR1/2, c-kit, FGFR1 and FLT3 (123). The synergistic effect of sorafenib and vorinostat treatment was demonstrated in colon cancer cells SW480, DLD-1 and HCT116 (124). It was shown that pErk1/2 was inhibited but pAkt was not. The authors also demonstrated that pErk was more important in HCT116 cells than pAkt for drug resistance. However, the effect of sorafenib on cells with mutated BRAF is limited. In obesity-associated colon cancer, activation of the MAPK pathway is not caused by gene mutations. Therefore, sorafenib may be effective for the disease.

PLX-4032 (Plexxikon)

PLX-4032 is small molecule inhibiting Raf. It was developed by Plexxikon due to the discovery that 80% of melanomas and 20% of colorectal cancers have BRaf activating mutations. PLX-4032 has been tested in melanoma to be effective (125-127). It increased the sensitivity of melanoma cells to radiotherapy (125). The phase I clinical trial was successful and now phase II and phase III clinical trials are underway (128).

GSK2118436

GSK2118436 was also studied in melanoma (83,129-132). It inhibited mutated B-Raf and increased clinical responses to chemotherapy markedly (83). However the use of GSK2118436 subsequently increased platelet derived growth factor receptor and resulted in the resistance to the treatment. The use of PI3K or mTORC1/2 inhibitors produced synergistic inhibition. Combinational use of MEK1/2, PI3K and mTORC1/2 in melanoma cancer cells triggered profound apoptosis.

RAF265 (Novartis)

RAF265 has been demonstrated to be effective in melanoma and endocrine cancers (133-136). The studies also found that Akt pathway may compensate to cause the resistance to RAF265. Thus dual inhibition approaches were tested (137-139). A phase I for advanced solid tumo with Ras or BRAFV600E mutations is recruited by Novartis (NCT01352273).

MEK1/2 inhibitors

CI-1040 (PD-184352) (Pfizer-oncology)
CI-1040 is the first MEK/12 inhibitor used for clinical trial. But the efficacy is not satisfactory. The compound was tested for several cancers including colon cancer (140-142). The IC50 for colon 26 is 17 nM (142). Pfizer has completed two phase II studies in colon cancer but the outcome is not satisfactory

Table 2. MAPK pathway inhibitors.

Signaling molecules	RAF	Mutated RAF	MEK
Inhibitors	sorafenib	PLX-4032, GSK2118436, RAF265	AZD6244, GSK1120212, CI-1040, PD-0325901

(NCT00034827 and NCT00033384). Therefore, second generation of MEK1/2 inhibitors were developed.

PD-0325901(Pfizer-oncology)

PD-0325901 has been studied in colon cancer in a pilot study (141,143-146). Initially, it was given orally at a dose of 20 mg twice daily for 21 days but changed to 15 mg because it was not well tolerated. The trial was terminated earlier due to side-effects. There is severe neurological toxicity for this compound and thus it is no longer being tested in clinical trials.

AZD6244 (AstraZeneca)

AZD has been tested in colon cancer (147-149). The agent has been used for phase I clinical trials with satisfactory results and the dosage used was well tolerated (150). FOXO3a was found to increase compensatorily (149). A phase II clinical trial for colorectal cancer is supported by AstraZeneca and expected to be completed in December 2011 (www.clinical trials.gov. NCT01116271). In the trial, AZD6244 is used in combination with irinotecan. Another phase I supported by NIH is also in recruiting, AZD6244 is used with cetuximab (NCT01287130).

GSK1120212

GSK1120212 (also called JTP-74057) was discovered by a high-throughput screening for compounds that induced the expression of p15INK4b, which is down-stream of ERK1/2 and inhibited by ERK1/2 (151). GSK1120212 was tested in colon cancer (151-153) and was shown to be much more potent than the second generation MEK1/2 inhibitors AZD6244 and PD0325901. It effectively inhibited MEK1/2 in 9 colon cancer cell lines and decreased cell proliferation with IC50 from 0.92 to 3.4 nM. In animal models, the compound reduced HT-29 xenograft tumo sizes (151). GSK1120212 was administered orally daily for 14 days at dosage of 0.3 and 1 mg/kg. Both dosages were effective but the higher dose (1 mg/kg) inhibited tumo growth completely. The compound had additive effects with oxaliplatin and 5-FU to cause colon cancer cell apoptosis. The combination with irinotecan metabolite SN-38 also produced synergistic effects. A phase I in combination with Akt inhibitor is recruited by GlaxoSmithKline (NCT01138085).

Dual inhibitors of Akt and MAPK

Perfosine (Keryx)

Perfosine (KRX-0401) is an oral anti-cancer agent which inhibits both Akt and MAPK. It acts on the PH domain of Akt and thus prevents Akt to be translocated to plasma membrane for phosphorylation. In a phase II clinical trial, it was very effective against colon cancer with doubled time for metastatic cancer to progress (154). Clinical trials showed its side-effects are fatigues and gastrointestinal toxicity. Perfosine is now in a phase III clinical trial for colorectal cancer in combination with capecitabine by Kerynx (NCT01097018). Perfosine has been approved by FDA to be used in colon cancer treatment.

Erucylphosphocholine

Erucylphosphocholine is derived from perfosine. It has been tested for glioblastoma. It caused decreased proliferation via inhibition of Erk and pro-apoptosis by activation of JNK (155). Erucylphosphocholine has also strong activity against endometrial and ovarian cancer cells (156).

STAT3 pathway inhibitors

STAT3 was demonstrated to be important for the carcinogenesis and metastasis of colon cancer (157,158). Inhibition of STAT3 is effective for cancer lines with increased STAT3 pathway but less effective in those cells with low STAT3 activity. In obesity-associated colon cancer, increased leptin has been shown to accelerate colon cancer partially via STAT3 (34). Therefore, inhibition of STAT3 may be used for the targeted therapy for obesity-associated colon cancer. STAT3 inhibitors include NSC74859, LLL12 and stattic.

NSC74859

NSC74859 is a salicylic acid-based inhibitor with a low molecular weight. It was discovered by Turkson through screening of a National Cancer Institute chemical compound library via in silico methods (159). IC50 for the inhibition of the

SH2 domain of STAT3 is 86 μM. NSC74859 has been shown to reduce the expression of down-stream targets of STAT3 such as cyclin D1, Bcl-xL and surviving (160).

LLL12

LLL 12 was developed by Dr. Pui-Kai Li at Ohio State University (161). It has been shown to induce apoptosis and inhibit cancer cell growth in several cancers including colon colon under stimulation of IL-6 (157,161-168).

Stattic

Stattic is the abbreviation for stat three inhibitory compounds. It was discovered after screening thousands of compounds. Stattic can inhibit the SH2 domain of STAT3 specifically (169). The effectiveness of Stattic has been tested in colon cancer. In ALDH+/CD133+ colon cancer stem cells, STAT3 activity was increased and stattic inhibited STAT3 and its down-stream targets (157). In obesity-associated colon cancer STAT3 pathway may be activated by leptin and IL-6. Therefore, inhibition of STAT3 by Stattic may be an approach for the treatment of the disease.

Selection of approaches to target activated multiple signaling pathways in obesity-associated colon cancer

As discussed above many inhibitors can be chosen to inhibit the activated signaling pathways in obesity-associated colon cancer. Studies have used some of these inhibitors to inhibit signaling molecules such as PI3K or mTOR and showed the effectiveness of tested inhibitors (30-32). Due to multiple factors and multiple signaling pathways are activated in obesity-associated colon cancer, inhibition of a single molecule may be not sufficient for treatment. More options exist to increase treatment efficacy for obesity-associated colon cancer.

Dual inhibitors of PI3K and mTOR such as Bez235 are particularly interesting. mTOR could be highly activated in obesity because it is activated by both the PI3K/Akt and MAPK pathways (26). Therefore, it can be used as a target for inhibition. However, mTOR is known to feedback inhibit the PI3K/Akt pathway. Inhibition of mTOR leads to increases the activity of PI3K/Akt. Dual inhibitors of PI3K/mTOR could abrogate this effect.

Dual inhibitors of Akt and MAPK could also be chosen for the treatment of obesity-associated colon cancer. These drugs inhibit key signaling molecules in two important signaling pathways in obesity and therefore could be more effective in reversing the activated multiple signaling pathways in obesity-associated colon cancer. As several studies have shown that one of the pathways may compensatorily increases when another is inhibited, the use of dual inhibitors may be particularly effective.

Another approach could be the combinational use of two or more inhibitors such as a dual inhibitor of PI3K/mTOR and a MAPK inhibitor. This could maximiz the inhibition of multiple signaling pathways in obesity-associated colon cancer. However, it is not known if the side-effects will also increase. These combinations warrant further investigation in cancer cell lines and animal models. If the results obtained are promising, combinational targeted therapy of obesity-associated colon cancer may be further validated in clinical trials.

Conclusions

Activation of multiple signaling pathways in obesity has been associated with the poorer treatment outcome of obesity-associated colon cancer. Therefore, targeted inhibition of these pathways could increase the efficacy of chemotherapy in this disease. At present, many inhibitors developed by different companies are available to inhibit these pathways. Most studies have tried to inhibit one signaling molecule for the disease with some effectiveness. However, it may be not sufficient to inhibit one signaling molecule for the activation of multiple signaling pathways in obesity-associated colon cancer. There are more options to inhibit several key signaling molecules to increase treatment efficacy for example, Bez235 can inhibit both PI3K and mTOR, perfosine can inhibit both Akt and MAPK. Two inhibitors may be used in combination to further increase treatment efficacy such as a dual inhibitor of PI3K/mTor and a MAPK inhibitor.

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