Critical Review

The Potential Therapeutic and Prognostic Impacts of the c-MET/HGF Signaling Pathway in Colorectal Cancer

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Abstract

Colorectal cancer (CRC) is the third most common cancer and a common cause of cancer-related mortality globally. In spite of the improvements in the early diagnosis of CRC, approximately one-third of patients develop metastasis and then have a very poor survival rate. The mesenchymal–epithelial transition factor (c-MET) is a tyrosine kinase cell surface receptor activated by hepatocyte growth factor (HGF). Activation of c-MET/HGF signaling pathway regulates a variety of biological processes including cell motility, cell proliferation, angiogenesis, the epithelial-to-mesenchymal transition, and the development and progression of cancer cells. Recent studies have suggested that the c-MET/HGF signaling pathway is involved in the carcinogenesis of CRC. In this review, we summarize the main findings of recent studies investigating the role of c-MET/HGF signaling pathway in CRC and the potential of the c-MET/HGF signaling pathways in the diagnosis and treatment of CRC. © 2019 IUBMB Life, 71(7):802–811, 2019

Keywords: c-MET/HGF signaling pathway; therapeutic; prognostic; colorectal cancer

Abbreviations: *CRC, colorectal cancer; c-MET, mesenchymal–epithelial transition factor; HGF, hepatocyte growth factor; TGF-β, transforming growth factor beta; SMAD4, mothers against decapentaplegic homolog 4; RAS, rat sarcoma viral oncogene homolog; EGFR, epidermal growth factor receptor; miRNA, microRNA; VEGF, vascular endothelial growth factor; PI3K/AKT, phosphatidylinositol-3-kinase (PI3K)/Akt; mTOR, mammalian target of rapamycin; FAK, focal adhesion kinase*

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INTRODUCTION

Colorectal cancer (CRC) is the third most common malignant neoplasm and one of the most common causes for cancer-related mortality globally, accounting for about 600,000 death annually (1). More than one million new cases are diagnosed worldwide per year (2). Although the incidence rate of CRC is not uniformly common globally, both genders have a similar incidence rate (3, 4). The survival rate in patients with CRC is dependent on the stage at diagnosis and treatment. In spite of extensive efforts and advances made in early diagnosis of CRC and timely and appropriate treatment of CRC, approximately one-third of patients developed distant metastasis inspite of chemoradiotherapy and surgery (5). Less than 10% five-year survival is expected for CRC patients in advanced and metastatic stages (2).

CRC carcinogenesis is a multistep process and is often a consequence of genetic and epigenetic alteration (6). Furthermore, in the carcinogenesis of CRC, several signaling pathways had been

reported to be involved during transition from normal colorectal epithelium to cancerous and also in CRC progression, including the toll-like receptor signaling pathway (7), the Wnt/β-catenin signaling pathway signaling pathway (8), the death receptor signaling pathway (9), the rat sarcoma viral oncogene homolog (RAS) signaling pathway (10), and the TGF-β/SMAD4 (mothers against decapentaplegic homolog 4) signaling pathway (11). Furthermore, the c-MET/HGF signaling pathway is another pathway that has been reported to be involved in CRC carcinogenesis. Consequently, targeting the c-MET/HGF signaling pathway has become a focus of interest either for efficient targeted therapy of CRC or for using to predict CRC patient's prognosis.

c-MET (mesenchymal–epithelial transition factor) is a tyrosine kinase cell surface receptor that upon binding of its ligand, hepatocyte growth factor (HGF), activates downstream effector pathways (12). Activation of the c-MET/HGF signaling pathway regulates a variety of biological processes including cell motility and proliferation, angiogenesis, the epithelial-to-mesenchymal transition, and also the development and progression of cancer cells (13). The c-MET receptor and HGF are expressed in normal epithelial cells; however, upregulation in c-MET and HGF expression has been found during carcinogenesis (14–16). In this regard, in several human malignancies such as bladder cancer, breast cancer, cervical cancer, esophageal cancer, gastric cancer, and also CRC, it has been reported that aberrant expression of c-MET triggers a series of signaling cascades and is associated with higher proliferation, prevention apoptosis, loss of intercellular junctions, cell dissociation, and poor prognosis (17–23). Involvement of the c-MET/HGF signaling pathway in several carcinogenetic processes and its interaction with other signaling pathways suggest that pharmacological manipulation of the c-MET/HGF signaling pathway may serve as a potential target for therapeutic management of CRC patients to avoid CRC progression and metastasis. The aim of this review is to summarize recent studies in exciting field of prognostic role of c-MET/HGF signaling pathway in CRC patients and using c-MET/HGF signaling pathways as a novel therapeutic target in CRC.

c-MET/HGF SIGNALING PATHWAY AND ITS INTERACTION WITH OTHER SIGNALING PATHWAYS

Signaling pathways of HGF and its receptor (HGFR or c-MET) are important in regeneration, organ protection, and tumor malignancy. c-MET is a receptor tyrosine kinase that has glycosylate alpha and transmembrane subunit beta in its mature form. Cytosine-rich MET-related sequence domain, Sema domain, and four immunoglobulin-like domains are other extracellular components of c-MET. The C-terminal regulatory tail, a tyrosine kinase domain, and a juxtamembrane domain form the intracellular portion of c-MET. The mature HGF is a heterodimer of alpha and beta chains. The alpha chain has one N-terminal hairpin and four kringle domains. The beta subunit also has an enzymatically inactive serine protease-like domain (24). The c-MET proto-oncogene is expressed by epithelial cells of many organs. Y1234 and Y1235 are tyrosine residues in the catalytic domain of c-MET, which becomes phosphorylated and homodimerized after binding of HGF to c-MET. Tyrosine 1356 and 1349 are two other tyrosines that can be phosphorylated later in the signaling pathways. Stereotypical signaling modulators are responsible for downstream response to c-MET activation. These responses include cell survival, transformation, motility, proliferation, and cell cycle progression (25). Mitogen-activated protein kinase cascade is an important cascade in cell proliferation and cell cycle proliferation. Activation of this cascade is regulated via activation of RAS. Cell survival response is related to phosphatidylinositol-3-kinase (PI3K) signaling activated by c-MET signaling. Invasion, branching morphogenesis, and tumorigenesis related to c-MET signaling activation are mediated by STAT3 activation in a tissue-dependent manner (26, 27). Also, cellular migration and adhesion are mediated by c-MET–SRC–FAK (focal adhesion kinase) interaction (17). Many other receptors such as neurophilins can also activate c-MET signaling and other downstream pathways. Stimulation of cells with different ligands such as epidermal growth factor receptor (EGFR) or platelet-derived growth factor receptor may result in c-MET signaling activation in the absence of c-MET ligand (28).

ROLE OF c-MET/HGF SIGNALING PATHWAY IN CARCINOGENESIS

Along with the roles in carcinogenesis described above, mutations and rearrangements are also responsible for the development of some cancers. Chromosomal rearrangements that place c-MET adjacent to a translocation promoter may result in the development of epithelial tumors. The overexpression of c-MET has been reported in some cancers in the absence of mentioned gene amplifications. c-MET amplification can be seen as a first-tire genetic aberration or acquired during carcinogenesis (25). Mutation of the MET gene can activate MET tyrosine kinase and induce carcinogenesis. A well-known mutation in MET gene can be seen in hepatocellular carcinoma of childhood. This cancer is caused because of a somatic mutation in the kinase domain of MET (29). Despite the presence of activating mutations, some MET mutations are considered to be inhibitors of downregulation. Deletion of the juxtamembrane domain is responsible for this downregulation delay (30). Even in the presence of intact MET, the activation of c-MET signaling pathway will occur by transactivation in some cancers. CD44 stimulation and MET expression are an example of transactivation in colon cancer. CD44 stimulation will result in MET expression and therefore amplification of integrins that mediate cancerous cell adhesion to adjacent epithelial cells (31). However, a recent study has shown that c-Met activation is independent of CD44 expression in HT29 LM3 cell lines (C27).

ROLE OF microRNAs IN TARGETING c-MET/HGF SIGNALING PATHWAY

microRNAs (miRNAs or miRs) are small, single-stranded, nonprotein-coding ribonucleic acids (RNAs) composed of approximately

19–22 nucleotides long (32). miRNAs can be found in different body fluids (33). These short-fragment RNAs acting as post-transcriptional regulators of gene expression play pivotal roles in many biological processes and cellular pathways including cell cycle progression, proliferation, differentiation, apoptosis, and angiogenesis (34, 35). Alteration of miRNAs' expression has been observed to result in dysregulation of these processes, and also there is increasing evidence that aberrant expression of miRNAs correlated with a number of cancers' initiation and progression including CRC (35). It has been found that miRNAs can play a role in cancer biology as tumor suppressors or oncogenes are associated with c-MET/HGF signaling pathway. Some miRNAs including miR-1, miR-34, miR-141, miR-199, and miR-206 have been identified to be able to affect the c-MET/HGF signaling pathway (12). Reid et al. investigated miRNAs' expression in untreated CRC patients (36). Forty CRC tissues matched with their adjacent normal colorectal tissues were obtained. They found that the expression of miR-1 was downregulated in CRC compared to non-cancerous colorectal tissue. Furthermore, they observed that miR-1 acts as tumor suppressor and can directly downregulate c-MET expression. In cell line investigation in this study (HT29, HCT116, and DLD-1 cells), Reid et al. also revealed that re-expression of miR-1 resulted in decrement in CRC cells' proliferation and their motility by inhibition of c-MET/HGF signaling pathway. Long et al. in an experimental study, evaluated the role of miR-141 as one of common cancer-associated miRNA in CRC cell line (SW480 cells). They found that overexpression of miR-141 resulted in cell cycle arrest and therefore a significant decrease in proliferation of CRC cells. Long et al. also reported that miR-141 inhibition led to increased c-MET phosphorylation. Finally, they concluded that miR-141 acts as a tumor suppressor by targeting HGF receptor, also known as c-MET, and zinc finger E-box-binding homeobox (37). Bleau et al. in an attempt to identify novel targets for treatment of CRC patients with liver metastasis used mouse model of CRC liver metastasis. In this experimental analysis, they showed that the expression of c-MET was upregulated while miR-146a expression was reduced in metastatic models. They found that miR-146a directly targets c-MET, and the overexpression of miR-146a in metastatic clones resulted in prevention of colonization of the metastatic cells in liver and reduces primary tumor growth. Bleau et al. evaluated a total of 21 metastatic samples and 52 primary tumors, and in spite of experimental assay, in CRC patients no significant differences were observed in c-MET and miR-146a between primary tumors and CRC patients with liver metastasis (38). The expression of miR-206 and its role in CRC progression were evaluated by Ren et al. in 40 CRC tissue samples matched with their adjacent normal colorectal tissues (39). They observed significant reduction in miR-206 expression compared with adjacent normal tissue. Furthermore, in CRC cell lines (SW620, LOVO, LS174T, SW480, HT29, and HCT116 cells), they found that miR-206 inhibited the proliferation of CRC cells and induced apoptosis and also prevented invasion and metastasis by directly targeting c-MET.

In addition to this role of miRNAs, some studies have also evaluated the possible therapeutic role of miRNAs altering c-MET pathways in CRC. Takeyama et al. studied miR-340 expression in bone marrow of CRC patients with liver metastasis. By transient miRNA transfection, they have shown that miR-340 and miR-542-3p can inhibit CRC cell proliferation. Also, low miR-340 and high c-MET levels in contrast to high miR-340 and low c-MET expression have been reported to have better prognosis (40). Chen et al. studied the role of miR-137 effect on tumor growth and metastasis and reported that mice with miRNA overexpression have smaller tumors and less metastasis. Also, they reported that miR-137 could affect tumor progression by downregulating c-MET expression. An interesting finding was observed in relation to the epigenetic regulation of miR-137. Mecp-2 can regulate epigenetic silencing of miR-137 and cause tumor progression by awaking the suppressed c-MET (41).

THE THERAPEUTIC TARGETING c-MET/HGF SIGNALING PATHWAY IN CRC

The effect of c-MET/HGF expression and its targeting in CRC is under active research. It has been reported that c-MET expression increases gradually during progression from normal epithelium to adenoma, to carcinoma, and to metastasis (42) (Table 1). Various treatment options have been reported for targeting c-MET/HGF signaling. HGF antagonists, such as NK4, have been tested in patients with metastatic CRC. This drug will successfully inhibit angiogenesis (53). Humanized molecular antibodies are another therapeutic choice for targeting c-MET pathway. Monoclonal antibodies have been developed that can bind to c-MET and inhibit receptor activation (onartuzumab) or even prevent phosphorylation of c-MET (rilotumumab) (54, 55). Tabernero et al. have evaluated the safety and tolerability of ficlatuzumab in advanced CRC patients and reported this drug as a favorable choice for altering c-MET pathway safely. The most common side effects were edema and gastrointestinal adverse events (44). Sun et al. have evaluated the effect of cabozantinib as a c-MET inhibitor of angiogenesis and tumor growth in a mouse model. They reported that cabozantinib can effectively suppress VEGF expression by modulating sonic hedgehog pathway (56). Lee et al. (51) had recently conducted the first clinical trial of SAIT301 as a human igG2 antibody targeting c-MET in CRC patients. The patients who have not responded to chemotherapy and overexpressed MET have responded dramatically to SAIT301 and alkaline phosphatase elevation or hyperphosphatemia as the dose-limiting toxicities. There are other drugs available that affect c-MET signaling. Quinazolinone has proven to possess antimalarial, antibacterial, and also antitumor activities. Quinazolinone can affect matrix metalloproteinases expression and inhibit metastasis. Chen et al. have evaluated the antimetastatic effect of a quinazolinone derivate and MJ-56 (6-pyrrolidinyl-2-(3-bromostyryl)quinazolin-4-one) in CRC cell lines. They have proven that MJ-56 can inhibit invasion and migration of HT29 cells by targeting EGFR and c-MET, and therefore ERK and PI3K/AKT/mTOR signaling. The blocking of matrix metalloproteinases is due to inhibition of

TABLE 1 ***Summary of the most relevant studies investigating c-MET/HGF signaling pathways as therapeutic factors in CRC***

Author and year	*Sample/cell line*	*Therapeutic agent*	*Chief findings*
Chen et al., 2013 (43)	Human CRC samples/HT29 cell line	MJ-56	Inhibition of invasion and migration Inactivation of ERK and PI3K/AKT/mTOR signaling pathways and blockade of NF-kB
Takeyama et al., 2014 (40)	Normal and tumor tissue/HCT116 and SW480 cell lines	miR-340 miR-542-3p	Inhibition of CRC cell proliferation after administration of miR-340 Association of higher miR-340 expression and better survival
Tabernero et al., 2014 (44)	15 patients with advanced unresectable CRC (phosphorylated c-MET)	Ficlatuzumab	Ficlatuzumab was well tolerated and safe in advanced CRC Ficlatuzumab modulate HGF/c-MET pathway, and the recommended dose was 20 mg/kg once/14 days cycles
Hu et al., 2016 (45)	DU145 cell line	Curcumin and dimethyl sulfoxide	Curcumin reduced HGF-induced invasive cells and blocked HGF stimulation Suppression of HGF-induced E-cadherin downregulation and vimentin expression upregulation
Bessudo et al., 2011 (46)	9 patients with previously treated metastatic CRC	Tivantinib and CPT-11 plus C	360 mg of RPTD twice daily was well tolerated with preliminary antitumor activity
Eng et al., 2016 (47)	122 locally advanced or metastatic CRC	Tivantinib and CETIRI	No improvement in OS and PFS by adding tivantinib to CETIRI
Pineda et al., 2017 (48)	27 metastatic CRC	CAPOX–bevacizumab	Increase sVEGFR1 and decrease VEGF-A achieved by bevacizumab and chemotherapy
Su et al., 2017 (49)	HCT116 cell line	Andrographolide	Andrographolide will enhance antitumor effect of 5-FU in CRC
Zhi et al., 2018 (50)	Human CRC cell lines RKO andHT29 (BRAFV600E mutant)	PHA-665752 andvemurafenib	c-MET targeting plus vemurafenib is more efficient in BRAF-positive CRC
Lee et al., 2018 (51)	15 patients with metastatic CRC	SAIT301	Dramatic response to SAIT301 in overexpressed MET CRC
Lev et al., 2017 (52)	26 MSI-high and 558 non-MSI-high CRC tumors	Crizotinib with mitomycin C	Combination therapy resulted in increased apoptosis and anticancer effect

CRC: colorectal cancer, c-MET: mesenchymal–epithelial transition factor, HGF: hepatocyte growth factor, OS: overall survival, PFS: progression-free survival, 5-FU: 5-fluorouracil, miR: microRNA, VEGF-A: vascular endothelial growth factor-A.

the NF-kB signaling pathway (43). Hu et al. used curcumin on DU145 cell lines, and have shown that curcumin can suppress HGF-induced effects that included upregulation of vimentin and downregulation of E-cadherin. Curcumin attenuated HGF-induced metastasis and migration as well as exhibited inhibitory effects on snail expression and MET/HGF signaling in the DU145 cell line (45).

THE PROGNOSTIC IMPACT OF c-MET/HGF SIGNALING PATHWAY IN CRC

High levels of c-MET expression have been reported to be associated with aggressive proliferation, invasion, and metastatic spread of CRC tumors in both early-stage CRC (stages I and II)

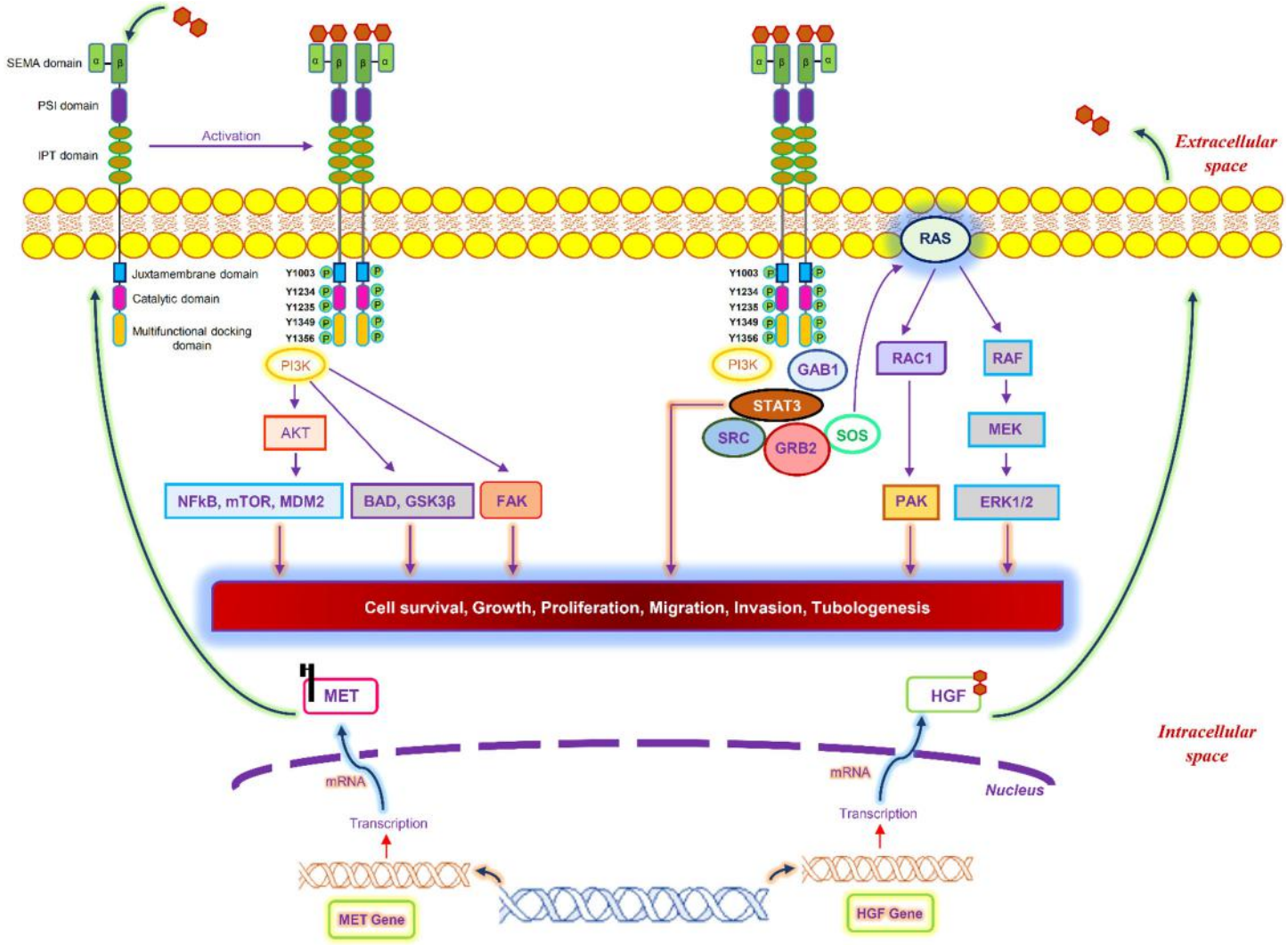

FIG 1 *HGF/c-MET signaling pathways and its role in cellular activity. The secreted HGF from different cells can dimerize the c-MET receptor and initiate the signaling by recruitment of several signaling proteins. These proteins will activate the downstream pathways and induce different cellular responses including survival, growth, proliferation, migration, invasion, and tubulogenesis, which are important during normal or cancer cell function.*

and advanced stage CRC (stages III and IV). Therefore, c-MET could be a useful biomarker in molecular staging and predicting CRC prognosis (Table 2).

Lee et al. (57) investigated the incidence and prognostic significance of c-MET expression in 255 metastatic CRC (stage IV) patients treated with bevacizumab. c-MET immunohistochemistry (IHC) was undertaken. They found c-MET overexpression in 15.3% of patients, and that c-MET expression was not significantly correlated with the response to chemotherapy. Furthermore, survival analysis showed that overexpression of c-MET was significantly associated with poorer overall survival (OS) and progression-free survival (PFS) irrespective of primary tumor sites. A retrospective tumor study was conducted by Resnick et al. on 134 CRC tissue specimens from stage II CRC patients who did not undergo adjuvant chemoradiotherapy. Standard IHC was used for evaluation of c-MET expression. In contrast with the previous study, they found no significant correlation between the expression level of c-MET and CRC patient's prognosis in stage II (60). With respect to limitation of conventional IHC in measuring the membranous, cytoplasmic, or nuclear c-MET expression (61), Ginty et al. evaluated the membranous, cytoplasmic, and nuclear levels of c-MET using an automated IHC in 583 patients including stage I–IV CRC (61). At the end of the study, the membranous level of c-MET was not found to be associated with prognosis in all disease stages. However, a lower level of membranous relative to cytoplasmic MET was a significant predictor of CRC patient's survival in stage I and II diseases. c-MET expression in 16 patients with colorectal adenoma, 123 patients with primary CRC, and 25 CRC patients with liver metastasis was determined by Di Renzo and colleagues. Despite overexpression of c-MET that was seen in

TABLE 2 ***Summary of the most relevant studies investigating c-MET/HGF signaling pathways as prognostic factors in CRC***

Author and year	*Population*	*Method*	*Chief findings*
Lee et al., 2018 (57)	255 metastatic CRC	IHC	Significant association between c-MET overexpression and poor OS and PFS
Kim et al., 2018 (58)	379 stage I–IV CRC	IHC	Significant association between c-MET overexpression and high expression of VEGF-C and VEGFR-3, but no significant association between c-MET expression and CRC prognosis was seen
Lorenzon et al., 2017 (59)	53 metastatic CRC	IHC	Association between the presence of c-MET overexpression in CRC patients with wild-type KRAS and poor outcomes
Resnick et al., 2004 (60)	134 stage II CRC	IHC	No significant correlation between the expression level of c-MET and CRC prognosis
Ginty et al., 2008 (61)	583 stage I–IV CRC	Automated IHC	Level of membranous relative to cytoplasmic MET was a significant predictor of CRC prognosis in stages I and II
Di Renzo et al., 1995 (62)	16 colorectal adenoma and 148 stage I–IV CRC	RNA isolation and Northern blotting	No significant association between c-MET overexpression and tumor grade or disease stage
Liu et al., 1992 (63)	-	mRNA expression	Significant higher expression of c-MET in cancerous tissues
Garouniatis et al., 2013 (64)	183 stage I–IV CRC	IHC	Significant association between c-MET expression and CRC tumor progression and patient survival
Abou-Bakr et al., 2013 (65)	238 stage I–IV CRC	IHC	Significantly higher DFS in low level compared with high level of c-MET
Takeuchi et al., 2003 (66)	36 early-stage CRC	Quantitative real-time PCR	Association between increased c-MET expression and depth of invasion and metastasis to lymph nodes
Zeng et al., 2004 (67)	130 stage I–IV CRC	IHC	Association between increasing CRC stage and an increase in the level of c-MET expression
Kishiki et al., 2014 (68)	91 metastatic CRC	IHC	Association between the presence of wild-type KRAS c-MET overexpression and decreased disease control rate and shorter PFS
Van Cutsem et al., 2014 (69)	142 metastatic CRC	–	Higher anticancerous effect and also higher PFS and OS by using a combination of panitumumab (anti-EGFR) and rilotumumab (anti-c-MET)
Inno et al., 2011 (70)	73 metastatic CRC	IHC	c-MET overexpression significantly associated with poor OS and PFS
Shoji et al., 2014 (71)	108 metastatic CRC	IHC	Association between increased c-MET overexpression and shorter RFS after hepatic metastasectomy

(Continues)

TABLE 2 *(Continued)*

Author and year	*Population*	*Method*	*Chief findings*
Zeng et al., 2008 (72)	247 primary CRC and 147 metastatic CRC	qPCR-LDR	c-MET gene amplification significantly correlated with CRC progression and metastasis and associated with poor prognosis
Gao et al., 2015 (73)	Meta-analysis (six studies that included 1,284 patients)	-	c-MET overexpression significantly associated with poor OS and DFS
Voutsina et al., 2013 (74)	83 stage I–IV CRC	IHC, qPCR	Association between c-MET overexpression and shorter OS
Liu et al., 2015 (75)	Meta-analysis (11 studies that included 1895 patients)	-	c-MET overexpression significantly associated with poor OS and PFS
De Oliveira et al., 2009 (76)	286 stage I–IV CRC	IHC	Significant association between c-MET overexpression and OS and CRC-related mortality. However no significant association was seen between c-MET and DFS and tumor recurrence
Lee et al., 2008 (77)	135 stage I–IV CRC	IHC	High expression of MET and RON significantly associated with poor survival and risk of tumor recurrence
Kammula et al., 2007 (19)	60 stage I–IV CRC	Quantitative real-time PCR	Significant association between lower expression of c-MET and/or HGF and fewer metastasis and better OS
Umeki et al., 1999 (78)	43 stage I–IV CRC	Southern blot, RT-PCR	No significant association between c-MET gene amplification and disease stage and OS

CRC: colorectal cancer, c-MET: mesenchymal–epithelial transition factor, OS: overall survival, PFS: progression-free survival, DFS: disease-free survival, RFS: relapse-free survival, IHC: immunohistochemistry, PCR: polymerase chain reaction, qPCR-LDR: quantitative polymerase chain reaction/ligase detection reaction, RT-PCR: reverse transcription-polymerase chain reaction, RON: recepteur d'origine nantais, HGF: hepatocyte growth factor, VEGF: vascular endothelial growth factor, VEGFR-3: vascular endothelial growth factor receptor-3, anti-EGFR: anti-epidermal growth factor receptor.

several patients with colon adenoma or CRC, no significant association was found between c-MET overexpression and tumor grade or disease stage (62). In an earlier study of Liu et al., a significant higher level of expression of c-MET in cancerous tissues was found compared with normal colorectal mucosa (63). Garouniatis et al. aimed to identify new biomarkers for prediction of tumor progression and survival in CRC patients. They assessed the expression of four receptor molecules including c-MET, EGFR, CD44v6, and focal adhesion kinase (FAK) using the IHC method in 183 postoperative patients at different stages of CRC, which were followed for up to 72 months. None of these patients underwent preoperative treatment. The authors reported that the expression of these receptors did not correlate with the tumor size or cell differentiation; however, they were associated with CRC tumor progression and patient survival (64). The results of this study are consistent with the results of Abou-Bakr et al. who evaluated c-MET expression in 238 CRC patients (65). These findings are in part corroborated by Takeuchi et al. who evaluated the expression level of c-MET and vascular endothelial growth factor (VEGF)-C in 36 early-stage CRC patients using quantitative real-time polymerase chain reaction (PCR). They found significantly higher c-MET and VEGF-C expression in colorectal cancerous tissues compared with normal colorectal mucosa. Furthermore, they reported that despite VEGF-C, the increased expression of c-MET was associated with depth of invasion in colorectal wall and also metastasis to regional lymph nodes in the early-stage CRC (66). Similarly, Zeng et al. confirmed that with an increase in the CRC stage, the level of c-MET expression significantly increases. In this study, they revealed that there was significant correlation between cancerous cells' invasion into small vessels and c-MET levels in the early stage of CRC (67). Zeng et al. also reported that poorly differentiated tumors had higher levels of c-MET in comparison with well-differentiated CRC; however, it was not statistically significant. It has been seen that there is a correlation between KRAS gene mutation and resistance to anti-EGFR receptor (79). The responsiveness

to anti-EGFR in advanced CRC was assessed by Kishiki and colleagues (68). Ninety-one patients with metastatic CRC were selected and treated with anti-EGFR monoclonal antibodies. Results of this study showed that in patients with wild-type KRAS, c-MET overexpression had decreased disease control rate and shortened PFS, suggesting that c-MET expression can be used as a predictive marker in CRC patients with metastasis and wild-type KRAS. Van Cutsem et al. reported that the effect of treatment with panitumumab alone or combination of panitumumab with rilotumumab or ganitumab in patients with cytologically or histologically confirmed metastatic CRC and wild-type KRAS was evaluated (69). Panitumumab is an anti-EGFR monoclonal antibody. On the other hand, rilotumumab (also called AMG 102) and ganitumab (also called AMG 479) are inhibitors of c-MET and insulin-like growth factor 1 receptor, respectively. Finally, Van Cutsem et al. reported that a combination of panitumumab plus rilotumumab resulted in higher anticancerous effect in treatment of metastatic CRC patients and also higher PFS and OS.

CONCLUSION AND FUTURE PROSPECTIVE

c-MET signaling pathway has been studied for a long time in different cancer types. This signaling pathway is well known because of its interactions with other signaling pathways that are important in tumorogenesis or even normal cellular functions. Although one can find various drug names in the present study that are used in managing CRC, these drugs are not widely used in clinics. Despite many ongoing clinical trials, there seems to be some important drawbacks for drugs' targeting of c-MET pathway. The c-MET signaling pathway is complex and has many overlaps with other cellular pathways. This complexity has made use of this pathway as a therapeutic target is more difficult. Despite the number of c-MET inhibitors available, it has to be clarified which of these options is preferable in which patient according to their CRC molecular and epigenetic profiles.

CONFLICT OF INTEREST

The authors have no conflict of interest to disclose.

REFERENCES

[1] Jemal, A., Bray, F., Center, M. M., Ferlay, J., Ward, E., et al. (2011) Global cancer statistics. Cancer J. Clin. 61, 69–90.

[2] Coppedè, F., Lopomo, A., Spisni, R., and Migliore, L. (2014) Genetic and epigenetic biomarkers for diagnosis, prognosis and treatment of colorectal cancer. World J. Gastroenter. 20, 943–956.

[3] Center, M. M., Jemal, A., Smith, R. A., and Ward, E. (2009) Worldwide variations in colorectal cancer. Cancer J. Clin. 59, 366–378.

[4] Haggar, F. A., and Boushey, R. P. (2009) Colorectal cancer epidemiology: incidence, mortality, survival, and risk factors. Clin. Colon Rectal Surg. 22, 191–197.

[5] Zhang, Y., Du, Z., and Zhang, M. (2016) Biomarker development in MET-targeted therapy. Oncotarget. 7, 37370.

[6] Grady, W. M., and Markowitz, S. D. (2002) Genetic and epigenetic alterations in colon cancer. Annu. Rev. Genomics Hum. Genet. 3, 101–128.

[7] Moradi-Marjaneh, R., Hassanian, S. M., Fiuji, H., Soleimanpour, S., Ferns, G. A., et al. (2018) Toll like receptor signaling pathway as a potential therapeutic target in colorectal cancer. J. Cell. Physiol. 233, 5613–5622.

[8] Rahmani, F., Avan, A., Hashemy, S. I., and Hassanian, S. M. (2018) Role of Wnt/β-catenin signaling regulatory microRNAs in the pathogenesis of colorectal cancer. J. Cell Physiol. 233, 811–817.

[9] Moradi Marjaneh, R., Hassanian, S. M., Ghobadi, N., Ferns, G. A., Karimi, A., et al. (2018) Targeting the death receptor signaling pathway as a potential therapeutic target in the treatment of colorectal cancer. J. Cell. Physiol. 233, 6538–6549.

[10] Bahrami, A., Hassanian, S. M., ShahidSales, S., Farjami, Z., Hasanzadeh, M., et al. (2018) Targeting RAS signaling pathway as a potential therapeutic target in the treatment of colorectal cancer. J. Cell. Physiol. 233, 2058–2066.

[11] Zhao, M., Mishra, L., and Deng, C.-X. (2018) The role of TGF-β/SMAD4 signaling in cancer. Int. J. Biol. Sci. 14, 111–123.

[12] Safaie Qamsari, E., Safaei Ghaderi, S., Zarei, B., Dorostkar, R., Bagheri, S., et al. (2017) The c-Met receptor: implication for targeted therapies in colorectal cancer. Tumor Biol. 39:1010428317699118, 101042831769911.

[13] Zhang, J., Jiang, X., Jiang, Y., Guo, M., Zhang, S., et al. (2016) Recent advances in the development of dual VEGFR and c-Met small molecule inhibitors as anticancer drugs. Eur. J. Med. Chem. 108, 495–504.

[14] Huntsman, D., Resau, J. H., Klineberg, E., and Auersperg, N. (1999) Comparison of c-Met expression in ovarian epithelial tumors and normal epithelia of the female reproductive tract by quantitative laser scan microscopy. Am. J. Pathol. 155, 343–348.

[15] Prat, M., Narsimhan, R. P., Crepaldi, T., Rita Nicotra, M., Natali, P. G., et al. (1991) The receptor encoded by the human C-MET oncogene is expressed in hepatocytes, epithelial cells and solid tumors. Int. J. Cancer. 49, 323–328.

[16] Wolf, H. K., Zarnegar, R., and Michalopoulos, G. K. (1991) Localization of hepatocyte growth factor in human and rat tissues: an immunohistochemical study. Hepatology. 14, 488–494.

[17] Birchmeier, C., Birchmeier, W., Gherardi, E., and Woude, G. F. V. (2003) Met, metastasis, motility and more. Nat. Rev. Mol. Cell Biol. 4, 915–925.

[18] Ghoussoub, R. A., Dillon, D. A., D'Aquila, T., Rimm, E. B., Fearon, E. R., et al. (1998) Expression of c-met is a strong independent prognostic factor in breast carcinoma. Cancer. 82, 1513–1520.

[19] Kammula, U. S., Kuntz, E. J., Francone, T. D., Zeng, Z., Shia, J., et al. (2007) Molecular co-expression of the c-Met oncogene and hepatocyte growth factor in primary colon cancer predicts tumor stage and clinical outcome. Cancer Lett. 248, 219–228.

[20] Li, Y., Chen, C. Q., He, Y. L., Cai, S. R., Yang, D. J., et al. (2012) Abnormal expression of E-cadherin in tumor cells is associated with poor prognosis of gastric carcinoma. J. Surg. Oncol. 106, 304–310.

[21] Miyata, Y., Sagara, Y., Kanda, S., Hayashi, T., and Kanetake, H. (2009) Phosphorylated hepatocyte growth factor receptor/c-Met is associated with tumor growth and prognosis in patients with bladder cancer: correlation with matrix metalloproteinase–2 and–7 and E-cadherin. Human Pathol. 40, 496–504.

[22] Tuynman, J. B., Lagarde, S. M., ten Kate, F. J., Richel, D. J., and van Lanschot, J. J. B. (2008) Met expression is an independent prognostic risk factor in patients with oesophageal adenocarcinoma. Br. J. Cancer. 98, 1102–1108.

[23] Walker, F., Kermorgant, S., Daraï, E., Madelenat, P., Cremieux, A. C., et al. (2003) Hepatocyte growth factor and c-Met in cervical intraepithelial neoplasia: overexpression of proteins associated with oncogenic human papillomavirus and human immunodeficiency virus. Clin. Cancer Res. 9, 273–284.

[24] You, W. K., and McDonald, D. M. (2008) The hepatocyte growth factor/c-Met signaling pathway as a therapeutic target to inhibit angiogenesis. BMB Rep. 41, 833–839.

[25] Organ, S. L., and Tsao, M. S. (2011) An overview of the c-MET signaling pathway. Ther. Adv. Med. Oncol. 3, S7–s19.

[26] Comoglio, P. M., Giordano, S., and Trusolino, L. (2008) Drug development of MET inhibitors: targeting oncogene addiction and expedience. Nat. Rev. Drug Discov. 7, 504–516.

[27] Maulik, G., Shrikhande, A., Kijima, T., Ma, P. C., Morrison, P. T., et al. (2002) Role of the hepatocyte growth factor receptor, c-Met, in oncogenesis and potential for therapeutic inhibition. Cytokine Growth Factor Rev. 13, 41–59.
[28] Nakamura, T., and Mizuno, S. (2010) The discovery of hepatocyte growth factor (HGF) and its significance for cell biology, life sciences and clinical medicine. Proc. Jpn. Acad. Ser B. 86, 588–610.
[29] Tovar, E. A., and Graveel, C. R. (2017) MET in human cancer: germline and somatic mutations. Ann. Transl. Med. 5, 205.
[30] Frampton, G. M., Ali, S. M., Rosenzweig, M., Chmielecki, J., Lu, X., et al. (2015) Activation of MET via diverse exon 14 splicing alterations occurs in multiple tumor types and confers clinical sensitivity to MET inhibitors. Cancer Discov. 5, 850–859.
[31] Fujisaki, T., Tanaka, Y., Fujii, K., Mine, S., Saito, K., et al. (1999) CD44 stimulation induces integrin-mediated adhesion of colon cancer cell lines to endothelial cells by up-regulation of integrins and c-Met and activation of integrins. Cancer Res. 59, 4427–4434.
[32] Parizadeh, S. M., Ghandehari, M., Heydari-Majd, M., Seifi, S., Mardani, R., et al. (2018) Toll-like receptors signaling pathways as a potential therapeutic target in cardiovascular disease. Curr. Pharm. Des. 24, 1887–1898.
[33] Parizadeh, S. M., Ferns, G. A., Ghandehari, M., Hassanian, S. M., Ghayour-Mobarhan, M., et al. (2018) The diagnostic and prognostic value of circulating microRNAs in coronary artery disease: a novel approach to disease diagnosis of stable CAD and acute coronary syndrome. J. Cell. Physiol. 233, 6418–6424.
[34] Ambros, V. (2004) The functions of animal microRNAs. Nature. 431, 350–355.
[35] Noto, J. M., and Peek, R. M., Jr. (2012) The role of microRNAs in helicobacter pylori pathogenesis and gastric carcinogenesis. Front. Cell. Infect. Microbiol. 1, 21.
[36] Reid, J. F., Sokolova, V., Zoni, E., Lampis, A., Pizzamiglio, S., et al. (2012) miRNA profiling in colorectal cancer highlights miR-1 involvement in MET-dependent proliferation. Mol. Cancer Res. 10, 504–515.
[37] Long, Z. H., Bai, Z. G., Song, J. N., Zheng, Z., Li, J., et al. (2017) miR-141 inhibits proliferation and migration of colorectal cancer SW480 cells. Anticancer Res. 37, 4345–4352.
[38] Bleau, A.-M., Redrado, M., Nistal-Villan, E., Villalba, M., Exposito, F., et al. (2018) miR-146a targets c-met and abolishes colorectal cancer liver metastasis. Cancer Lett. 414, 257–267.
[39] Ren, X., He, G., Li, X., Men, H., Yi, L., et al. (2016) MicroRNA-206 functions as a tumor suppressor in colorectal cancer by targeting FMNL2. J. Cancer Res. Clin. Oncol. 142, 581–592.
[40] Takeyama, H., Yamamoto, H., Yamashita, S., Wu, X., Takahashi, H., et al. (2014) Decreased miR-340 expression in bone marrow is associated with liver metastasis of colorectal cancer. Mol. Cancer Ther. 13, 976–985.
[41] Chen, T., Cai, S.-L., Li, J., Qi, Z.-P., Li, X.-Q., et al. (2017) Mecp2-mediated epigenetic silencing of miR-137 contributes to colorectal adenoma-carcinoma sequence and tumor progression via relieving the suppression of c-Met. Sci. Rep. 7, 44543.
[42] Gayyed, M. F., El-Maqsoud, N. M. A., El-Heeny, A. A. E.-H., and Mohammed, M. F. (2015) c-MET expression in colorectal adenomas and primary carcinomas with its corresponding metastases. J. Gastrointest. Oncol. 6, 618.
[43] Chen, H.-J., Jiang, Y.-L., Lin, C.-M., Tsai, S.-C., Peng, S.-F., et al. (2013) Dual inhibition of EGFR and c-Met kinase activation by MJ-56 reduces metastasis of HT29 human colorectal cancer cells. Int. J. Oncol. 43, 141–150.
[44] Tabernero, J., Elez, M. E., Herranz, M., Rico, I., Prudkin, L., et al. (2014) A pharmacodynamic/pharmacokinetic study of ficlatuzumab in patients with advanced solid tumors and liver metastases. Clin. Cancer Res. 20, 2793–2804.
[45] Hu, H. J., Lin, X. L., Liu, M. H., Fan, X. J., and Zou, W. W. (2016) Curcumin mediates reversion of HGF-induced epithelial-mesenchymal transition via inhibition of c-Met expression in DU145 cells. Oncology Lett. 11, 1499–1505.
[46] Bessudo, A., Bendell, J., Gabrail, N., Kopp, M., Mueller, L., et al. (2011) Phase I results of the randomized, placebo controlled, phase I/II study of the novel oral c-MET inhibitor, ARQ 197, irinotecan (CPT-11), and cetuximab (C) in patients (pts) with wild-type (WT) KRAS metastatic colorectal cancer (mCRC) who have received front-line systemic therapy. J. Clin. Oncol. 29(15_suppl, 3582.
[47] Eng, C., Bessudo, A., Hart, L. L., Severtsev, A., Gladkov, O., et al. (2016) A randomized, placebo-controlled, phase 1/2 study of tivantinib (ARQ 197) in combination with irinotecan and cetuximab in patients with metastatic colorectal cancer with wild-type KRAS who have received first-line systemic therapy. Int. J. Cancer 139, 177–186.
[48] Pineda, E., Salud, A., Vila-Navarro, E., Safont, M., Llorente, B., et al. (2017) Dynamic soluble changes in sVEGFR1, HGF, and VEGF promote chemotherapy and bevacizumab resistance: a prospective translational study in the BECOX (GEMCAD 09-01) trial. Tumor Biol. 39, 1010428317705509.
[49] Su, M., Qin, B., Liu, F., Chen, Y., and Zhang, R. (2017) Andrographolide enhanced 5-fluorouracil-induced antitumor effect in colorectal cancer via inhibition of c-MET pathway. Drug Des. Devel. Ther. 11, 3333.
[50] Zhi, J., Li, Z., Lv, J., Feng, B., Yang, D., et al. (2018) Effects of PHA-665752 and vemurafenib combination treatment on in vitro and murine xenograft growth of human colorectal cancer cells with BRAFV600E mutations. Oncol. Lett. 15, 3904–3910.
[51] Lee, J., Kim, S. T., Park, S., Lee, S., Park, S. H., et al. (2018) Phase I trial of anti-MET monoclonal antibody in MET-overexpressed refractory cancer. Clin. Colorectal Cancer. 17, 140–146.
[52] Lev, A., Deihimi, S., Shagisultanova, E., Xiu, J., Lulla, A. R., et al. (2017) Preclinical rationale for combination of crizotinib with mitomycin C for the treatment of advanced colorectal cancer. Cancer Biol. Ther. 18, 694–704.
[53] Wen, J., Matsumoto, K., Taniura, N., Tomioka, D., and Nakamura, T. (2004) Hepatic gene expression of NK4, an HGF-antagonist/angiogenesis inhibitor, suppresses liver metastasis and invasive growth of colon cancer in mice. Cancer Gene Ther. 11, 419–430.
[54] Bendell, J. C., Ervin, T. J., Gallinson, D., Singh, J., Wallace, J. A., et al. (2013) Treatment rationale and study design for a randomized, double-blind, placebo-controlled phase II study evaluating onartuzumab (MetMAb) in combination with bevacizumab plus mFOLFOX-6 in patients with previously untreated metastatic colorectal cancer. Clin. Colorectal Cancer. 12, 218–222.
[55] Giordano, S. (2009) Rilotumumab, a mAb against human hepatocyte growth factor for the treatment of cancer. Curr. Opin. Mol. Ther. 11, 448–455.
[56] Sun, Y., Sun, L., An, Y., and Shen, X. (2015) Cabozantinib, a novel c-met inhibitor, inhibits colorectal cancer development in a xenograft model. Med. Sci. Monit: Int. Med. J. Exp. Clin. Res 21, 2316–2321.
[57] Lee, S. J., Lee, J., Park, S. H., Park, J. O., Lim, H. Y., et al. (2018) c-MET overexpression in colorectal cancer: a poor prognostic factor for survival. Clin. Colorectal Cancer. 17, 165–169.
[58] Kim, H. J., Baek, M.-J., Kang, D. H., Lee, S.-C., Bae, S. B., et al. (2018) Association between c-Met and lymphangiogenic factors in patients with colorectal cancer. Ann. Coloproctol. 34, 88.
[59] Lorenzon, L., Ricca, L., Pilozzi, E., Lemoine, A., Riggio, V., et al. (2017) Tumor regression grades, K-RAS mutational profile and c-MET in colorectal liver metastases. Pathol. Res. Pract. 213, 1002–1009.
[60] Resnick, M. B., Routhier, J., Konkin, T., Sabo, E., and Pricolo, V. E. (2004) Epidermal growth factor receptor, c-MET, β-catenin, and p53 expression as prognostic indicators in stage II colon cancer: a tissue microarray study. Clin. Cancer Res. 10, 3069–3075.
[61] Ginty, F., Adak, S., Can, A., Gerdes, M., Larsen, M., et al. (2008) The relative distribution of membranous and cytoplasmic met is a prognostic indicator in stage I and II colon cancer. Clin. Cancer Res. 14, 3814–3822.
[62] Di Renzo, M. F., Olivero, M., Giacomini, A., Porte, H., Chastre, E., et al. (1995) Overexpression and amplification of the met/HGF receptor gene during the progression of colorectal cancer. Clin. Cancer Res. 1, 147–154.
[63] Liu, C., Park, M., and Tsao, M. (1992) Overexpression of c-met proto-oncogene but not epidermal growth factor receptor or c-erbB-2 in primary human colorectal carcinomas. Oncogene. 7, 181–185.
[64] Garouniatis, A., Zizi-Sermpetzoglou, A., Rizos, S., Kostakis, A., Nikiteas, N., et al. (2013) FAK, CD44v6, c-Met and EGFR in colorectal cancer parameters: tumour progression, metastasis, patient survival and receptor crosstalk. Int. J colorectal Dis. 28, 9–18.
[65] Abou-Bakr, A., and Elbasmi, A. (2013) c-MET overexpression as a prognostic biomarker in colorectal adenocarcinoma. Gulf J. Oncol. 1, 28–34.

[66] Takeuchi, H., Bilchik, A., Saha, S., Turner, R., Wiese, D., et al. (2003) c-MET expression level in primary colon cancer: a predictor of tumor invasion and lymph node metastases. Clin. Cancer Res. 9, 1480–1488.

[67] Zeng, Z., Weiser, M. R., D'Alessio, M., Grace, A., Shia, J., et al. (2004) Immunoblot analysis of c-Met expression in human colorectal cancer: overexpression is associated with advanced stage cancer. Clin. Exp. Metastasis. 21, 409–417.

[68] Kishiki, T., Ohnishi, H., Masaki, T., Ohtsuka, K., Ohkura, Y., et al. (2014) Overexpression of MET is a new predictive marker for anti-EGFR therapy in metastatic colorectal cancer with wild-type KRAS. Cancer Chemother. Pharmacol. 73, 749–757.

[69] Van Cutsem, E., Eng, C., Nowara, E., Świeboda-Sadlej, A., Tebbutt, N. C., et al. (2014) Randomized phase Ib/II trial of rilotumumab or ganitumab with panitumumab versus panitumumab alone in patients with wild-type KRAS metastatic colorectal cancer. Clin. Cancer Res. 20, 4240–4250.

[70] Inno, A., Di Salvatore, M., Cenci, T., Martini, M., Orlandi, A., et al. (2011) Is there a role for IGF1R and c-MET pathways in resistance to cetuximab in metastatic colorectal cancer? Clin. Colorectal Cancer. 10, 325–332.

[71] Shoji, H., Yamada, Y., Taniguchi, H., Nagashima, K., Okita, N., et al. (2014) Clinical impact of c-MET expression and genetic mutational status in colorectal cancer patients after liver resection. Cancer Sci. 105, 1002–1007.

[72] Zeng, Z.-S., Weiser, M. R., Kuntz, E., Chen, C.-T., Khan, S. A., et al. (2008) c-Met gene amplification is associated with advanced stage colorectal cancer and liver metastases. Cancer Lett. 265, 258–269.

[73] Gao, H., Guan, M., Sun, Z., and Bai, C. (2015) High c-Met expression is a negative prognostic marker for colorectal cancer: a meta-analysis. Tumor Biol. 36, 515–520.

[74] Voutsina, A., Tzardi, M., Kalikaki, A., Zafeiriou, Z., Papadimitraki, E., et al. (2013) Combined analysis of KRAS and PIK3CA mutations, MET and PTEN expression in primary tumors and corresponding metastases in colorectal cancer. Mod. Pathol. 26, 302.

[75] Liu, Y., Yu, X.-F., Zou, J., and Luo, Z.-H. (2015) Prognostic value of c-Met in colorectal cancer: a meta-analysis. World J. Gastroenterol. 21, 3706.

[76] DE OLIVEIRA, A. T. T., Matos, D., Logullo, A. F., DA SILVA, S. R. M., Neto, R. A., et al. (2009) MET Is highly expressed in advanced stages of colorectal cancer and indicates worse prognosis and mortality. Anticancer Res. 29, 4807–4811.

[77] Lee, C.-T., Chow, N.-H., Su, P.-F., Lin, S.-C., Lin, P.-C., et al. (2008) The prognostic significance of RON and MET receptor coexpression in patients with colorectal cancer. Dis. Colon Rectum. 51, 1268–1274.

[78] Umeki, K., Shiota, G., and Kawasaki, H. (1999) Clinical significance of c-met oncogene alterations in human colorectal cancer. Oncology. 56, 314–321.

[79] Benvenuti, S., Sartore-Bianchi, A., Di Nicolantonio, F., Zanon, C., Moroni, M., et al. (2007) Oncogenic activation of the RAS/RAF signaling pathway impairs the response of metastatic colorectal cancers to anti–epidermal growth factor receptor antibody therapies. Cancer Res. 67, 2643–2648.