Association between the HGF/c-MET signaling pathway and tumorigenesis, progression and prognosis of hepatocellular carcinoma (Review)

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Abstract. Hepatocellular carcinoma (HCC) is one of the most aggressive and lethal malignancies with a rising incidence, and is characterized by rapid progression, frequent metastasis, late diagnosis, high postoperative recurrence and poor prognosis. Therefore, novel treatment strategies for HCC, particularly advanced HCC, are urgently required. The hepatocyte growth factor (HGF)/c-mesenchymal-epithelial transition receptor (c-MET) axis is a key signaling pathway in HCC and is strongly associated with its highly malignant features. Available treatments based on HGF/c-MET inhibition may prolong the lifespan of patients with HCC; however, they do not achieve the desired therapeutic effects. The aim of the present article was to review the basic knowledge regarding the role of the HGF/c-MET signaling pathway in HCC, and examine the association between the HGF/c-MET signaling pathway and the tumorigenesis, progression and prognosis of HCC.

Contents

1. Introduction

The liver is a critical organ involved in numerous physiological processes, including immune system support, blood volume regulation, endocrine control of growth signaling pathways and macronutrient metabolism. Due to the liver's unique metabolism and relationship with the gastrointestinal tract, hepatocytes are exposed to several toxins, which may result in several anomalies, such as primary liver cancer (1). Primary liver cancer comprises hepatocellular carcinoma (HCC; 75-85%) and intrahepatic cholangiocarcinoma (10-15%), as well as other rare types (2). HCC, the most common hepatobiliary malignancy, ranks as the sixth most common type and the fourth most common primary cause of cancer-associated mortality worldwide (2). HCC is associated with strong propensity for invasion and metastasis, poor prognosis and a persistently high mortality due to early metastasis and late diagnosis (3). The most relevant risk factors of HCC include chronic infection with hepatitis B or hepatitis C virus, aflatoxin exposure, excessive alcohol intake, metabolic syndrome, obesity, smoking and type 2 diabetes (4).

The Barcelona Clinic Liver Cancer staging system, established in 1999, is the primary means of evaluating prognosis and selecting the appropriate treatment for HCC (5,6). The survival rate of patients with HCC is determined by the stage of diagnosis and treatment. In general, surgical resection, local ablation and liver transplantation are the preferred methods for early-stage HCC, while patients with intermediate-stage HCC may benefit from chemoembolization. The prognosis of HCC has not considerably improved over the past few years, despite the advances of classical therapies. Patients with advanced HCC or extensive extrahepatic disease usually have a survival of <3 months and, thus, pain and symptom control should be the primary focus for improving their quality of life (7,8). Overall, the 5-year survival rate of patients with HCC remains relatively poor at 20% (9), while that of patients with advanced HCC is <10% (10). The high mortality rate is due to the lack of effective treatments and increased resistance to conventional chemotherapy and radiotherapy (11). Therefore, the development of novel, tolerable and effective therapeutic agents is a pressing issue. The emergence of targeted therapies and the approval of the kinase inhibitor sorafenib have offered some hope for the future. Based on their physiological and pathological significance, growth factors and their receptors have become targets for drug discovery and development. Selective inhibitors against ligand growth factors and their growth factor receptors are currently indispensable in the molecular-targeted therapy of malignant

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tumors. Even if the molecular mechanisms responsible for the onset and progression of HCC remain largely unknown, novel therapeutic targets have recently become the focus of attention. One of these targets is the hepatocyte growth factor (HGF)/c-mesenchymal-epithelial transition receptor (c-MET) signaling pathway, which is known to promote tumor growth and metastasis in a number of human organs.

2. HGF/c-MET signaling pathway

Structure and function of HGF. HGF is a large multidomain heterodimeric protein, which belongs to the peptidase S1 family of serine proteases. HGF was discovered in 1989 and was cloned and expressed shortly after (12). In 1991, the scatter factor and the tumor cytotoxic factor were identified as HGF (13,14). The *HGF* gene is located on chromosome 7q21 and contains 18 exons and 17 introns (15). HGF is secreted in the form of a single-chain precursor HGF and processed into a double-chain mature HGF by extracellular proteases. The active state of HGF consists of an α chain (69 kDa) and a β chain (34 kDa), which are connected by a disulfide bridge. The α chain contains an N-terminal hairpin domain (N) and four Kringle domains (K1-K4). The first two Kringle domains and hairpin domain are crucial for HGF to perform its biological function. The β chain contains a serine protease homology domain, which is the binding site of c-MET (16). Serine proteases, such as matriptase and HGF-activator, are involved in the processing of HGF (17).

HGF is a multifunctional cytokine and acts on a great variety of epithelial cells as a mitogen (stimulation of cell proliferation), a motogen (stimulation of cell motility) and a morphogen (induction of multicellular tissue-like structure) (18). Due to these functions, previous studies have demonstrated that HGF serves a crucial biological and pathophysiological role in tissue regeneration, tumorigenesis, tumor invasion and epithelial wound healing (19,20).

Structure and function of c-MET. c-MET was initially identified as the fusion gene (tpr-met), which is the receptor of HGF encoded by c-MET proto-oncogene, in a chemically transformed human osteosarcoma cell line (21). It was identified as the transmembrane receptor tyrosine kinase (RTK) in 1991 (22,23). The gene encoding c-MET is located on human chromosome 7q21-31 and contains 21 exons and 20 introns. The encoded protein is ~120 kDa in size (24). c-MET is generated as a single-chain precursor and converted by post-translational modification. Mature c-MET is a disulfide-linked heterodimer consisting of a 50-kDa highly glycosylated extracellular α-chain and a 140-kDa transmembrane-spanning β-chain (25). The transmembrane chain includes a Sema homology region (SEMA domain), a PSI domain (plexin-semaphorin-integrin; PSI), four immunoglobulin-like regions in plexins and transcription factors (IPT domains), a transmembrane domain, a juxtamembrane domain, a tyrosine kinase domain and a c-terminal docking site (carboxyl terminal; CT). Among them, SEMA is the site where HGF binds directly to c-MET, and PSI can stabilize this interaction (26-29). c-MET activation is pleiotropic, since its cytoplasmic domain can interact with various proteins involved in multiple cellular signaling pathways. Upon binding to HGF, c-MET becomes active and drives a complex biological program, contributing to the promotion of several biological activities, including cell proliferation, cell invasion and protection from apoptosis. By controlling the epithelial-mesenchymal transition (EMT) of myogenic progenitor cells, c-MET promotes the development of placental tissue, liver and neuronal precursors, as well as the migration and development of muscle tissue (30,31). Inappropriate c-MET activation promotes the onset, proliferation, invasion and metastasis of multiple cancer types, including HCC (32-34).

HGF/c-MET axis (Fig. 1). The binding of HGF and c-MET triggers dimerization of two subunits, resulting in autophosphorylation on the tyrosine residues Y1234 and Y1235 at the tyrosine kinase domain. Subsequently, it activates autophosphorylation of Y1349 and Y1356 residues near the COOH terminus, which has been identified to be able to recruit intracellular adapters via Src and to activate downstream signaling events (35). Numerous adaptor proteins, such as Shc, Src, the adaptor protein growth factor receptor-bound protein 2 (Grb2) and the p85 regulatory subunit of the effector molecules, such as phosphoinositol 3-kinase (PI3K), bind directly or indirectly to c-MET (36,37). Most of them consist of a Src homologous 2 domain interacting with c-MET and a Src homologous 3 domain binding to downstream signaling molecules (38). This recruitment triggers activation of certain important intracellular signaling pathways, such as the Src, signal transducer and activator of transcription 3 (STAT3), Ras-MAPK, PI3K-AKT and phospholipase C (PLCγ) signaling pathways (39,40). Through these intermediary pathways, HGF-induced c-MET activation induces a variety of cellular responses, including proliferation, survival, motility, invasion, angiogenesis, EMT and branching morphogenesis (41,42).

However, inappropriate amplification of the c-MET gene and activation of the HGF/c-MET axis, as well as eventually elevated protein expression and constitutive kinase activation, may contribute to proliferation, survival, invasion, migration, drug resistance and angiogenesis in a variety of tumors, and are associated with poor clinical outcomes (43,44). It has been reported that HGF and c-MET expression can be upregulated by interleukin (IL)-1, IL-6, basic fibroblast growth factor (bFGF), oncostatin M (OSM), tumor necrosis factor (TNF)-α and several other cytokines (45). The HGF/c-MET axis triggers a series of signaling cascades and is associated with higher proliferation, cell dissociation, poor prognosis, prevention of apoptosis and loss of intercellular junctions. During the past three decades, its abnormal activity has been documented as a common characteristic in a wide range of human malignancies, including colorectal cancer (46), breast cancer (47), bladder cancer (48), gastric cancer (49) and cervical cancer (50), as well as HCC.

3. Role of HGF/c-MET in HCC

Over the past few years, the availability of data regarding signaling pathways regulating the growth and progression of HCC has improved, and several studies have proposed that HGF/c-MET signaling is one of the most promising molecular signaling pathways with which to guide the treatment of HCC (51,52). Under physiological conditions, the HGF/c-MET signaling pathway mediates multiple cellular responses, such

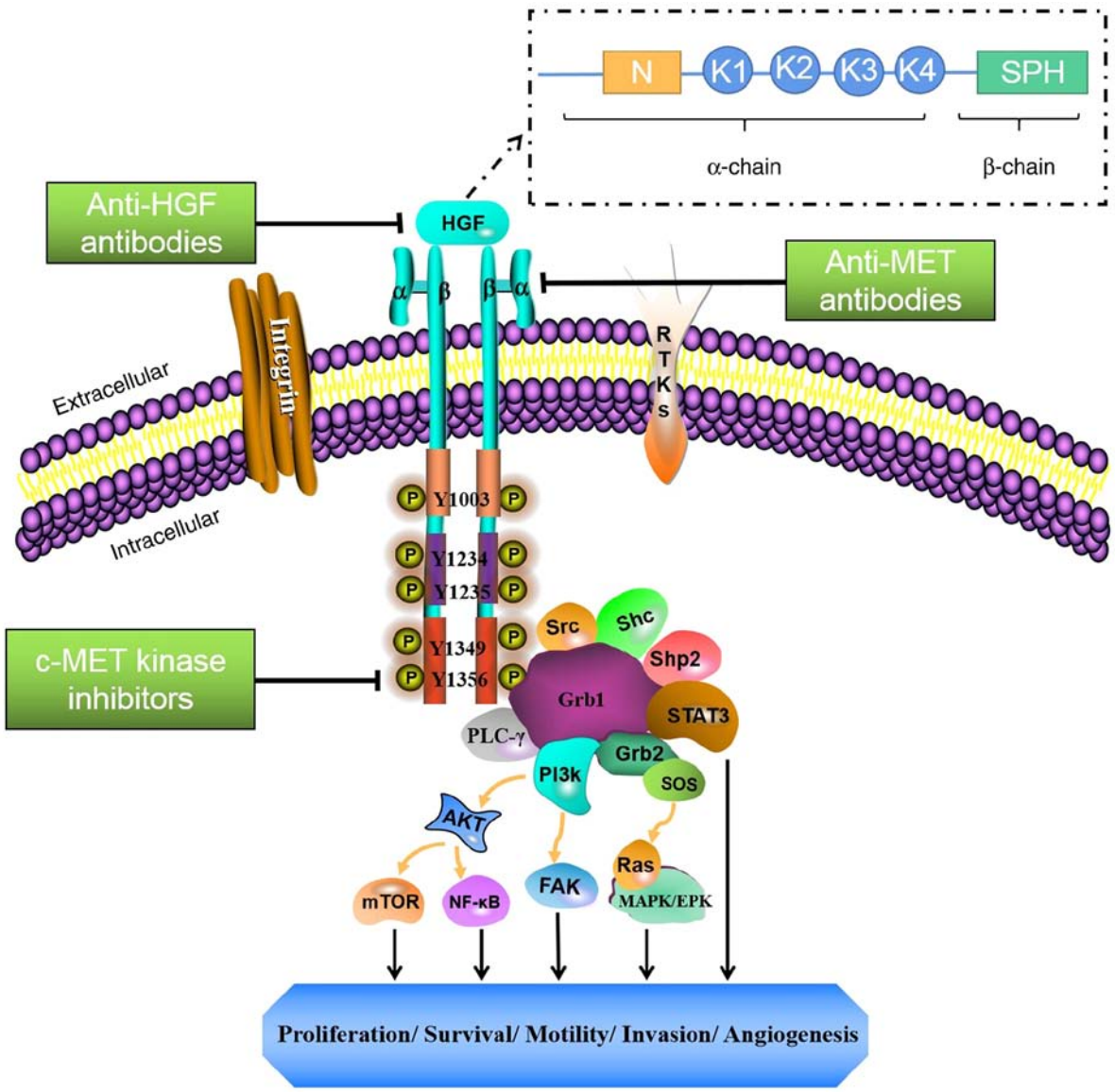

Figure 1. The HGF/c-MET axis signaling network and targeted therapy strategies. PI3K, phosphoinositol 3-kinase; RAS, renin-angiotensin system; Akt, protein kinase B; mTOR, mammalian target of rapamycin; MAPK/ERK, mitogen-activated protein kinases/extracellular signal-regulated kinase; FAK, focal adhesion kinase; STAT, signal transducer and activator of transcription factor; GRB2, growth factor receptor-bound protein 2; SOS, Son of Sevenless; PLCγ, phospholipase C.

as tissue regeneration and cell migration. HGF-induced c-MET activation is strictly regulated; however, aberrant activation of the signaling pathway leads to increased cell motility and cell cycle progression, as well as numerous other protumorigenic signaling events, which has been demonstrated to be involved in multiple malignant neoplasms, including HCC (35).

HGF/c-MET expression in HCC. c-MET amplification, c-MET point mutations, exon 14 skipping mutations and excessive autocrine/paracrine HGF secretion may be the molecular mechanisms that cause aberration in the HGF/c-MET signaling pathway. Upregulation of c-MET expression at the transcriptional level can be caused by activation of hypoxia-inducible factor (HIF) and transcription factors, and downregulation of inhibitor microRNAs. Due to the mutation of deoxyadenosine tract element in the HGF gene promoter, HGF expression can be upregulated by transcriptional upregulation (53).

c-MET amplification is almost undetectable in patients with HCC and may lead to upregulation of protein expression and structural activation of c-MET receptor kinase (54-56). The incidence of upregulation of c-MET expression has been observed in multiple studies. In one study, high expression levels of c-MET were observed in 25.4% of 59 patients with HCC (54). Another study revealed upregulation of c-MET expression in 80.6% of 93 patients with HCC (57). Furthermore, 282 c-MET^{+} patients (54.2%) were identified among a total of 520 patients with HCC, and upregulation of c-MET was associated with a shorter 7-year overall survival (OS) time (58). Compared with those in adjacent normal hepatic tissues, c-MET transcription levels in HCC tissues are increased by 30-100%, and protein levels are increased by 25-100% (59). Ang *et al* (60) evaluated the expression levels of c-MET and HGF in 49 patients with early HCC, and analyzed the results in terms of their association with the characteristics

of disease and survival, revealing that the expression levels of c-MET and HGF are upregulated in well-characterized early disease; however, these are not associated with survival.

Association of HGF/c-MET with invasion and metastasis of HCC. Modern medical studies have demonstrated that the tumor microenvironment (TME) provides conditions for tumor metastasis, and EMT induced by different components in the TME is a key factor for distant metastasis of HCC (61). HGF can cause metastatic changes, including EMT, enhancement of motility and invasiveness of various tumor cells, and thus can be referred to as a 'metastatic growth factor'. Among the metastatic factors, HGF serves a significant role in HCC progression (62). A number of studies have reported that the high expression levels of c-MET in HCC can improve the motility of cells, and generate a variety of signaling molecules via downstream signaling pathways, such as vascular epidermal growth factor (VEGF) and Rac signaling molecules, thereby promoting tumor neovascularization and tumor cell metastasis (63).

One study has demonstrated that HGF-induced c-MET activation can induce the invasion and migration of HCC cells (64). RNA interference (small interfering RNA) silencing of c-MET expression in the MHCC97-H HCC cell line decreased the proliferation, motility and invasion of MHCC97-H cells, indicating that the upregulation of c-MET protein expression serves a crucial role in the invasion of HCC cells (65). Zhang *et al* (66) aimed to explore how HGF/c-MET regulates EMT and the metastasis of HCC cells at the epigenetic level, and revealed that HGF/c-MET signaling can induce HCC cells to express high levels of sumo-specific protease1 (Senp1). Senp1 silencing can reduce HGF-mediated proliferation and migration of HCC cells, and Senp1 inhibition can also induce apoptosis and growth arrest. Liu *et al* (51) used HGF to treat Hep3B HCC cells with p53 deficiency, and revealed that it could promote the invasion and metastasis of Hep3B cells, as well as the occurrence of EMT. Additionally, they revealed that p53 defects could enhance the HGF/c-MET signaling pathway, thus upregulating the transcription factor Snail to promote the invasion of HCC.

HGF/c-MET levels as a diagnostic, prognostic and predictive biomarker. The poor survival rate and the increasing incidence of HCC emphasize the importance of detecting novel screening biomarkers in the early treatable stage to move towards personalized medicine (67). Different tissue-based and circulation-based aberrations of HGF/c-MET may be considered as tumor diagnostic, prognostic and predictive biomarkers in HCC.

Circulating HGF level as a diagnostic biomarker. HCC develops along different clinical backgrounds, including alcoholism, cirrhosis and chronic hepatitis. All these factors result in continuous inflammation and regeneration of hepatocytes, which is challenging for the early diagnosis of HCC. The diagnostic value of serum HGF in HCC has been demonstrated (68). A study revealed that the serum HGF levels of patients with HCC were higher than those of patients without HCC, suggesting that the evaluation of HGF levels is of clinical significance in the diagnosis of HCC (69). Karabulut *et al* (70) investigated the relationship between serum HGF levels and tumor progression in patients with HCC and revealed that the baseline levels of serum HGF were higher in patients with HCC than in controls, demonstrating the diagnostic value of serum HGF. However, Unic *et al* (71) demonstrated that the evidence for the diagnostic value of HGF was inadequate. It is clear that these issues must be addressed in larger randomized clinical trials.

HGF or c-MET aberrant activation as a prognostic biomarker. Several studies have demonstrated the prognostic value of circulating HGF levels, and most studies revealed a negative association between HGF levels and survival in patients with different types of cancer (72). Pretreatment plasma HGF has been reported to be a useful biomarker for predicting the susceptibility to radiation-induced liver dysfunction and survival after radiotherapy and liver transplantation (73). Rimassa *et al* (74) reported that patients with higher baseline HGF had a distinctly shorter survival, indicating that the circulating HGF level may be a prognostic biomarker in secondary HCC. However, no prognostic value was identified in another study on patients with HCC (70).

Multiple studies have demonstrated the prognostic value of c-MET levels on tumor grade, tumor recurrence, intrahepatic metastases and overall survival, as well as portal vein invasion or thrombosis (75-78). It has been demonstrated that upregulation of c-MET expression is an adverse prognostic marker for recurrence and survival in HCC. In a meta-analysis, patients with HCC with high c-MET expression had worse relapse-free survival and OS compared with patients with HCC with low c-MET expression (79). Zhuang *et al* (80) revealed that the expression levels of c-MET protein in HCC tissues are higher than those in adjacent normal tissues, further supporting the prognostic value of c-MET protein expression in patients with HCC. In a retrospective study of 194 patients with HCC treated by hepatic resection or microwave ablation, upregulation of c-MET expression was revealed to be associated with poor survival outcomes (81).

c-MET aberrant activation as a predictive biomarker. The c-MET status of patients may serve as a potential biomarker for predicting the response to HGF/c-MET-targeted inhibitors. Several clinical studies have addressed the predictive role of c-MET dysregulation as an actionable target in HCC. A review discussed the importance of accurate HGF/c-MET signaling detection as a predictive biomarker for the selection of c-MET-targeted therapies and considered the c-MET status of patients as a predictor of the clinical response to HGF/c-MET inhibitors (82). Xiang *et al* (83) proposed that the activation of c-MET in HCC might predict the efficacy of cabozantinib therapy. Chu *et al* (57) explored the clinical and prognostic significance of c-MET expression in patients with HCC, suggesting that high c-MET expression may be a promising efficacy-predicting biomarker for the prediction of the response to sorafenib treatment, thus achieving individualized therapy for patients with HCC.

4. HCC therapy via targeting of the HGF/c-MET signaling pathway

Despite extensive efforts and recent advances made in the diagnosis and treatment of HCC, the prognosis of patients

Table I. c-MET kinase inhibitors in hepatocellular carcinoma.

Agent	Targets	Phase	Mechanism	(Refs.)
Foretinib	c-MET, AXL, RON, VEGFR-2, TIE-2	I/II	ATP competitive	(96)
Gefitinib	c-MET, EGFR, HGF	II	ATP competitive	(104)
Cabozantinib	c-MET,VEGFR2, RET,	III	ATP competitive	(105)
BMS-777607	c-MET, RON	I/II	ATP competitive	(106)
Golvantinib	c-MET,VEGFR-2	I/II	ATP competitive	(107)
Crizotinib	c-MET, ALK, ROS1	II	ATP competitive	(108)
MK2461	c-MET, RON, TIE-2,	I/II	ATP competitive	(109)
AMG337	c-MET	I	ATP competitive	(110)
Tepotinib	c-MET	Ib/II	ATP competitive	(111)
Capmatinib	c-MET	II	ATP competitive	(112)
Tivantinib	c-MET	III	Non-ATP competitive	(113)

c-MET, c-mesenchymal-epithelial transition receptor; HGF, hepatocyte growth factor; RON, recepteur d'origine nantais; VEGFR2, vascular endothelial growth factor receptor 2; AXL, anexelekto; EGFR, epidermal growth factor receptor; TIE-2, tyrosine kinase receptor 2; RET, rearranged during transfection; ALK, anaplastic lymphoma kinase; ROS1, c-ros oncogene 1.

with HCC is still relatively poor, and definitive treatments remain to be improved, particularly for patients with advanced HCC (84). RTK c-MET expression is frequently upregulated in tumor tissues, and the activation of c-MET signaling is associated with drug resistance and the processes of carcinogenesis, invasion and metastasis. Furthermore, inhibiting HGF/c-MET signaling appears to be safe, considering that neutralization of HGF or c-MET has no noticeable adverse effects (25). Therefore, c-MET and HGF are considered to be primary targets for the development of anticancer drugs. Therapeutic strategies for the prevention of HCC tumor progression via targeting of the HGF/c-MET signaling pathway have been intensively investigated. Due to its indisputable role in HCC, the HGF/c-MET axis has been considered as a promising therapeutic target for the development of novel anticancer treatments (85). The binding of HGF to the RTK c-MET is involved in the malignant process of HCC and disrupting this interaction may represent a promising therapeutic strategy. On the premise of understanding the HGF/c-MET signaling pathway, several strategies have been designed to interfere with this signaling pathway: i) c-MET kinase inhibitors (inhibiting c-MET kinase activity); ii) c-MET adaptor inhibitors (inhibiting c-MET and adaptor interaction); and iii) antibody-based inhibitors (blocking ligand and receptor interaction) (86). Numerous preclinical and clinical studies have been devoted to developing anticancer drugs targeting the HGF/c-MET signaling pathway (87,88).

c-MET kinase inhibitors. RTKs are key regulators in normal growth, development and regeneration of mammals. Dysregulation of RTKs is attributed to gene mutation, gene amplification, chromosome rearrangement, transcriptional upregulation, etc., which have been identified as causative factors in the development of human malignancies (89). Most small molecule-kinase inhibitors can block the phosphorylation of the catalytic domain within the receptor by competitively antagonizing the occupation of the intracellular ATP binding sites, thus impeding the recruitment of signal transducers and mediators, and consequently preventing the transmission of downstream signals. To date, numerous small-molecule kinase inhibitors targeting c-MET have entered clinical trials, with hundreds of trials completed or ongoing, either as a single drug or in conjunction with other cancer drugs (90), which represents a potential promising target for the treatment of patients with HCC with an active HGF/c-MET signaling pathway (91).

Sorafenib is a multi-kinase inhibitor of VEGF, and is the first approved systemic therapy for unresectable and advanced HCC and the first-line clinical treatment choice (92,93). However, the survival benefits of sorafenib are limited and development of novel effective therapies is urgently required (10). The overall results are far from satisfactory, with the overall survival improved by <1 year (94). Furthermore, acquired drug resistance and side effects of sorafenib have also raised concerns (95). Targeted molecular therapies other than sorafenib are still being pursued and may be the second-line drugs for patients who fail or cannot tolerate sorafenib. The candidates are listed in Table I. Foretinib, a multikinase inhibitor with potent activity against c-MET, recepteur d'origine nantais (RON), AXL receptor tyrosine kinase (AXL), tyrosine-protein kinase receptor Tie-2 and vascular endothelial growth factor receptor 2 (VEGFR2), is currently in a phase I/II trial to estimate its safety and tolerability in patients with advanced HCC (96). Cabozantinib is an oral inhibitor of c-MET, VEGFR and ret proto-oncogene, and a phase II randomized discontinuation trial has been performed on 41 patients with advanced HCC and Child-Pugh cirrhosis (97). Furthermore, a phase III trial is ongoing (98). Tivantinib, a staurosporine derivative, has been reported to exhibit promising activity in a variety of phase I/II clinical trials, particularly in highly selective cancers targeting c-MET-driven signaling (99). Unfortunately, it failed to reach the primary endpoint in a phase III clinical trial (85).

Table II. Antibodies targeting the HGF/c-MET axis.

Anti-MET antibody	Phase	Format	(Refs.)
Onartuzumab	II/III	mAb (IgG1)	(118)
Emibetuzumab	II	mAb (IgG1)	(119)
Amivantamab	I	bsAb (DuoBody)	(120)
LY3164530	I	bsAb	(121)
SAIT301	I	mAb	(122)
Telisotuzumab	I	mAb	(123)
ARGX-111	I	mAb	(124)
DN30	Investigational	Fab	(125)
Anti-HGF antibody			
Rilotumumab	II/III	mAb (IgG2)	(126)
Ficlatuzumab	II	mAb (IgG1)	(127)
HuL2G7	I	mAb (IgG1)	(128)
YYB-101	I	mAb	(129)

HGF, hepatocyte growth factor; c-MET, c-mesenchymal-epithelial transition receptor; mAb, monoclonal antibody; bsAb, bi-specific antibody; Fab, antigen-binding fragment.

All these small-molecule c-MET kinase inhibitors have exhibited antitumor activity in nonclinical studies of HCC; however, most of them are still in the clinical trial phase due to other efficacy, tolerance and safety issues (100-102). Firstly, it has been demonstrated that c-MET inhibitors have numerous side effects, such as anemia, liver and bone marrow toxicity, and neutropenia. Furthermore, the efficacy of individual c-MET-based target therapy is limited for patients with HCC, particularly for patients with c-MET-negative HCC. Finally, advanced HCC is often accompanied by fibrosis and cirrhosis, resulting in the reduction of hepatic drug clearance and metabolic enzyme activity (103).

c-MET adaptor inhibitors. Adaptor proteins, such as Grb1, Grb2 and PI3K, are important components of the HGF/c-MET signaling pathway. Multiple tumor effects induced by HGF/c-MET signaling can be inhibited by blocking the binding of one or more adaptor proteins to c-MET or by inhibiting the activation of these adaptor proteins. Grb2 is regarded as a key protein in the HGF/c-MET axis, since it interacts with Y1356 of c-MET to transduce HGF signaling to the cytoplasm and connects to several signaling transducers, such as Ras, Son of Sevenless (SOS) and GRB2 associated binding protein 1 (GAB1) (85). As a small selective antagonist of Grb2, C90 can effectively block the cell motility and matrix invasion of gastric cancer cells *in vitro* and reduce the metastasis of major solid tumors produced by human prostate adenocarcinoma cells *in vivo* (114,115). The efficacy of c-MET adaptor inhibitors in the treatment of HCC still requires further study.

Antibody-based inhibitors. In terms of the progress of humanized antibody drugs, anti-HGF and anti-MET antibodies have entered the clinical trial stage. At least eight anti-MET [onartuzumab (116), emibetuzumab (117), LY3164530, JNJ-61186372, SAIT301, ABT-700, ARGX-111 and DN30] and four anti-HGF [rilotumumab (AMG102), ficlatuzumab (AV-299), HuL2G7 (TAK-701) and YYB-101] antibodies have been examined or are being examined in clinical trials (Table II). The mechanism of these antibodies is blocking the binding of ligand HGF and receptor c-MET to achieve an antitumor therapeutic effect. Compared with small-molecule chemical drugs, antibody drugs have the characteristics of strong targeting specificity, high activity, long half-life and low toxicity. Furthermore, antibody drugs have excellent predictability in pharmacology, thus their safety is better.

Using herbal medicinal antagonists to achieve more effective and safer HGF/c-MET targeting. Using natural herbs instead of synthetic chemicals is another strategy to avoid the issues of HGF/c-MET-targeted therapy. For example, the medicinal peptide LZ8 (also known as Ling-Zhi or Reishi), a well-known traditional Chinese medicine extracted from *Ganoderma lucidum*, has antitumor activity against cervical cancer, breast cancer, lung cancer and HCC (130-132). LZ8 can inhibit the progression of HCC by blocking both the c-MET-dependent and -independent MAPK signaling pathway (133). Resveratrol, one of the major polyphenols found in red wine, inhibits the progression of HCC via downregulation of HGF/c-MET signaling (134). Furthermore, our previous study revealed that the traditional Chinese medicine compound QHF has an anti-angiogenic effect on H22 cells, and it can suppress tumor growth by prohibiting the HGF/c-MET signaling pathway (135). Zhang *et al* (136) reported the synergistic effect of astragaloside IV and curcumin on the inhibition of tumor growth and angiogenesis in HCC mouse models, and revealed that this synergistic effect is associated with HGF.

5. Future directions and conclusions

HCC is a complicated pathology with interconnected regulatory networks. Due to the limited clinical efficacy of current therapeutic drugs and the lack of biomarkers for early diagnosis, HCC is among the cancers with the worst prognosis. In recent years, great achievements have been made in understanding the role of HGF/c-MET signaling in overexpression, invasion, migration and metastasis of HCC. Additionally, the discovery of novel drugs related to the HGF/c-MET signaling pathway provides a promising clinical approach for designing improved specific individualized therapy. Accordingly, targeting the HGF/c-MET signaling pathway has become a research 'hotspot' for efficient targeted therapy and prognosis of patients with HCC. In terms of biomarker development and drug combination, more efforts are required for novel strategies to ensure optimal use of the drugs in the treatment of HCC. Therefore, it is worthwhile to explore the detailed mechanisms of HGF/c-MET signaling and the complex multistep process of HCC, which will help to promote the development of preventive measures, early diagnostic methods and more appropriate targets, in order to develop more effective and safer therapeutic strategies.

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Authors' contributions

WM designed and wrote this review. TC reviewed the literature data and edited the manuscript. Both authors read and approved the manuscript and agree to be accountable for all aspects of the research in ensuring that the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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