Review

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c-Met: A potential therapeutic target for hepatocellular carcinoma

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ABSTRACT: The approval of receptor tyrosine kinase (RTK) targeted agent sorafenib as the first effective drug for the systemic treatment of advanced hepatocellular carcinoma (HCC) represents a milestone in the treatment of this disease. A better understanding of HCC pathogenesis will lead to development of novel targeted treatments. As a typical member of the RTK family, c-Met represents an intriguing target for cancer therapy. The c-Met signaling pathway has been shown to be deregulated and to correlate with poor prognosis in a number of major human cancers. This review discusses the possibility of c-Met as a target in HCC treatment from the following respects: *i*) c-Met expression and activation profile in HCC, *ii*) relationship between c-Met and clinicopathologic state and prognosis of HCC, *iii*) role of c-Met signaling activity in HCC genesis and progression, and *iv*) strategy of c-Met pathway targeting therapy in HCC treatment.

Keywords: Receptor tyrosine kinases, cancer therapy, clinicopathological features, prognosis, hepatocellular carcinoma

1. Introduction

Liver cancer ranked fifth in incidence and third in mortality in global cancer burden in 2008 according to the statistics published by World Health Organization (*1*). Among the diverse, histologically distinct primary hepatic neoplasms, hepatocellular carcinoma (HCC) is the most common type of liver cancer, accounting for 83% of all cases (*2*). Therapeutic approaches including hepatic resection, liver transplantation, and loco-regional therapies play a major role in the clinical management of HCC (*3*). In recent years, introduction of molecular targeted therapies has opened new prospects in treatment of HCC. Systemic treatment with sorafenib, a multikinase inhibitor targeting Raf kinase and receptor tyrosine kinases (RTKs) including platelet-derived growth factor receptor (PDGFR), vascular endothelial growth factor (VEGF) receptor (VEGFR) and c-kit (receptor specific for stem cell factor), is recommended for patients at a more advanced stage of HCC (*4*). In addition, several other RTKs targeted drugs such as evacizumab, erlotinib, gefitinib, lapatinib, cetuximab, sunitinib, and brivanib have entered into clinical trials for treatment of advanced HCC (*5*). These studies illustrate the utility of targeting the protein class RTKs in HCC management.

c-Met is a prototypic member of RTKs. The ligand for c-Met is a growth factor known as hepatocyte growth factor (HGF) (*6*). c-Met signaling pathway is involved in diverse cellular responses such as mitogenesis, motogenesis, or morphogenesis depending on the particular cell type and the microenvironment (*7,8*). In circumstances of tissue removal or damage such as liver regeneration or renal and lung injury, c-Met expression is induced as an important mediator in the wound healing and tissue repair processes (*9-11*). Deregulation and activation of c-Met may result in unregulated cell growth and differentiation, contributing to malignant transformation (*12*). c-Met overexpression or enhanced activation relative to normal tissues is demonstrated in several human cancers including gastric, colorectal, pancreatic, lung, head and neck, ovarian, renal, glioma, melanoma, prostatic and breast carcinoma (*13-15*). This review provides a systematic retrospective about the role of c-Met in HCC pathogenesis and discusses the possibility of molecular targeting of c-Met as a potential therapeutic strategy for HCC.

2. c-Met expression and activation profile in HCC

2.1. *c-Met expression*

c-Met expression in human HCC and non-HCC liver tissues was examined in a number of studies in the past twenty years. c-Met positive rates and expression levels in HCCs are usually higher than those in normal or adjacent non-tumorous liver tissue either at the mRNA or protein level (Tables 1 and 2) (*16-30*). These studies

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Table 1. c-Met positive rates in human HCC and non-HCC liver tissues in various studies

Authors	Level	HCC tissues			Non-HCC tissues		
		Sample tested (*n*)	Positive (*n*)	Positive rate (%)	Sample tested (*n*)	Positive (*n*)	Positive rate (%)
Annen (*16*)	protein	18	12	66.7	18[a]	8	44.4
Xie *et al*. (*17*)	protein	47	18	38.3	25[b]	3	12.0
Wu *et al*. (*18*)	protein	25	21	84.0	25[c]	5	20.0
	mRNA	25	25	100.0	25[c]	6	24.0
Ueki *et al*. (*19*)	protein	62	40	64.5	62[d]	4	6.4
Ljubimova *et al*. (*22*)	protein	6	6	100.0	9[e]	9	100.0
	mRNA	12	10	83.3	30[f]	13	43.3
Chau *et al*. (*20*)	protein	40	35	87.5	40[g]	34	85.0
Kiss *et al*. (*21*)	protein	86	83	96.5	86[h]	86	100.0
D'Errico *et al*. (*26*)	protein	20	20	100.0	10[i]	10	100.0

[a] adjacent non-cancerous tissues; [b] adjacent non-cancerous tissues; [c] adjacent non-cancerous tissues; [d] adjacent non-cancerous tissues; [e] 3 normal, 3 HCV, and 3 alcoholic liver disease (ALD) cirrhotic specimens; [f] 7 normal, 9 HCV cirrhosis, 8 ALD, 4 ALD/HCV, 2 liver adenoma specimens; [g] adjacent non-cancerous tissues; [h] adjacent non-cancerous tissues; [i] 5 focal nodularhyperplasias, 4 fulminant hepatitis, 1 regenerated liver.

Table 2. Expression levels of c-Met in human HCC and non-HCC liver tissues

Authors	Level	c-Met expression	Method of detection
Ueki *et al*. (*19*)	protein	The mean expression level of c-Met was significantly higher in HCC tissues than in non-tumorous tissue.	Western blot
Kiss *et al*. (*21*)	protein	Overexpression in 20% of 86 HCC specimens when compared to the surrounding hepatic tissue.	Immunohistochemistry
Ljubimova *et al*. (*22*)	protein	In normal liver the staining intensity was usually weaker compared with HCC and some areas of cirrhotic livers.	Immunohistochemistry
Osada *et al*. (*23*)	protein	Expression at higher levels in 19 of 30 HCCs compared with non-tumorous tissue.	Western blot
Suzuki *et al*. (*24*)	protein	Detection in 16 of 23 patients (69.6%), overexpression in HCC compared with the surrounding normal liver.	Immunohistochemistry
	mRNA	c-Met mRNA was detected in 6 of 19 HCCs (31.6%); c-Met mRNA was overexpressed in HCC compared with the surrounding normal liver.	Northern blot
Zhang *et al*. (*25*)	protein	9 of the 20 HCCs exhibited c-Met overexpression, with an increase ranging between 2- and 7-fold when compared by densitometry with the surrounding non-tumor liver.	Immunohistochemistry
D'Errico *et al*. (*26*)	protein	The c-Met protooncogene product was expressed in all cases (20 HCCs, 5 focal nodularhyperplasias, 4 fulminant hepatitis, 1 regenerated liver), with marked overexpression in the HCCs.	Immunohistochemistry
Osada *et al*. (*27*)	protein	The mean value of c-Met in tumor tissue, 1.36 ± 0.12*, was clearly higher than in non-tumor tissue, 1.07 ± 0.06*. Data was obtained from specimens of 30 HCC patients.	Western blot
Boix *et al*. (*28*)	mRNA	c-Met overexpressed in 8 of 18 HCCs, with an increase ranging between 2- and 10-fold when compared by densitometry with the surrounding liver.	Northern blot
Noguchi *et al*. (*29*)	mRNA	Overall level of c-Met mRNA was significantly higher in HCC tissues than that in non-HCC surrounding regions (0.41 ± 0.20 *vs*. 0.08 ± 0.02 pg/μg total RNA) in 11 HCC specimens.	Competitive RT-PCR
Okano *et al*. (*30*)	protein	The expression of c-Met protein was higher in patients with HCC and acute hepatitis than in those with chronic hepatitis.	Immunohistochemistry

* The expression level of c-Met was presented as the optical density (OD) ratio of c-Met/β-actin.

suggested that c-Met expression, at least in part, was deregulated in the genesis and progression of HCC.

2.2. *Mechanisms underlying aberrant c-Met expression in HCC*

Mechanisms involved in c-Met aberrant expression are commonly found in the following repects.

Inducible endogenous or exogenous factors c-Met gene expression is inducible by its own ligand HGF (*31*). Besides HGF, other cytokines including epidermal growth factor (EGF), interleukin (IL)-1, IL-6, and tumor necrosis factor-α can induce c-Met expression in HCC cells *in vitro* (*31*). In HepG2 cells, *c-Met* gene promoter activity was up-regulated when treated with HGF, IL-1, and IL-6. The activator protein (AP)-1 was considered to participate in HGF and IL-6-induced *c-Met* gene transcription (*31,32*). In addition to the above endogenous

factors, hepatitis B virus X protein (HBX) which acted as a weak to moderately strong transcriptional transactivator was proven to be an exogenous inducible factor for c-Met expression (*33*). Activation of transcription factors AP-2 and specificity protein (SP)-1 at the promoter region of the *c-Met* gene contributed to transcriptional regulation of c-Met expression by HBX (*33*).

MicroRNAs (miRNAs) miRNAs are small RNA molecules which are approximately 22 nucleotides long and negatively control their target genes expression posttranscriptionally (*34*). miRNAs including miR-34a, miR-23b and miR-199a-3p targeting c-Met are dysregulated in HCC tissues (*35*). Li *et al*. demonstrated that down-regulation of miR-34a expression was highly significant in 19 of 25 (76%) HCC tissues compared with adjacent normal tissues and an inverse correlation between miR-34a and c-Met expression was observed in resected normal/tumor tissues (*36*). miR-23b was found down-regulated in 82% (14/17) HCC tissues compared with adjacent non-HCC tissues as indicated by Salvi *et al*. (*37*). Similarly, a significant down-regulation of miR-199a-3p expression was observed in HCC tissues (*38*). Thus, overexpression of c-Met may be partially ascribed to down-regulaton of miRNAs targeting c-Met in HCC.

Amplified maturation process During the maturation of c-Met, the primary single chain precursor protein ($p170^{met}$) is cleaved to produce the α subunit ($p50^{met}$) and β subunit ($p140^{met}$) which are disulfide linked to form the mature receptor (*6*). This process is probably amplified in carcinogenesis of the liver. Annen *et al*. showed that expression of $p170^{met}$ precursor was significantly higher in non-cancerous regions than in cancerous regions, while the $p140^{met}$ signal was obviously stronger in cancerous regions than in non-cancerous regions. These results imply that the processing pathway from the pro-receptor to the mature receptor is possibly facilitated in HCC (*16*).

2.3. *c-Met activation*

The classical mode of c-Met activation requires the binding of HGF to c-Met. In addition to this HGF-dependent form, an HGF-independent pattern of c-Met activation, especially found in tumor development, has also been reported.

2.3.1. *HGF-dependent activation*

Under physiological conditions, c-Met expression is mainly observed in the epithelial compartment of various tissues, while its ligand HGF is expressed in cells of mesenchymal origin (*39*,*40*). Accordingly, HGF and c-Met constitute a paracrine signaling system which plays a critical role in development and organogenesis (*40*). In normal human liver, HGF was detected in bile duct epithelia and in endothelial cells of both the central-lobular vein and portal tract vessels whereas c-Met was identified in mature hepatocytes (*41-43*). In HCC, a somewhat different scenario exists. In addition to paracrine activation, intracytoplasmic positivity for HGF was also evident in a large number of neoplastic cells in some cases of HCCs, which supported that an autocrine pattern of action of HGF also existed in HCC (*19*,*26*). Thus, c-Met can be activated in both autocrine and paracrine patterns in HCC.

Table 3. c-Met mutations detected in HCC

Exon	Codon	Nucletide	Amino acid
17	1191	ACT → ATT	Thr → Ile
19	1268	ATG → ATA	Met → Ile
19	1262	AAG → AGG	Lys → Arg

2.3.2. *HGF-independent activation*

In addition to the HGF-dependent pattern, c-Met activation can occur through alternative mechanisms in HCCs including: *i*) active mutants of c-Met constitutively phosphorylating the downstream kinases; *ii*) activation by cell attachment; *iii*) transactivation by EGF receptor (EGFR); and *iv*) activation by des-γ-carboxy prothrombin (DCP).

Mutations that either promote receptor dimerization/oligomerization or alter catalytic activity or substrate specificity, would possibly activate RTKs. Constitutive activating mutations of c-Met may play an important role in the development of HCC by conferring cells a selective growth advantage. In HCC, three missense mutations K1262R, M1268I, and T1191I in the tyrosine kinase domain were exclusively detected in childhood HCCs (Table 3) (*44*). Missense mutations K1262R and M1268I in the kinase domain of c-Met are located in a specific region which is believed to act as an intramolecular substrate that, in the absence of ligand, functions to inhibit enzymatic activity by blocking the active site (*44*). It is speculated that these mutations stimulate the kinase activity of c-Met by altering the structure of the intramolecular substrate such that it is constitutively disengaged from the active site (*44*).

A mechanism of activation of c-Met that did not rely on mutation but depended on cell adhesion was demonstrated by Wang *et al*. (*45*). In their study, overexpression of the human wild-type c-Met which could not respond to murine HGF but was enzymatically active in mice hepatocytes allowed activation of the receptor (*46*,*47*). The activation of c-Met in this case was considered to be dependent on cell adherence, but not HGF (*45*). Furthermore, this style of activation might depend on overexpression of c-Met (*45*). These results indicate that cell adherence may be an alternative activation mechanism for tumor development in cancers related to hyperactivation or overexpression of wild-type tyrosine kinase receptors.

Cross-talk can occur between different growth factor receptors, which may induce mitogenic or motogenic

signal amplification. EGFR exists on the cell surface and is activated by binding of its specific ligands including EGF and transforming growth factor α (TGFα) (*48*). It has been shown that cross-talk between c-Met and EGFR occur in HCC. HCC cell lines expressing TGFα in an autocrine manner displayed constitutive phosphorylation of EGFR and c-Met in the absence of HGF (*49*). The association between these two receptors was demonstrated to happen either directly, or *via* adapter molecules, before or during tumorigenesis, and might enable TGFα or EGF to phosphorylate c-Met through EGFR (*49*).

DCP is employed as a tumor marker in the clinic for its high sensitivity and specificity in the screening and diagnosis of HCC (*50-52*). Two kringle domains in the structure of DCP are similar to those of HGF which are considered to be mandatory for HGF to bind to c-Met (*53*). Based on this similarity, DCP binds and induces the phosphorylation of c-Met (*54*). However, the manner of activation of c-Met by DCP is different from that by HGF. Tyrosines-1234 and -1235 in the tyrosine kinase domain and tyrosines-1349 and -1356 in the multifunctional docking site were phosphorylated when c-Met was activated by HGF (*55-57*). However, when binding DCP to c-Met phosphorylation occurred in those tyrosine residues located in the kinase activation loop (Tyr1234/1235) but not in the C-terminal tail (Tyr1349) (*54*).

3. c-Met as an indicator for clinicopathologic state and prognosis of HCC

3.1. *c-Met and clinicopathologic characteristics of HCC*

The relationship between c-Met protein expression in HCC tissues and clinicopathologic characteristics is indicated in Table 4. Generally, tumor proliferative index was high in HCCs with c-Met expression (*24*,*26*). In addition, HCCs with multiple nodular tumors showed higher c-Met expression (*58*). On the other hand, no relevance was observed between c-Met expression and serum alpha fetoprotein (AFP) level, sex, or age (*17*,*19*,*30*,*58*). Conflicting results were reported regarding characteristics such as tumor size, differentiation degree, stage, invasion, and metastasis (*17*,*19*,*24*,*26*,*27*,*30*,*58*). However, characteristics like tumor invasion and metastasis, and differentiation degree were more frequently reported to be correlated with c-Met expression. In those studies, level of c-Met expression was significantly higher in invasive or poorly differentiated HCCs. With respect to tumor size, most studies suggested it was unrelated to c-Met expression. When referring to tumor stage, contradictory results were obtained by Ke *et al*. and Xie *et al*. (*17*,*58*). The former study demonstrated that c-Met expression was obviously higher in advanced HCCs (TNM stage III or IV), whereas the latter one indicated that no difference of c-Met expression existed in early and advanced stages of HCCs. The sample size which is 520 in the former study and 20 in the latter study may influence the consistency of results. Taken together, the expression of c-Met in HCC may be important to evaluate the status of this disease, especially to caution for tumor cells actively proliferating and the presence of intrahepatic metastasis or multiple nodular tumors.

3.2. *c-Met and prognosis of HCC*

Currently much work is underway to determine molecular predictors of the outcome of HCC (*59*). Expression of c-Met in HCC tissue was considered to be one of the independent prognostic factors indicating metastasis and recurrence in patients with HCC (*60*). Patients with high c-Met expression HCC usually had a significantly shorter 5-year survival than patients with low c-Met expression HCC after curative surgical resections (*19*). In addition, the sustained high level of serum HGF after hepatectomy was suggested to be related to early tumor recurrence and metastasis (*18*). Using transcriptome analysis, a group of HCCs (27%) with potentially activated c-Met signaling were classified based on a c-Met induced transcription signature (*61*). These tumors were characterized by higher vascular invasion rate, increased microvessel density, and shortened survival. Moreover, a predictive model was established according to *c-Met* gene signatures, which was able to diversify HCC patients into good and bad prognostic groups with 83-95% accuracy (*61*). These results suggest that expression and

Table 4. The relationship between c-Met protein expression and clinicopathologic characteristics of HCC

Studies	No. of cases	Tumor size	Proliferation activity	Differentiation degree	Tumor stage	Invasion and metastasis	Sex	Age	Serum AFP level
Xie *et al*. (*17*)	47	--	ND	+	--	+	--	--	ND
Ueki *et al*. (*19*)	62	--	ND	--	ND	+	--	--	ND
Suzuki *et al*. (*24*)	23	ND	NS	+	ND	ND	ND	ND	ND
D'Errico *et al*. (*26*)	50	ND	+	+	ND	ND	ND	ND	ND
Osada *et al*. (*27*)	30	ND	ND	ND	ND	+	ND	ND	ND
Okano *et al*. (*30*)	26	--	ND	--	ND	--	ND	ND	--
Ke *et al*. (*58*)	520	+	ND	+	+	+	--	--	--

ND: not determined; NS: not significant; +: positive; --: negative.

activation of c-Met in HCC tissues indicate an adverse prognosis for HCC patients.

4. c-Met signaling in HCC tumorigenesis and progression

Signal transduction is the communication process utilized by regulatory cytokines to mediate essential cell processes (including growth, differentiation, and survival) in response to stimuli. Enhanced signal transduction may lead to increased cell proliferation, sustained angiogenesis, tissue invasion and metastases, and inhibition of apoptosis during tumor development and progression. On the other hand, blocking tumor-dependent signal transduction pathways might slow down tumor progression.

4.1. *c-Met signaling in HCC*

The c-Met protein is first synthesized in the hepatocytes as a single chain precursor ($p170^{met}$), and then processed to a mature glycosylated heterodimer receptor ($p190^{met}$) which consists of an extracellular α subunit ($p50^{met}$) and a transmembrane β subunit ($p140^{met}$) (*6,62*). The β subunit has a protein kinase domain and a docking site for cell-signaling molecules (*55,63*). c-Met signal transduction involved in HCC is illustrated in Figure 1. When activated by HGF, the intracellular tyrosine kinase domain of c-Met is highly phosphorylated at two tyrosine residues (Tyr-1234 and Tyr-1235) that are essential for the catalytic activity of the enzyme (*64,65*). Phosphorylation also occurrs at two tyrosine residues (Tyr-1349 and Tyr-1356) located in the

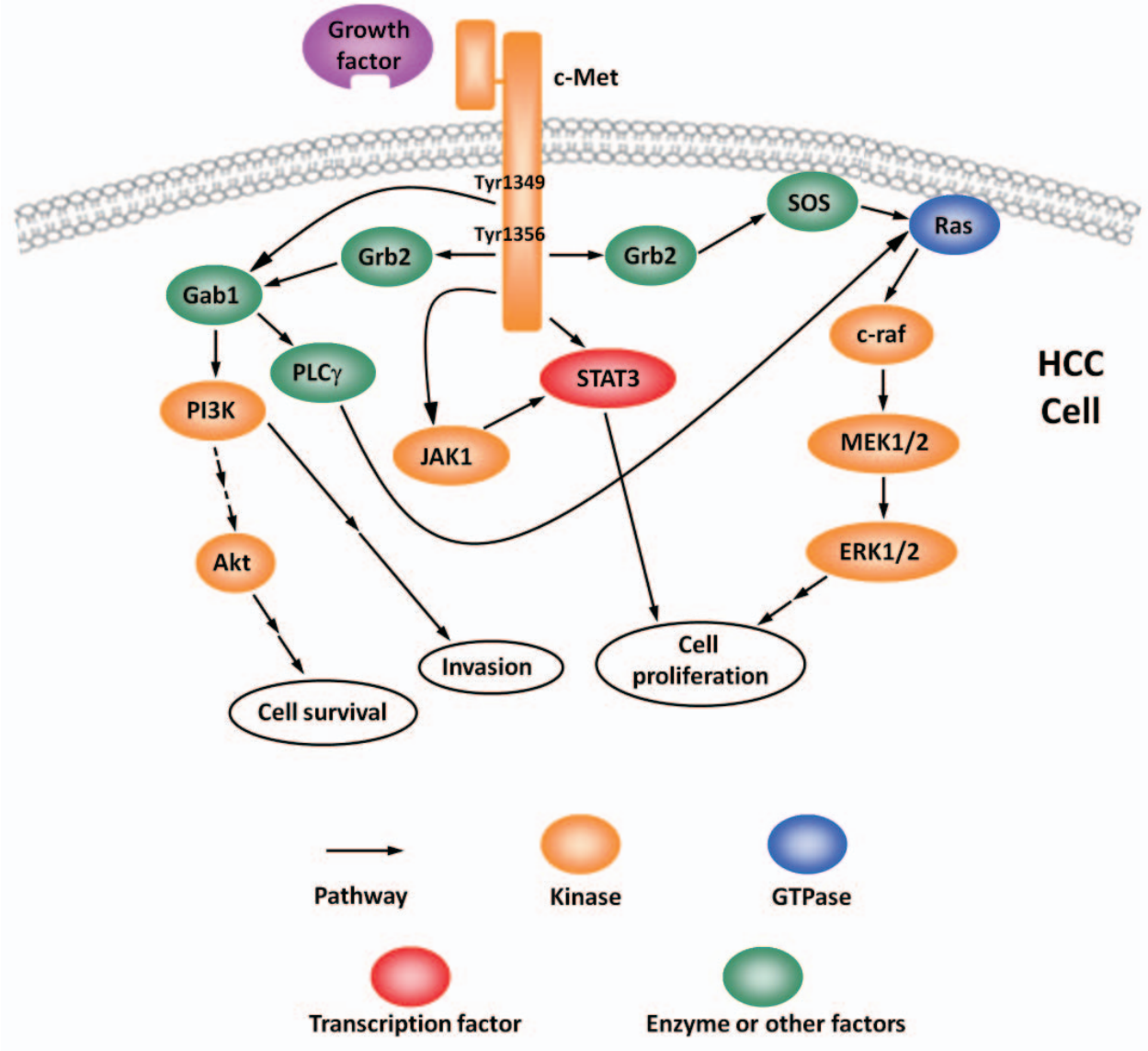

Figure 1. Schematic representation of the c-Met signaling pathway suggested in HCC cells. The activation of c-Met in HGF-dependent and/or HGF-independent ways induces phosphorylation of specific tyrosine residues within the c-Met intracellular domain and, in turn, initiates activation of the downstream signaling cascades.

carboxyl-terminal region of the β-subunit which acts as a multifunctional docking site and binds numerous srchomology 2 (SH2) domain-containing effectors such as the growth factor receptor-bound protein 2 (Grb2) and transcription factor STAT3 (*55,66,67*). Upon phosphorylation, this docking motif can also associate with Grb2-associated binding protein 1 (Gab-1), a multi-adaptor protein that provides binding sites for molecules such as phosphatidylinositol 3 kinase (PI3K) and phospholipase Cγ1 (PLCγ1) (*68*). It was suggested that Gab-1 interacted with the c-Met multifunctional docking site both directly and indirectly (*68*). On one side, Gab1 might interact directly with tyrosine-1349 of c-Met. On the other side, Gab1 indirectly associated with c-Met, in which Grb2 acted as an adapter by binding tyrosine-1356 of c-Met with the SH2 domain and the proline rich sequences of Gab1 with the srchomology 3 (SH3) domain (*68*). Downstream of adaptors the regulation of cell proliferation, invasion and metastasis by c-Met was related with extracellular signal-regulated protein kinase (ERK) and PI3K pathways. In addition, Suzuki *et al*. demonstrated DCP induced the JAK1-STAT3 signaling pathway, while it did not affect the ERK or PI3K pathway (*54*).

4.2. *Role of c-Met signaling in hepatocarcinogenesis*

As the natural ligand of c-Met, HGF is a potent mitogen for hepatocytes and various epithelial cells and activation of the ERK pathway plays an important role in the regulation of cell proliferation by HGF (*69*). That c-Met signaling is involved in hepatocarcinogenesis is evidenced by the fact that c-Met transgenic mice would develop HCC (*45*). In these mice, inactivation of the transgene led to regression of even highly advanced tumors, apparently mediated by apoptosis and cessation of cellular proliferation (*45*). HCC could also be initiated by hydrodynamic transfection of c-Met in combination with constitutively active versions of β-catenin into the livers of adult mice (*70*). Inactivation of c-Met transgene led to regression of hepatocellular carcinomas despite the persistence of activated β-catenin. The tumors eventually recurred in the absence of c-Met expression, however, presumably after the occurrence of one or more events that cooperated with activated β-catenin in lieu of c-Met (*70*). These studies implied that enhanced c-Met signal transduction played a critical role in the malignant transformation of normal hepatocytes.

4.3. *Role of c-Met signaling in HCC invasion and metastasis*

Tumor metastasis is a continuous dynamic process involving releasing of tumor cells, their migrating and crossing the blood vessel barriers, and colonizing at distant sites. The motility of HCC cell lines (Hep3B, HepG2, PLC, and Huh-7) and HCC cells harvested from patients was stimulated by HGF (*71*). Tyrosine phosphorylation of c-Met and activation of PI3K were regarded to play a critical role in these processes (*71*). Neaud *et al*. showed that addition of human liver myofibroblasts (MF) conditioned medium induced cell scattering and increased about 100-fold the ability of HepG2 to invade Matrigel, and that the HGF secreted by MF played a critical role in these processes (*72*). Up-regulating of urokinase type plasminogen activator (uPA) induced by c-Met signaling was thought to contribute to the invasion and metastasis of HCC cells (*73*). Angiogenesis is the physiological process involving the growth of new blood vessels from pre-existing vessels, which is a fundamental step in the transition of tumors from a dormant state to a malignant one. Enhanced angiogenesis was observed in HCCs developed in HGF transgenic mice in which expression of VEGF was up-regulated in parallel with HGF transgene expression (*74*). Moreover, HGF as well as inducible nitric oxide synthase are involved in multidrug resistance (MDR) induced angiogenesis in HCC cell lines (*75*). Thus, HGF/c-Met signaling is possibly implicated in HCC metastasis through promoting cell motility, stimulating protease production that facilitates cellular invasion and strengthening angiogenesis which helps HCC cells colonize in other organs.

5. The strategy of c-Met signaling targeting therapy for HCC treatment

Based on the current understanding of the c-Met pathway in HCC, several strategies to intervene in the pathway could be proposed at different levels: *i*) inhibition of HGF expression or activity; *ii*) inhibition of c-Met expression or kinase activity; and *iii*) interference with downstream effector functions.

Even though HGF is a potent mitogen for hepatocytes, the effect of HGF on the growth of HCC cells is controversial. In addition to stimulating HCC cells proliferation, HGF also exhibits anti-proliferative effects on HCC cells (*76*). Besides that, both HCC stimulatory and inhibitory effects of exogenous administration of HGF on carcinogen-treated rats have been reported (*77-79*). There are also conflicting reports in HGF transgenic mice. Mice harboring a full-length mouse HGF cDNA under the control of the mouse metallothionein gene promoter induced liver tumors, which arose spontaneously in six independent transgenic lines after 17 months (*80*). In contrast, overexpression of a human HGF cDNA under the regulation of the albumin promoter in transgenic mice did not induce HCC (*81*). Moreover, the HGF transgene appeared to inhibit hepatocarcinogenesis in bitransgenic mice overexpressing c-Myc or TGF-α (*82*). In addition, D'Errico *et al*. reported that liver HGF did not always correlate with hepatocellular proliferation in human HCC, while its specific receptor c-Met did (*26*). Therefore,

whether or how HGF participates in hepatocarcinogenesis remains to be clarified. Subsequently the feasibility of HGF targeting therapies for HCC treatment needs to be futher studied.

The antitumor effects of reducing and/or silencing of c-Met expression in HCC cells using antisense or RNAi sequences targeting c-Met mRNA have been examined in various studies (*25,36-38,83,84*). These studies showed that down-regulation of c-Met significantly decreased the proliferation, motility, and invasive ability of HCC cells both *in vitro* and *in vivo*. The efficacy of inhibition of c-Met in HCC treatments is verified. So far, many approaches including biologic inhibitors (ribozymes, dominant-negative receptors, decoy receptors, peptides, and c-Met antagonist antibodies) and small-molecule c-Met inhibitors have been designed to inhibit c-Met expression or activity. Recently, small-molecule kinase inhibitors emerged as a major approach being investigated in the clinic. Several c-Met kinase inhibitors such as ARQ197, SGX523, and PF2341066 are rapidly progressing through various stages of development, with those in clinical trials having already demonstrated convincing early evidence of clinical activity in many types of human cancers (*85-87*). Agents that may interfere with c-Met downstream effector functions, including the MAPK and PI3K pathways may serve as an option for HCC treatment. However, targeting these downstream effectors might not be c-Met pathway-specific. Taken together we suggest that c-Met selective targeting therapies are possibly a promising strategy for HCC treatment. Finally, it should be noted that the intact HGF/c-Met signaling pathway was suggested to be essential for maintaining normal redox homeostasis in the liver and had tumor suppressor effects during the early stages of nitrosodiethylamine-induced hepatocarcinogenesis (*88*). Thus, the level of c-Met signaling activity has a range suitable for maintaining normal cell activity.

6. Conclusion

The demonstrated role of c-Met in experimental oncogenesis, its dysregulation and correlation with disease prognosis, and antitumor effects by suppression of its activity may suggest the potential of c-Met as a therapeutic target in HCC. However, identification of the subclass of patients with c-Met signaling dependent HCCs is of special importance in predicting drug efficiency and reducing side effects. So far, the efficacy of these approaches has not nearly been verified in HCC. It is necessary to apply these approaches to HCC treatments in the future.

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