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Review Article

Hepatocyte growth factor/MET in cancer progression and biomarker discovery

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Signaling driven by hepatocyte growth factor (HGF) and MET receptor facilitates conspicuous biological responses such as epithelial cell migration, 3-D morphogenesis, and survival. The dynamic migration and promotion of cell survival induced by MET activation are bases for invasion–metastasis and resistance, respectively, against targeted drugs in cancers. Recent studies indicated that MET in tumor-derived exosomes facilitates metastatic niche formation and metastasis in malignant melanoma. In lung cancer, gene amplification-induced MET activation and ligand-dependent MET activation in an autocrine/paracrine manner are causes for resistance to epidermal growth factor receptor tyrosine kinase inhibitors and anaplastic lymphoma kinase inhibitors. Hepatocyte growth factor secreted in the tumor microenvironment contributes to the innate and acquired resistance to RAF inhibitors. Changes in serum/plasma HGF, soluble MET (sMET), and phospho-MET have been confirmed to be associated with disease progression, metastasis, therapy response, and survival. Higher serum/plasma HGF levels are associated with therapy resistance and/or metastasis, while lower HGF levels are associated with progression-free survival and overall survival after treatment with targeted drugs in lung cancer, gastric cancer, colon cancer, and malignant melanoma. Urinary sMET levels in patients with bladder cancer are higher than those in patients without bladder cancer and associated with disease progression. Some of the multi-kinase inhibitors that target MET have received regulatory approval, whereas none of the selective HGF-MET inhibitors have shown efficacy in phase III clinical trials. Validation of the HGF-MET pathway as a critical driver in cancer development/progression and utilization of appropriate biomarkers are key to development and approval of HGF-MET inhibitors for clinical use.

The *MET* oncogene was first isolated on the basis of its transforming activity, caused by a fusion of genes composed of the translocated promoter region (TPR) locus on chromosome 1 and MET sequence on chromosome 7 (TPR-MET).[1] Isolation of the full-length MET proto-oncogene sequence revealed that it encoded a transmembrane receptor tyrosine kinase (TK).[2] MET was thereafter identified as the receptor for hepatocyte growth factor (HGF).[3] Hepatocyte growth factor was identified and cloned as a mitogenic protein for hepatocytes,[4,5] while subsequent studies indicated that it was the same as scatter factor, an epithelial cell motility factor derived from fibroblasts and mesenchymal cells.[6–8]

Conspicuous responses that are driven by the HGF-MET receptor pathway are dynamic 3-D morphogenesis and survival of cells. The induction of epithelial branching tubulogenesis in a 3-D collagen matrix by HGF had particular impact, because HGF was the first bioactive molecule to induce epithelial tubulogenesis.[9] Impairment in the hepatic progenitor cell survival and the migration of myogenic precursor cells seen in *MET* knockout mice indicate potent actions of HGF in dynamic migration and promotion of cell survival.[10] It was easy to speculate that the dynamic migration induced by HGF could also contribute critically to the biological basis of invasion and metastasis in tumor tissues. Meanwhile, involvement of the HGF-MET pathway in acquisition of a resistant phenotype against molecular targeted drugs was elucidated.[11,12] The potent action of HGF to promote cell survival is a prevalent biological basis for drug resistance in cancers.

Both HGF and MET are targets in anticancer drug discovery.[13] More than 10 different HGF-MET inhibitors entered into clinical trials, many of which were completed with unsatisfactory results. Recently, previously overlooked mutations in *MET*, resulting in deletions in the cytoplasmic juxtamembrane (JM) domain, have been found to be potential oncoprotein in non-small-cell lung cancer (NSCLC). Clinical studies have indicated favorable responses to MET inhibitors in patients

with this variant MET.[14,15] We describe here recent progress in HGF-MET research on tumor biology and biomarker discovery.

Structures and Regulation of HGF-MET

The mature form of MET is composed of a 50-kDa β-chain and 145-kDa α-chain (Fig. 1a). The extracellular region is composed of SEMA, plexin–semaphorin–integrin (PSI), and immunoglobulin-like fold–plexin–transcription factor (IPT) 1–IPT4 domains. The intracellular region contains JM and TK domains. The binding of HGF to MET induces MET clustering and phosphorylation of Y1234 and Y1235, followed by phosphorylation of Y1349 and Y1356 in the carboxyl terminal region, to which adaptor molecules associate and transmit signals downstream.[7,8,13] Hepatocyte growth factor is secreted as a single-chain precursor (pro-HGF) and extracellular processing into a two-chain mature HGF is coupled to the activation of HGF (Fig. 1b). Hepatocyte growth factor-activator and matriptase are the main proteases responsible for the processing of HGF.[16] Hepatocyte growth factor binds to MET through two interfaces: the NK1 (N-terminal and first kringle domains) binds with high affinity whereas the β-chain binds with low affinity. The structure of the complex between the β-chain of HGF and the SEMA-PSI domains of MET were revealed by crystallographic analysis (Fig. 1c).[17] The activation of MET receptor by bivalent MET-binding macrocyclic peptides indicate that stable dimerization of MET with ligands of appropriate length provides a fundamental structural basis for activation of MET.[18]

The JM domain, which is composed of 47 highly conserved amino acids, contains two protein phosphorylation sites and acts as a negative regulator in terms of MET-dependent signal transduction. One is Y1003 phosphorylation and the other is S985 phosphorylation. The CBL ubiquitin ligase binds phosphorylated Y1003, and this CBL binding results in MET ubiquitination, endocytosis, and degradation.[19] The CBL-mediated degradation of activated MET provides a mechanism that either attenuates or terminates MET-mediated signaling. Ser985 is phosphorylated by protein kinase-C and is dephosphorylated by protein phosphatase-2A.[20] When MET-S985 is phosphorylated, HGF-induced MET activation and subsequent biological responses are suppressed.[20]

Metastasis and Tumor Microenvironment

A definitive role of stromal fibroblasts in invasion of cancer cells into 3-D collagen was first noted using human oral squamous cell carcinoma cells,[21] and subsequent study indicated neutralization of HGF inhibited 3-D invasion induced by stromal fibroblasts. Independently, induction of invasiveness into collagen by HGF/scatter factor was noted during characterization of scatter factor.[6] These early studies showed the importance of HGF as a fibroblast-derived factor that facilitates the aggressive invasion of cancer cells.

The metastatic tumor microenvironment (premetastatic/metastatic niche) emerged as an important player in metastatic colonization and growth. A variety of stromal cells, such as macrophages, inflammatory cells, endothelial cells, and cancer-associated fibroblasts contribute to the formation of the metastatic microenvironment.[22] Growth factors play promoting roles in forming the metastatic microenvironment. Hepatocyte growth factor functions as a stromal cell-derived factor that strongly influences cancer cell invasiveness in the tumor

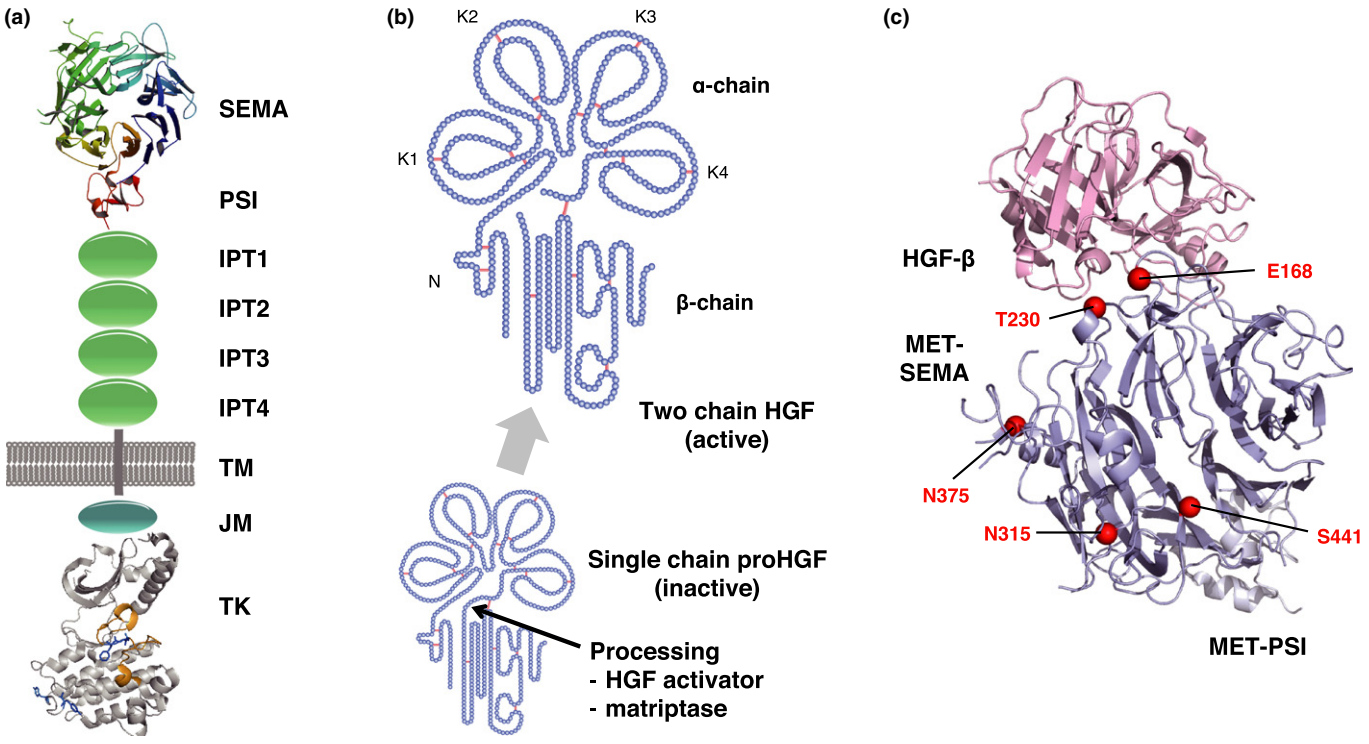

Fig. 1. Structures of MET (a), hepatocyte growth factor (HGF) (b), and the complex between the β-chain of HGF and SEMA and plexin–semaphorin–integrin (PSI) domains of MET (c). In (a), tyrosine residues (Y1234, Y1235, Y1349, and Y1356) phosphorylated following HGF stimulation in the tyrosine kinase (TK) domain are shown in blue. In (c), positions of missense mutations found in cancer patients are indicated by red balls. The image of PDB ID 1SHY (Stamos J, Lazarus RA, Yao X, Kirchhofer D, Wiesmann C. Crystal structure of the HGF β-chain in complex with the Sema domain of the Met receptor. EMBO J. 23: 2325, 2004) was created with PyMOL.

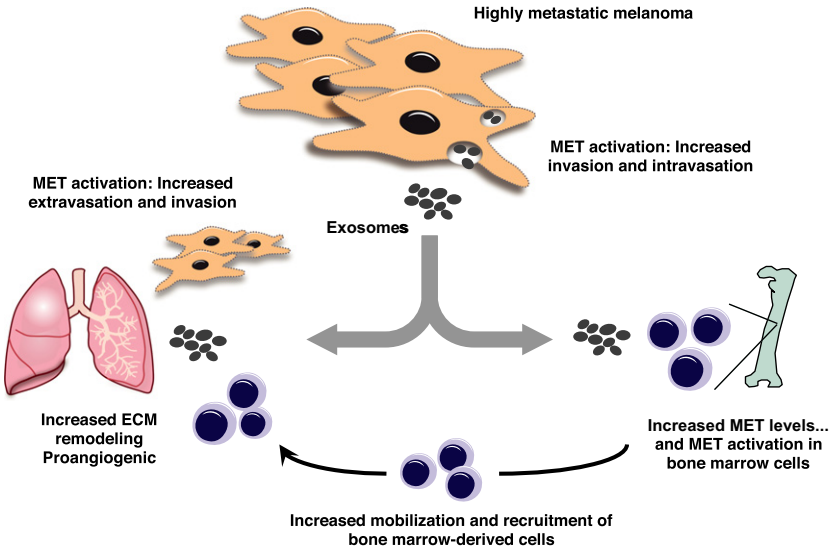

Fig. 2. Outline of the mechanism for metastasis promoted by the hepatocyte growth factor (HGF)-MET pathway and tumor-derived exosomes in advanced metastatic melanoma. Peinado *et al.* showed that tumor-derived exosomes from advanced metastatic melanoma contained high levels of MET, and the exosomes induced an increase in the phosphorylated/activated MET in bone marrow-derived cells, thereby resulting in a mobilization of the bone marrow-derived cells to the lungs and lymph nodes, where they initiated metastatic niche formation.[28] Collectively, HGF facilitates local invasion, extravasation, and intravasation, and MET in exosomes facilitates angiogenesis and metastatic niche formation.

microenvironment.[22] Selective inhibition of the HGF-MET pathway suppressed metastasis in experimental models.[7,8,13]

A recent topic in cancer metastasis is the involvement of exosomes in metastasis.[23] MET in exosomes promotes metastatic microenvironment formation in metastatic melanoma (Fig. 2).[23] The exosomes from highly metastatic mouse and human melanoma cells contained high levels of MET, and exosomes in circulation localized to sites of metastatic tissues and increased vascular permeability, which promotes the migration of tumor cells. The exosomes also increased activated MET in bone marrow-derived cells, thereby being reprogrammed to a proangiogenic phenotype, and the bone marrow-derived cells mobilized to lungs where they could aid angiogenesis, invasion, and metastasis. Administration of exosomes that contained high levels of MET facilitated metastasis of melanoma cells with lower metastatic ability.[24]

Drug Resistance

The tumor microenvironment participates not only in cancer metastasis but also resistance to molecular-targeted drugs. Stromal cells influenced the sensitivity to anticancer drugs, and proteomic analysis revealed that stromal cell-derived HGF is a predominant factor that confers resistance to molecular-targeted drugs such as RAF inhibitor.[25] The biochemical basis as to how HGF so potently promotes survival as well as cell motility might relate to the adaptor protein GRB2-associated binding protein 1 (GAB1). The GAB1 protein has a unique recognition structure "MET-binding domain" that mediates its binding to phosphorylated MET.[26] Indeed, phenotypes in $MET^{-/-}$ and $GAB1^{-/-}$ mice showed extensive similarities.[27]

Non-small-cell lung cancer patients developed acquired resistance to epidermal growth factor receptor (EGFR) TK inhibitors (TKIs) within a few years, and 20–25% of the patients showed intrinsic resistance to EGFR-TKIs. As an acquired resistance mechanism, the T790M second mutation in EGFR occurs in approximately half of all patients.[28] As a bypass pathway, MET activation caused by *MET* gene amplification[11] and HGF-dependent MET activation[12] have been noted as mechanisms by which NSCLC acquires resistance to EGFR-TKIs. *MET* gene amplification was detected in 5–10% of patients with acquired resistance to EGFR-TKIs, and overexpression of HGF was seen in approximately 61% and 29% of patients with acquired and intrinsic resistance, respectively.[29]

After the discovery of *EML4-ALK* as a driver oncogene in patients with NSCLC,[30] alectinib was developed as a selective anaplastic lymphoma kinase (ALK) TKI.[31] Based on its high objective response rate, long median progression-free survival, and favorable toxicity profile, alectinib has been approved in Japan and the USA. However, patients eventually acquire resistance to alectinib. Among several different mechanisms, alectinib-resistant EML4-ALK-positive NSCLC cells can acquire the ability to express HGF and the ensuing autocrine activation of MET caused by cancer cell-derived HGF confers acquired resistance to alectinib.[32] Collectively, the expression of HGF in cancer cells and/or stromal cells in the tumor microenvironment participates in the resistance to EGFR and ALK TKIs.

MET Mutations

The tight association between MET mutation and cancer development was first reported in hereditary and sporadic forms of papillary renal cell carcinoma.[33] Germline and somatic missense mutations (M1131T, V1188L, L1195V, V1220I, D1228N/H, Y1230C/H, M1250T/I) located in the TK domain of MET are found in papillary renal carcinomas (Fig. 3), and these are likely to be gain-of-function mutations. Missense mutations have been found in childhood hepatocellular carcinoma, head and neck squamous cell carcinoma, ovarian cancer, and small-cell lung cancer.[34]

The JM-deleted MET generated by exon 14 skipping (MET-Δexon14) due to intronic mutations was noted in NSCLC cancer tissues and cells.[35] The expression of MET-Δexon14 in cells resulted in the loss of association with the CBL E3 ubiquitin ligase, decreased ubiquitination and prolonged activation of signaling molecules.[35] Considering the notion that MET-Y1003 phosphorylation in the JM domain provides CBL-binding for ubiquitination, MET-Δexon14 variant may have a longer lifespan in terms of protein stability and signaling.

Another mutant variant of MET with deleted extracellular IPT domains was found in approximately 6% of high-grade gliomas.[36] The mutation is caused by intronic mutations and the skipping of exon 7 (encoding a part of IPT1) and exon 8 (encoding a part of IPT2) generates a single pseudo-IPT domain. This MET exon 7–8 skipping variant is mainly

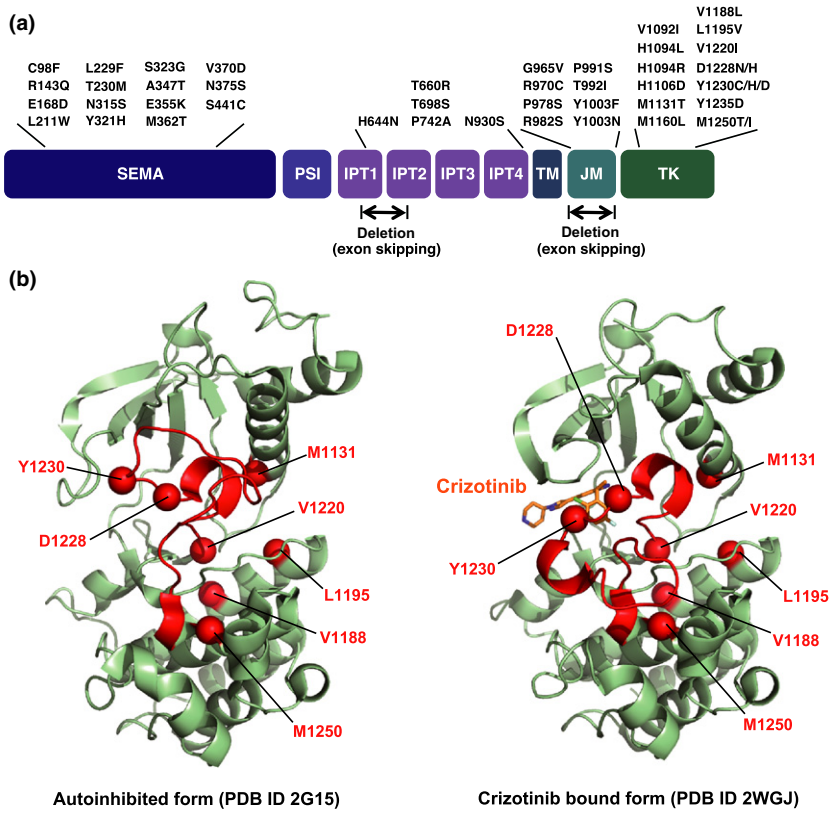

Fig. 3. MET mutations found in cancer patients. (a) Positions of missense and deletion mutations in each domain of MET. The deletion mutations in extracellular immunoglobulin-like fold–plexin–transcription factor (IPT) domains and the intracellular juxtamembrane (JM) domain are caused by exon skipping.[43–45] (b) Crystal structures of MET tyrosine kinase (TK) domain and positions of missense activating mutations found in patients with papillary renal cell carcinoma. Amino acids changed by missense mutations are indicated by red balls. The autoinhibited form (left panel, PDB ID 2G15) and crizotinib (a dual inhibitor for anaplastic lymphoma kinase and MET) bound form (right panel, PDB ID 2WGJ) are shown. The structural change of the activation loop (A1221–K1248, colored red) occurs following Y1234/Y1235 phosphorylation and upregulates enzymatic activity. The images of PDB ID 2G15 (left) (Wang W, Marimuthu A, Tsai J, Kumar A, Krupka HI, Zhang C, Powell B, Suzuki Y, Nguyen H, Tabrizizad M, Luu C, West BL. Structural characterization of autoinhibited c-Met kinase produced by coexpression in bacteria with phosphatase. Proc Natl Acad Sci USA. 103: 3563-3568, 2006) and PDB ID 2WGJ (right) (Cui JJ, Tran-Dubé M, Shen H, Nambu M, Kung PP, Pairish M, Jia L, Meng J, Funk L, Botrous I, McTigue M, Grodsky N, Ryan K, Padrique E, Alton G, Timofeevski S, Yamazaki S, Li Q, Zou H, Christensen J, Mroczkowski B, Bender S, Kania RS, Edwards MP. Structure based drug design of crizotinib (PF-02341066), a potent and selective dual inhibitor of mesenchymal-epithelial transition factor (c-MET) kinase and anaplastic lymphoma kinase (ALK). J Med Chem. 54: 6342-6363, 2011) were created with PyMOL.

present as an unprocessed single chain form and located in the cytoplasm, suggesting an impairment in biosynthetic processing and subsequent translocation to the cell membrane. Missense mutations in MET have been found in a variety of cancers, and the positions of mutational changes are located not only in the intracellular domains, but also extracellular regions (Figs 1C,3A). The significance of these extracellular mutations is unknown.

Discovery of HGF/MET as Biomarkers

Collectively, HGF and sMET in blood, tissues, and/or urine are associated with changes in tumor characteristics and therapeutic responses in several types of tumors, indicating the significance of HGF, sMET, and related molecules as possible biomarkers for evaluation of tumor characteristics and therapeutic responses (Table 1). A substantial number of reports have documented increased circulating levels of HGF in a wide spectrum of cancers, and robust and sensitive immunoassays of soluble HGF protein have become widely available. Inflammatory mediators, including interleukin-1α (IL-1α), IL-1β, tumor necrosis factor-α, and prostaglandin E_2 increase gene expression of HGF in stromal cells.[37] Because these inflammatory mediators are increased in the tumor microenvironment and contribute to a drug-resistant and/or metastatic tumor microenvironment, it is likely that these inflammatory mediators participate in upregulation of HGF in tumors.

MET gene amplification and/or protein overexpression also frequently occur in cancer, which has accelerated investigations into *MET* gene copy number in tumors or by circulating soluble DNA, as well as MET protein content and phosphorylation (activation) state in tumor samples using a variety of approaches. Technical difficulties associated with the lability of MET and phospho-MET in formalin-fixed, paraffin-embedded samples have hindered the development of clinically validated assays for use with archival tumor specimens, but recently reported assays for use with flash-frozen biopsy samples have provided reliable alternatives.[38] Athauda *et al.*[39] developed two-site electrochemiluminescent immunoassays of MET in flash-frozen samples and sMET ectodomain for plasma, serum, and urine samples, later adapting the assay to detect phospho-MET.[40] Efforts along these lines have identified specific contexts in which HGF/MET signaling contributes to cancer, and for some cancers, may help identify those patients in whom pathway inhibition is likely to have therapeutic benefit.

Table 1. Changes in serum/plasma/tissue hepatocyte growth factor (HGF) levels, soluble MET, and MET expression/phosphorylation in tumors

Tumor type	Subtype, specification	Marker type	Changes and significance as biomarkers	References
Gastric cancer	Resection	Serum HGF	Higher preoperative HGF levels than the control group (391 *vs* 193 pg/mL)	41
	Response to trastuzumab	Serum HGF	Lower HGF levels in the responsive group (PR+SD) than in those with PD. Association between high HGF levels with worse OS	42
	Helicobacter pylori-infected	Plasma sMET	Lower sMET levels compared to matched controls (1.390 *vs* 1.610 ng/mL)	43
	Resection	Serum sMET, tissue MET, serum and tissue HGF	Association between advanced progression and preoperative serum HGF. Correlation of tissue MET with lymphatic vessel invasion, lymph node metastasis, maximum tumor diameter, and OS. No correlation between serum HGF and tissue HGF or MET content	42
Lung cancer	Small-cell lung cancer	Serum HGF	Higher HGF levels compared to healthy individuals (1886 pg/mL *vs* 1131 pg/mL). Association between higher HGF levels and worse PFS and liver metastases. Increased HGF levels at progression after two to three cycles of chemotherapy. Longer OS in patients with decreased HGF levels at response time from baseline levels than patients with increased levels. Shorter OS in patients with higher HGF levels than those with lower HGF levels. Association with tumor epithelial–mesenchymal transition markers in patients with high HGF levels (>median)	44
	Small-cell lung cancer	Serum HGF	Higher HGF levels compared to and healthy subjects. No difference with cancer stage	45
	Small-cell lung cancer	Tissue MET, tissue pMET	MET overexpression and increased pMET in 54% and 43% patients, respectively. Correlation between pMET status and OS	46
	Lung adenocarcinoma	Tissue HGF	High HGF immunoreactivity in patients with acquired gefitinib resistance in the absence of T790M EGFR mutation and *MET* gene amplification. Low HGF immunoreactivity in majority of responders to gefitinib	12
	Lung adenocarcinoma	Plasma HGF	High HGF levels in 13% of patients resistant to EGFR-TKI without detectable T790M circulating DNA. High HGF levels in 25% of patients resistant to EGFR-TKI with detectable T790M circulating DNA	47
	Lung adenocarcinoma	Plasma HGF	Higher HGF levels than normal and pretreatment with EGFR-TKI. Increase after administration of EGFR-TKI. Higher HGF levels in patients with PD compared to PR and SD (724.1 $\pm$ 216.4 pg/mL *vs* 381.7 $\pm$ 179.0 pg/mL and 396.5 $\pm$ 148.3 pg/mL, respectively)	48
	Lung adenocarcinoma	Plasma HGF	Higher HGF levels in gefitinib non-responders than in responders. Association between low HGF levels and longer RFS and OS independent of EGFR mutation status	49
	Lung adenocarcinoma	Plasma sMET, tissue MET	Association between sMET and tissue MET expression level. Decrease in sMET levels after surgical resection to levels close to those in disease-free volunteers	50
	Lung adenocarcinoma	Plasma sMET, tissue MET	Association between sMET levels and tissue MET expression levels in advanced patients. Association between high sMET levels and poor OS (9.5 *vs* 22.2 months)	51

Table 1 (Continued)

Tumor type	Subtype, specification	Marker type	Changes and significance as biomarkers	References
Breast cancer	Stage II/III	Serum HGF	Higher HGF levels in CR or PR in patients treated with neoadjuvant chemotherapy doxorubicin and docetaxel. Longer RFS in patients with highest HGF levels when HGF levels were divided into four groups	52
		Tissue HGF	Association between high tissue HGF levels and lymph node metastasis. Higher sensitivity to chemotherapy (CR, PR, and SD) in HGF-low patients than in HGF-high patients	53
	Meta-analysis	MET levels	Association between MET overexpression and worse PFS compared to normal expression	54
	Breast cancer cell lines	Reverse phase protein array	Higher pMET (Y1234/35) levels in triple-negative (negative for estrogen receptor, progesterone receptor, and ERBB2/HER2) cases	55
		Tissue MET and pMET by reverse phase protein array	Determination of dichotomized values of MET and pMET as significant prognostic factors for RFS and OS. Association between high MET levels and worse RFS and OS in hormone receptor-positive cases. Association between high pMET levels and worse RFS and OS in HER2-positive cases. Higher risk of recurrence and death in patients with high MET. Higher risk of recurrence in patients with high pMET	56
Prostate cancer		Plasma HGF	Higher median HGF level in prostate cancer patients compared to control group (505 *vs* 397 pg/mL). Higher HGF levels in subset of patients with lymph node and/or seminal invasion	57
		Urinary sMET	Higher sMET levels in patients with metastatic cancer than in localized cancer	58
		Plasma sMET	Higher sMET levels in patients than those in healthy group	40
Renal cell carcinoma	Clear cell type	Serum HGF	Higher HGF levels in patients than healthy individuals. Higher median HGF level in stage 3–4 than stage 1–2 (1252.9 *vs* 948.7 pg/mL). Higher HGF levels in patients with distant metastasis than those without metastasis (1375 *vs* 836.6 pg/mL)	59
	Clinical trial with pazopanib	Plasma HGF	Correlation between low HGF baseline level and larger decrease in tumor burden after pazopanib treatment. Correlation between low baseline HGF levels and PFS (48.1 *vs* 32.1 weeks)	60
	Clinical trial with rilotumumab	Plasma HGF and sMET, tissue MET	No correlation of these values with treatment efficacy	61
Malignant melanoma		Serum HGF	Higher HGF levels in advanced disease. Higher HGF levels in patients with progressive disease. Correlation of baseline high level (above median) with lower PFS and OS	62
		Serum sMET	Lower sMET levels in metastasis-free patients and healthy donors than those with metastatic disease. Superior changes in sMET than those in lactate hydrogenase and S100 for liver function	63

Table 1 (Continued)

Tumor type	Subtype, specification	Marker type	Changes and significance as biomarkers	References
Multiple myeloma		HGF mRNA in bone marrow	Higher HGF mRNA expression levels in patients than those of healthy individuals. No relation to the number of myeloma cells	64
		Serum HGF	Higher median HGF levels at diagnosis *vs* in remission (2001 *vs* 1049 pg/mL); Higher median HGF levels in relapsed *vs* in remission patients (1370 *vs* 1049 pg/mL)	65
		Serum sMET	No significant difference in sMET between patients and healthy individuals; Negative correlations of sMET with disease stage and bone marrow plasma cell percentage	66
Colon cancer	Patients underwent carcinoma resection	Serum HGF	Correlation of higher HGF levels with advanced stage (stage III/IV), tumor size, lymph node metastasis, and distant metastasis. Poor prognosis in patients with elevated HGF	67
	Metastatic cancer, treated with anti-EGFR antibody KRAS wild-type	Serum HGF	Correlation between low HGF levels and longer PFS and OS	68
Hepatocellular carcinoma		Serum HGF	Correlation between higher HGF levels post-hepatectomy with metastasis. Higher HGF levels in patients with hepatocellular carcinoma than those with C-viral chronic hepatitis or liver cirrhosis	69–71
		Serum HGF	Higher pre-hepatectomy portal HGF levels than peripheral HGF levels. Higher post-hepatectomy portal HGF levels compared to pre-hepatectomy portal levels	69
	Metastatic patients treated with sorafenib ± erlotinib	Plasma HGF	Correlation of higher baseline HGF levels with poor OS regardless of treatment compared to those with lower HGF levels	72
	Clinical trial of tivantinib	Serum HGF	Correlation of low baseline HGF with longer OS. Longer OS in patients treated with tivantinib with low HGF than in those with high HGF	73
Ovarian cancer		Serum HGF	Higher preoperative HGF levels than those with benign tumors or borderline tumors. Higher HGF levels in advanced-stage (III/IV) patients than those in early stage (I/II). Correlation of higher preoperative HGF levels with lower OS (23 *vs* 41 months). Longer disease-free survival in patients with low preoperative HGF	74
Bladder cancer		Urinary sMET	Higher sMET levels in bladder cancer patients compared to individuals in the same urology clinic but negative for any genitourinary malignancy. Distinguishable by urinary sMET between bladder cancer patients with muscle-invasive disease from those with non-muscle-invasive disease	75
Glioma	Treated by radiotherapy	Serum HGF	Lower median serum HGF in patients with high and moderately differentiated tumors than those with poorly differentiated tumors (964.8 pg/mL *vs* 1576.1 pg/mL). Different median time to progression (6 *vs* 17 months) for patients with HGF levels below *vs* above value of overall median serum HGF level (1219.5 pg/mL)	76

CR, complete response; EGFR, epidermal growth factor receptor; ERBB2, Erb-B2 receptor tyrosine kinase 2; HER2, human epidermal growth factor receptor 2; OS, overall survival; PD, progressive disease; PFS, progression-free survival; pMET, phosphorylated MET; PR, partial response; RFS, relapse-free survival; SD, stable disease; sMET, soluble MET; TKI, tyrosine kinase inhibitor.

Table 2. Clinical trials of hepatocyte growth factor (HGF)-MET inhibitors

Drug	Design	Phase	Patient population	Combinations
INCB28060/(INC280)	Safety/tolerability	I	c-MET-dependent advanced solid tumors	
Cabozantinib (XL184)	Safety/PK	I	Hepatic impaired adult subjects	
Onartuzumab (MetMAb)	Safety/efficacy	II	NSCLC	Bevacizumab/platinum/paclitaxel and pemetrexed/platinum
Onartuzumab (MetMAb)	Safety/efficacy	II	NSCLC	Paclitaxel/platinum
Cabozantinib (XL184)	Safety/efficacy	III	Previously treated, symptomatic castration-resistant prostate cancer	Mitoxantrone/prednisone
Crizotinib (PF02341066)	Safety/efficacy	II	Altered ALK and/or MET in locally advanced and/or metastatic anaplastic large cell lymphoma, inflammatory myofibroblastic tumor, papillary renal cell carcinoma type 1, alveolar soft part sarcoma, clear cell sarcoma, and alveolar rhabdomyosarcoma	
Crizotinib (PF02341066)	Safety/efficacy	I	Advanced malignancies	Vemurafenib, sorafenib
INCB28060/(INC280)	Safety	I	Japanese patients with advanced solid tumors	
Crizotinib (PF02341066)	Safety/efficacy	I	Advanced malignancies	Pemetrexed or pazopanib
Cabozantinib (XL184)	Safety/efficacy	I	Multiple myeloma with bone disease	
Cabozantinib (XL184)	Efficacy	II	Solid tumors	
Onartuzumab (MetMAb)	Safety/efficacy	II	Gastric cancer	mFOLFOX6
Cabozantinib (XL184)	Efficacy	II	Castration-resistant prostate cancer with bone metastases	
LY2875358	Safety	I	Japanese participants with advanced cancer	Erlotinib or gefitinib
Cabozantinib (XL184)	Safety/efficacy	III	Metastatic castration-resistant prostate cancer previously treated with docetaxel and abiraterone or MDV3100	Prednisone
Crizotinib (PF02341066)	Safety	I	Younger patients with relapsed or refractory solid tumors or anaplastic large cell lymphoma	Cyclophosphamide, dexrazoxane, doxorubicin, topotecan, vincristine
INCB28060/(INC280)	Safety/efficacy	Ib/II	NSCLC, EGFR-mutated, c-MET-amplified, EGFR-inhibitor insensitive	Gefitinib
Cabozantinib (XL184)	Safety/efficacy	II	Advanced NSCLC, KIF5B/RET-positive	
Crizotinib (PF02341066)	Safety/efficacy	I	Diffuse intrinsic pontine glioma, high grade glioma, pediatric	Dasatinib
SAR125844	Safety/efficacy/PD	I	Asian advanced malignant solid tumor patients	
Onartuzumab (MetMAb)	Safety/efficacy	III	Metastatic gastric cancer, HER2−, Met-positive	mFOLFOX6
Cabozantinib (XL184)	Expanded access		Medullary thyroid cancer	
Cabozantinib (XL184)	Safety	I	Advanced prostate cancer	Docetaxel, prednisone
Cabozantinib (XL184)	Efficacy	II	Advanced urothelial cancer	
Rilotumumab (AMG 102)	Efficacy	III	Locally advanced/metastatic gastric or esophagogastric junction adenocarcinoma	
Cabozantinib (XL184)	Efficacy	III	Castration-resistant prostate cancer	
Cabozantinib (XL184)	Efficacy	II	Stage IV NSCLC, EGFR wild-type	Erlotinib
Crizotinib (PF02341066)	Safety/efficacy	I/II	NSCLC	HSP90 inhibitor AT13387
Cabozantinib (XL184)	Efficacy	II	Persistent or recurrent ovarian epithelial cancer, fallopian tube, or peritoneal cancer	Randomized *vs* paclitaxel
BMS-777607 (ASLAN002)	Safety	I	Advanced or metastatic solid tumors	
INCB28060 (INC280)	Safety/efficacy	II	Advanced hepatocellular carcinoma with c-MET dysregulation	
Cabozantinib (XL184)	Safety/efficacy	II	Metastatic triple-negative breast cancer	
Cabozantinib (XL184)	Efficacy	II	Adults with advanced soft tissue sarcoma	

Table 2 (Continued)

Drug	Design	Phase	Patient population	Combinations
Volitinib savolitinib/ AZD6094/HMPL-50	Safety/PK	I	Advanced solid tumors	
Rilotumumab (AMG 102)	Safety/efficacy	I/Ib	Japanese subjects with advanced solid tumors or advanced or metastatic gastric or esophagogastric junction adenocarcinoma	
MSC2156119J/ EMD1214063	Safety/efficacy	I	Solid tumors	
Cabozantinib (XL184)	Efficacy	II	Castration-resistant prostate cancer with visceral metastases	
Met RNA CAR T cells	Safety/efficacy	I	Metastatic breast cancer, triple-negative breast cancer	
Cabozantinib (XL184)	Safety/efficacy	III	Subjects with metastatic renal cell carcinoma	Randomized *vs* everolimus
INCB28060 (INC280)	Safety/efficacy	Ib/II	Recurrent glioblastoma	Buparlisib
LY2875358	Efficacy	II	Gastric cancer	
Onartuzumab (MetMAb)	Safety/efficacy	III	Met-positive, stage IIIb or IV NSCLC with activating EGFR mutation	Erlotinib
Onartuzumab (MetMAb)	Safety/PK	Ib	Advanced hepatocellular carcinoma	Alone or sorafenib
LY2875358	Efficacy	II	NSCLC with activating EGFR mutations	Erlotinib
LY2875358	Efficacy	II	NSCLC	Erlotinib
Cabozantinib (XL184)	Safety/efficacy	III	Subjects with hepatocellular carcinoma who have received prior sorafenib treatment	Randomized *vs* placebo
INCB28060 (INC280)	Safety	I	Met-positive NSCLC	Erlotinib
MGCD265	Safety	I	Healthy subjects in fasting state	
INCB28060 (INC280)	Safety/efficacy	II	Advanced hepatocellular carcinoma after progression or sorafenib intolerance	
Onartuzumab (MetMAb)	Safety/PK	Ib	Advanced solid malignancies	Vemurafenib, and/or cobimetinib
LY2801653	PK/radiolabeled	I	Healthy participants	
MSC2156119J	Safety/efficacy	I/II	Advanced NSCLC	Gefitinib
MSC2156119J	Safety/efficacy	I/II	Asian subjects with hepatocellular carcinoma	
Crizotinib (PF02341066)	Safety	I	Advanced solid tumors	Axitinib
AMG 337	Efficacy	II	MET-amplified gastric/esophageal adenocarcinoma or other solid tumors	
INCB28060 (INC280)	Efficacy	II	Papillary renal cell carcinoma	
Onartuzumab (MetMAb)	Safety/efficacy	I	Chinese patients with locally advanced or metastatic solid tumors	
Onartuzumab (MetMAb)	Efficacy	III	Met-positive, incurable stage IIIb or IV NSCLC	Erlotinib
Foretinib (GSK1363089)	Efficacy	II	Genomic subpopulations of NSCLC	
LY2875358	Safety/efficacy	I/II	Advanced cancer	Ramucirumab
AMG 337	Safety/efficacy	I/II	Advanced solid tumor, gastric/esophageal adenocarcinoma or other solid tumors	
MSC2156119J	Safety/efficacy	I/II	Second-line hepatocellular carcinoma	
Volitinib Savolitinib/ AZD6094/HMPL-50	Safety/efficacy	II	Papillary renal cell cancer	
Crizotinib (PF02341066)	Efficacy	II	Patients with stage IV NSCLC that has progressed after crizotinib treatment	Pemetrexed disodium
Rilotumumab (AMG 102)	Efficacy	III	Gastric cancer	Cisplatin and capecitabine *vs* placebo
Volitinib Savolitinib/ AZD6094/HMPL-50	Safety/efficacy	Ib	EGFR mutation-positive advanced lung cancer	AZD9291
INCB28060 (INC280)	Safety/efficacy/PK	I	Squamous cell carcinoma of head and neck	Cetuximab
INCB28060 (INC280)	Safety/efficacy/PK	II	Metastatic colorectal cancer	

Table 2 (Continued)

Drug	Design	Phase	Patient population	Combinations
INCB28060 (INC280)	Safety/efficacy	II	Chinese patients with advanced NSCLC	
Ficlatuzumab (AV-299)	Safety/efficacy	I	Ficlatuzumab, cisplatin, and IMRT in locally advanced squamous cell carcinoma of the head and neck	Cisplatin and intensity modulated radiotherapy
Ficlatuzumab (AV-299)	Safety/efficacy	I	Recurrent/metastatic squamous cell carcinoma of the head and neck	Cetuximab
SAIT301	Safety	I	Subjects with advanced c-MET-positive solid tumors followed by expansion in selected tumor types	
AMG 337	Safety/efficacy	I/II	Advanced stomach or esophageal cancer	Fluorouracil, oxaliplatin, leucovorin
Volitinib Savolitinib/ AZD6094/HMPL-50	Safety/PK/preliminary efficacy	1b	EGFR mutation-positive NSCLC patients that progressed on EGFR tyrosine kinase inhibitor	Gefitinib
INCB28060 (INC280)	Efficacy	II	Advanced NSCLC patients that have received one or two prior lines of therapy	
Crizotinib (PF02341066)	Safety/efficacy			
Volitinib Savolitinib/ AZD6094/HMPL-50	Safety/efficacy	II	Advanced gastric adenocarcinoma patients with MET overexpression as a second-line treatment	Docetaxel
Volitinib Savolitinib/ AZD6094/HMPL-50	Safety/efficacy	Ib/II	Phase 1b in any solid cancer and sequential phase II in advanced gastric adenocarcinoma patients with MET amplification as a second line treatment	Docetaxel
Volitinib Savolitinib/ AZD6094/HMPL-50	Safety/efficacy	II	Advanced gastric adenocarcinoma patients with MET amplification as a third-line treatment	
INCB28060 (INC280)	Drug–drug interaction: PK of midazolam and caffeine	I	Patients with MET-dysregulated advanced solid tumors	Midazolam, caffeine
Crizotinib (PF02341066)	Safety/efficacy	II	Met or Ron-positive metastatic urothelial cancer	
INCB28060 (INC280)	Drug–drug interaction: PK of digoxin and rosuvastatin	I	Patients with MET-dysregulated advanced solid tumors	Digoxin, rosuvastatin
Volitinib Savolitinib/ AZD6094/HMPL-50	Safety/PK	I	Ras wild-type colorectal cancer	Cetuximab
Volitinib Savolitinib/ AZD6094/HMPL-50	Safety/efficacy	I	Locally advanced or metastatic kidney cancer	Randomized multi-arm study comparing cabozantinib, crizotinib, volitinib, or sunitinib
Rilotumumab (AMG 102)	Efficacy	III	Stage IV SCLC	Hydrochloride or erlotinib
INC280	Safety/efficacy	I	Glioblastoma multiforme, gliosarcoma, colorectal cancer, renal cell carcinoma	
Capmatinib (INC280)	Safety	II	Malignant NSCLC with exon14 alteration	
JNJ-38877605	Safety/efficacy	I	Advanced or refractory solid tumors	
SGX523	Safety/efficacy	I	Advanced cancer	

Experimental therapeutics (left column) are listed by generic name or alphanumeric identifier. For brevity, this table lists only those trials not tabulated in a prior comprehensive review by Cecchi *et al.*[13] A complete listing of trials with links to several relevant cancer information sources can be found online (https://ccrod.cancer.gov/confluence/display/CCRHGF/Home). ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; HSP90, heat shock protein 90; IMRT, intensity-modulated radiation therapy; mFOLFOX6, 5-fluorouracil, leucovorin, oxaliplatin; NSCLC, non-small-cell lung cancer; PD, pharmacodynamics; PK, pharmacokinetics; SCLC, small-cell lung cancer.

Experimental Cancer Therapeutics Targeting the HGF/MET Pathway

The prevalence of HGF/MET pathway activation in human malignancies has driven rapid growth in drug development programs. The most advanced agents currently under development as HGF/MET pathway inhibitors include mAbs directed at HGF and low molecular weight compounds that competitively antagonize ATP binding to MET (Table 2). Although some of the multi-kinase inhibitors that target MET have received regulatory approval in several indications, it remains unclear whether the MET kinase is a primary target. None of the more selective MET inhibitors have shown efficacy in phase II or III clinical trials, although few of these agents have reached this level of development.

A recent topic in HGF/MET pathway inhibition is clinical studies in lung cancer patients with *MET-Δexon14* alteration. Paik *et al.*[14] reported that *MET-Δexon14* mutation is approximately 4% of lung adenocarcinoma, and three out of four patients with stage IV lung adenocarcinomas harboring *MET-Δexon14* mutation had a response to MET TKI. Among 38 028 cancer patients, *MET-Δexon14* mutations were found in 221 cases, and *MET-Δexon14* mutations are detected most frequently in lung adenocarcinoma (3%), but also frequently in other lung neoplasms (2.3%) and brain glioma (0.4%).[15] In 11 205 lung cancers profiled by comprehensive genomic profiling, 298 (2.7%) carcinomas harbored *MET-Δexon14* alterations.[77] Eight patients harboring *MET-Δexon14* showed controlled responses, including four cases with partial responses, two cases with complete responses, and two cases with stable disease.[77] Among 1296 Chinese patients with NSCLC, 12 patients (0.9%) had *MET-Δexon14* mutation, suggesting a difference in frequency by ethnicity.[78] It is anticipated that ongoing clinical studies will reveal the significance of MET-Δexon14 alteration as a biomarker and therapeutic target for clinical use of HGF-MET inhibitors.

Conclusions

Therapeutic resistance and metastasis are major obstacles to achieving durable clinical responses with molecular-targeted therapies. Signaling pathways driven by HGF and MET participate in invasion, metastasis, and resistance to molecular-targeted drugs. Although selective MET inhibitors have yet shown efficacy in phase II and III clinical trials, ongoing clinical trials have indicated favorable response to MET inhibitors in patients with NSCLC expressing variant MET deleted within the JM domain. Biomarker discovery and the utilization of appropriate biomarkers to validate HGF-MET signaling as a driver in cancer development, metastasis, and drug resistance appears to be key for regulatory approval of HGF-MET inhibitors for clinical use.

Because HGF is biosynthesized as a zymogen-like single chain inactive precursor (capable of MET binding but incapable of MET activation) and the processing to two-chain HGF is coupled to its activation, the measurement and evaluation of HGF activation is also key to understanding the tumor microenvironment that permits tumor metastasis and drug resistance. In the future, elucidation of the 3-D structure(s) of the HGF-MET complex and the MET activation process will provide an opportunity to discover molecular tools applicable to sensitive and specific detection of activation of HGF and MET for diagnosis and evaluation of therapeutics.

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Disclosure Statement

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