CLINICAL INVESTIGATION

Therapeutic potential of c-MET inhibitors: background and clinical data

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In the last 30 years, since the discovery of the HGFR (also known as c-MET), much has been learned about its roles in a broad spectrum of cellular phenotypes, including mitogenesis, morphogenesis, angiogenesis and invasiveness. While these phenotypes are tightly regulated during embryogenesis and in adulthood processes, such as wound healing and liver regeneration, they can be responsible for tumor initiation and progression when c-MET is aberrantly activated by mutation, gene amplification and/or protein overexpression. As such, both c-MET and HGF have several targeted inhibitors currently in clinical trials. This manuscript provides an overview of the c-MET signaling pathway, including its role in the development of cancers, and presents data that support this pathway as a relevant target for personalized cancer treatment.

Keywords: cancer • HGF • HGFR • MET • personalized medicine • receptor tyrosine kinases • target therapy

Receptor tyrosine kinases (RTKs) are key regulatory proteins responsible for many essential processes in mammalian physiology [1,2]. However, in the last few decades, RTK signaling has come under intense interest due to its role in the pathogenesis and biology of many cancer types through aberrant activation [3,4]. An example of this is the HGFR RTK, more commonly known as c-MET, and its ligand HGF. Expression of both the ligand and/or the receptor has been detected in the majority of solid cancers and evidence for c-MET signaling activity has also been detected in a large number of human cancers [5–7]. This article will provide a brief overview of the c-MET signaling pathway, describe the mechanisms that have been found to be responsible for its aberrant regulation in different cancers and then provide a summary of the inhibitors of this pathway that are currently undergoing clinical trials.

HGF & c-MET: structure & function

The proto-oncogene *MET* is located on chromosome 7q31.2, with its transcription being regulated by multiple transcription factors such as Ets, Pax3, AP2 and Tcf-4 [8–11]. The protein product of this gene is c-MET. This cell-surface RTK is expressed in endothelial and epithelial cells during both embryogenesis and adulthood [12], while its ligand is expressed mainly in cells of mesenchymal origin. However, some reports have shown that HGF is also expressed by some neoplastic epithelial cells [13–17].

c-MET is transcribed as a single transcript, although the mature protein is formed by proteolytic processing in the post-Golgi compartment into a single-pass, transmembrane, disulphide-linked α/β heterodimer [18]. The extracellular portion of c-MET is composed of three domain types. The 500 N-terminal residues form the SEMA domain, folding to form a 7-bladed β-propeller that

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encompasses the whole α-subunit and part of the β-subunit [19,20]. The SEMA domain shares sequence homology with domains found in the semaphorin and plexin families and has been found to function as a protein–protein interaction domain [19,21–23]. The PSI (found in plexins, semaphorins and integrins) domain, which spans approximately 50 amino acids, is a cysteine-rich module that forms a three-stranded antiparallel β-sheet and two α-helices that function as a wedge between the SEMA β-propeller and the immunoglobulin-like domains [24]. Intracellularly, the c-MET receptor contains a tyrosine kinase catalytic domain, flanked by distinctive juxtamembrane and carboxy-terminal sequences.

The ligand for c-MET was identified concurrently by two independent studies as both a mitogen for hepatocytes and a motility factor for epithelial cells, and was called both HGF and scatter factor before it was revealed to be the same molecule [25–27]. HGF promotes several phenotypes, including cell proliferation, survival, motility, scattering, differentiation and morphogenesis, also known as an 'invasive growth program' [5,18,28]. In addition, HGF appears to play a protective role in several diseases, including liver cirrhosis [29], lung fibrosis [30], and progressive nephropathies [31,32].

Under normal conditions, HGF is secreted by mesenchymal cells as a single-chain, biologically inert precursor before it is cleaved by extracellular proteases, such as urokinase, between Arg-494 and Val-495 [33]. The mature, bioactive form of HGF consists of a disulphide bond-linked α- and β-chain. The α-chain contains an N-terminal hairpin loop, followed by four kringle domains (80 amino acid double-looped structures formed by three internal disulphide bridges), while the β-chain is homologous to serine proteases of the blood-clotting cascade, although it does not demonstrate any protease activity (Figure 1B) [34]. Interestingly, cleavage of HGF is required for its biological activity, but not for receptor binding [35]. This finding introduced the possibility of using mimetics of the HGF kringle domains as competitive inhibitors of HGF/c-MET binding, such as the NK4 fragment [36]; however, this strategy has not yet found its way into clinical trials. Antibodies that block the binding of HGF to c-MET by competitively binding to the ligand have also been studied as a means of inhibiting c-MET activation; an example of this is undergoing clinical trials and will be discussed later in this article.

HGF/c-MET signal transduction

c-MET activation & signaling adaptors

The complex phenotype that results from c-MET signaling involves a number of molecular events that have been described in detail in previous articles [5,7,37–40], while recent large-scale phosphoproteomic studies have provided even more insight into the intricacies of the HGF/c-MET signaling axis [41–43]. HGF binding to c-MET results in receptor homodimerization and phosphorylation of two tyrosine residues (Tyr-1234 and -1235) located within the catalytic loop of the tyrosine kinase domain [44]. Subsequently, Tyr-1349 and -1356 in the carboxy-terminal tail become phosphorylated. These two tyrosines form a tandem SH2 recognition motif unique to c-MET ($Y^{1349}VHVX_3Y^{1356}VNV$) [45]. When these tyrosines become phosphorylated, they recruit signaling effectors including the adaptor proteins GRB2 [46], SHC [47], and CRK and CRKL [48,49]; the effector molecules PI3K, PLC-γ and SRC [45]; SHIP-2 [50]; and STAT3 (Figure 2) [51,52]. In addition, unique to c-MET is its association with the adaptor protein GAB1, which has been shown by several studies to be the most crucial substrate for c-MET signaling [53]. GAB1 is a multiadaptor protein that binds to activated c-MET via a unique MET binding site [54]. Once bound, GAB1 is phosphorylated and creates binding sites for further downstream adaptors. GAB1 can bind directly to the c-MET docking tyrosines [45], or indirectly, through GRB2 [55]. Additional tyrosines can also contribute to c-MET signaling. When Tyr-1313 is phosphorylated, it binds PI3K, which probably promotes cell viability and motility [56]. Additionally, Tyr-1365 regulates cell morphogenesis when phosphorylated [56].

Downstream signaling modulators

The downstream response to c-MET activation relies on stereotypical signaling modulators common to many RTKs. These pathways have previously been reviewed in detail [40] and are summarized in Figure 2. These include the two major arms of c-MET signaling, including the MAPK cascades and the PI3K/AKT signaling pathways. Binding of GRB2 and SHC to activated c-MET stimulates the activity of the RAS guanine nucleotide exchanger SOS [57], leading to the activation of RAS. This results in the indirect activation of RAF kinase, which can subsequently activate the MAPK effector kinase MEK and finally ERK. Translocation of MAPK to the nucleus regulates ETS/AP1 transcription factors responsible for regulating a large number of genes. In the context of c-MET signaling, this results in phenotypes such as cell proliferation, cell motility and cell cycle progression [46,58]. SHP2 can also link c-MET signaling to the MAPK cascade, as sequestration of SHP2 to GAB1 is responsible for extending the duration of MAPK phosphorylation [59,60].

The other major arm of c-MET signaling is the

PI3K/AKT signaling axis. The p85 subunit of PI3K can bind either directly to c-MET or indirectly through GAB1, which then signals through AKT/PKB. This axis is primarily responsible for the cell-survival response of c-MET signaling [61].

The transformation phenotype downstream of c-MET activation has been shown to be mediated by the phosphorylation of JNK via its binding to CRK [48,62], as well as putatively through STAT3. STAT3 binds directly to c-MET, resulting in STAT3 phosphorylation, dimerization and translocation to the nucleus. Although this has been shown to be involved in tubulogenesis [51] and invasion [63], conflicting reports have found that although STAT3 plays a role in c-MET-mediated tumorigenesis, it is not through these two phenotypes [52].

In response to changes in the extracellular environment, activation of c-MET can regulate processes involved in cellular migration, mediated in part by FAK. FAK is activated through phosphorylation by SRC family kinases, which have been shown to associate directly with c-MET [45]. The c-MET–SRC–FAK interaction leads to cell migration as well as the promotion of anchorage-independent survival and growth [64,65]. In addition, SRC activation may feedback positively on c-MET phosphorylation [43,64]. Owing to this, combinatorial therapies involving both c-MET and SRC inhibitors show promise in the treatment of cancers that are dependent on either kinase [66–68].

Negative regulation of c-MET

Negative regulation of the c-MET receptor is crucial for its tightly controlled activity and can occur through a number of mechanisms. The Tyr-1003 site, located in the juxtamembrane domain, is a negative regulatory site for c-MET signaling (absent in the TPR–MET oncoprotein) that acts as a binding site for the E3 ubiquitin ligase CBL, resulting in c-MET ubiquitination, endocytosis and degradation [69,70]. Regulation of c-MET signaling is also accomplished via its binding to various protein-tyrosine phosphatases (PTPs), including dEP1 (or PTPrI) and LAR (or PTPrF) [71,72] and the nonreceptor PTPs PTP1B and TCPTP [73]. These PTPs modulate c-MET signaling by dephosphorylation of either the tyrosines in the c-MET kinase domain (in the case of PTP1b and TCPTP) or the docking tyrosines (in the case of dEP1). Binding of PLCγ to c-MET results in the activation of PKC, which can then negatively regulate c-MET receptor phosphorylation and activity [74,75]. Independent of PKC activation, an increase in intracellular calcium levels can also lead to negative c-MET regulation [76].

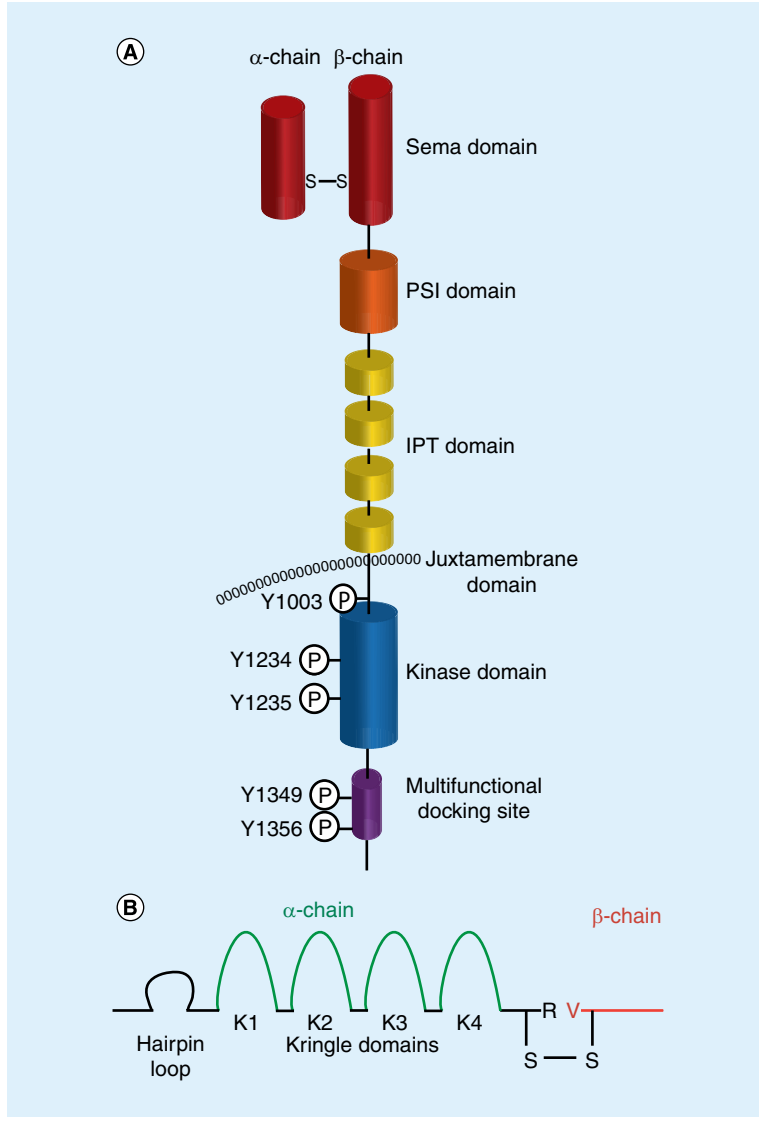

Figure 1. Domain structure of c-MET and HGF. (A) c-MET is formed by proteolytic processing into an α/β heterodimer. The N-terminal 500 residues, including the α-subunit and part of the β-subunit, form a Sema domain. The PSI domain spans 50 residues and is followed by four IPT domains. Intracellularly, c-MET contains the tyrosine kinase domain, flanked by distinctive juxtamembrane and carboxy-terminal sequences. This portion of c-MET contains the catalytic Tyr-1234 and -1235, while the juxtamembrane Tyr-1003 negatively regulates c-MET. The C-terminal tail contains Tyr-1349 and -1356, which form a docking site for signaling molecules when c-MET is active. Domains in bold contain mutations identified in human cancers. **(B)** The c-MET ligand, HGF, is secreted by mesenchymal cells as a biologically inert precursor and is activated when extracellular proteases cleave between Arg-494 and Val-495. Mature HGF consists of a disulphide-bonded α- and β-chain. The α-chain contains an N-terminal hairpin loop followed by four kringle domains (K1–4). The β-chain is homologous to serine proteases.
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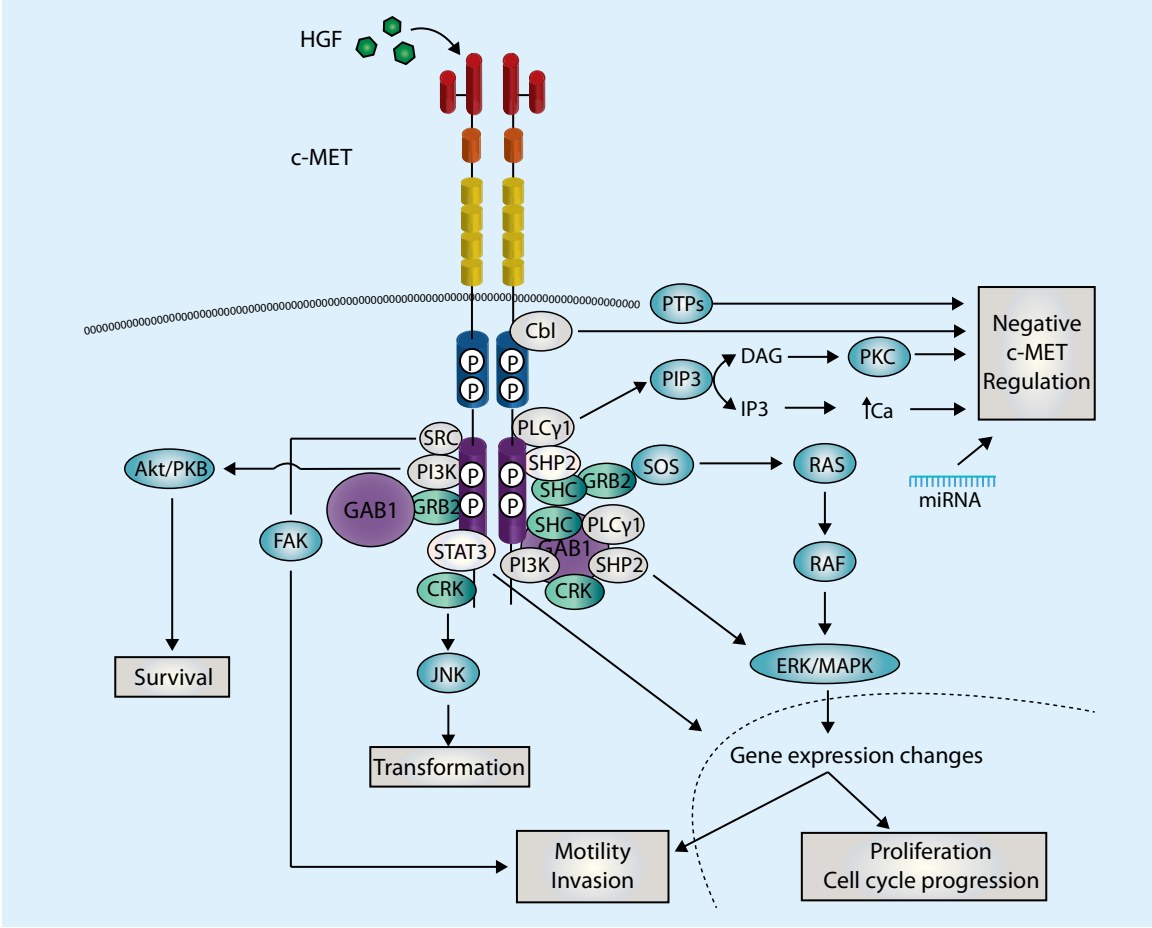

Figure 2. c-MET signaling adaptors and mediators. An overview of the signaling adaptors and mediators of HGF/c-MET signaling. HGF binding to c-MET results in receptor homodimerization and phosphorylation of two tyrosine residues within the c-MET catalytic loop. Subsequently, Tyr-1349 and -1356 in the carboxy-terminal tail become phosphorylated. These two tyrosines form a tandem SH2 recognition motif unique to c-MET and, when phosphorylated, recruit signaling effectors. Unique to c-MET is its binding with GAB1, a multiadaptor protein that, once bound to and phosphorylated by c-MET, creates binding sites for numerous downstream adaptors. GAB1 can bind either directly to c-MET or indirectly, through GRB2. Additional tyrosines, including Tyr-1313 and -1365, can also contribute to c-MET signaling as is described in the text. Negative regulation of the c-MET receptor is crucial for its tightly controlled activity and can occur through a number of mechanisms including recruitment of CBL, receptor dephosphorylation by phosphatases, the PLCγ pathway and miRNAs.
Reprinted with permission from [37].

Downregulation of c-MET protein expression can occur by means of a relatively novel mechanism involving miRNAs, which are endogenous small noncoding RNAs that negatively regulate protein expression by blocking the translation of and degrading the target's mRNA [77,78]. miRNAs have been shown to control a range of important cancer-related processes, such as proliferation, survival and metastasis. Both c-MET and HGF expression are regulated by miRNAs. c-MET has been reported as being downregulated by miR-152, miR-34b, miR-34c, miR-199*, miR-130a, miR-340, miR-198, miR-449, miR-133b, miR-1, miR-206 and miR-23b [79–90]. Little is currently known about miRNAs that modulate HGF expression; however, several studies report miRNAs that are suppressed upon HGF stimulation. Suzuki *et al.* reported that let-7a, miR-23a and miR-200C (which target RAS, MYC and ZEB1, respectively) were downregulated in head and neck carcinoma cells stimulated with HGF [91]. Garofalo and collaborators also reported that EGFR and c-MET can control the expression of miR-30b, miR-30C, miR-221 and miR-222, whereas miR-103 and miR-203 are uniquely controlled by c-MET expression/activity [92]. Similarly, upon HGF

stimulation, hepatic stellate cells upregulate the expression of miR-29, which targets and therefore decreases the synthesis of collagen I and IV [93]. Lastly, miR-519c, a negative regulator of HIF-1α, and therefore angiogenesis in general, is downregulated when HUVEC cells are HGF stimulated [94]. Even without a complete understanding of how miRNAs control HGF/cMET expression, it is likely that they will be found to play important roles in cancer progression.

c-MET transactivation by coreceptors

The potency, endurance and specificity of c-MET-triggered pathways is secured by a network of upstream signaling coreceptors that physically associate with c-MET at the cell surface [40]. For instance, the v6 splice variant of the hyaluronan receptor CD44 links c-MET signaling to the actin cytoskeleton via GRB2 and the ezrin-radixin-moesin family of proteins in order to recruit SOS, which then amplifies RAS ERK signaling [95]. ICAM-1 can also substitute for CD44v6 as a coreceptor for c-MET in *CD44v6* knockout mice, resulting in similar c-MET pathway activation [96]. c-MET binding to the integrin α6β4 creates a supplementary docking platform on integrin to bind signaling adaptors, leading to specific enhancement of PI3K, RAS and SRC activation [97,98]. The G-protein-coupled receptor agonists lysophosphatidic acid, bradykinin, thrombin and carbachol, can induce c-MET phosphorylation [99], although the functional consequences of these interactions are still unclear.

Several other RTKs form a crucial subset of c-MET coreceptors that result in c-MET transactivation and they have been studied in great depth due to their potential importance in the development of resistance to cancer therapeutics [100]. For instance, several members from the family of semaphorin receptors, including the plexins and neuropillins can transactivate c-MET in the absence of HGF when stimulated by their semaphorin ligands [101–103]. Interaction of c-MET with the closely related RON receptor has also been shown to cause transphosphorylation of the c-MET receptor in the absence of HGF [104]. Interestingly, it was recently shown that transactivation of RON by c-MET may be a feature of cancer cells that are 'addicted' to c-MET signaling [105]. Transactivation between c-MET and both the PDGFR and AXL was found to play a role in bladder cancer [106].

c-MET has also been shown by multiple studies to interact directly with the EGFR, allowing activation of c-MET after stimulation of cells with the EGFR ligands EGF or TGF-α [107]. Stimulation of cells expressing both c-MET and EGFR with EGF resulted in phosphorylation of c-MET and stimulation with ligands for both receptors resulted in synergistic activation of downstream modulators, indicating mutual activation of these two pathways [108]. Evidence also exists for c-MET interaction with the other EGFR family members ERBB2 and ERBB3, causing transactivation of both receptors [109,110]. c-MET/EGFR cross-talk has important clinical significance, as several studies have shown that patients treated with EGFR TKIs can develop resistance to the drug by amplification of the *MET* gene. Further discussion of this important finding can be found later in this article.

HGF/c-MET deregulation in cancer

MET was originally identified as an oncogene in the 1980s [111], isolated first from a human osteosarcoma cell line treated with the carcinogen *N*-methyl-*N*-nitro-*N*-nitrosoguanidine. The *MET* identified in this cell line contained a chromosomal rearrangement that fused the tyrosine kinase domain of c-MET to an upstream translocating promoter region (TPR). This rearrangement caused constitutive dimerization and therefore activation of the encoded protein [112]. Expression of *TPR–MET* in transgenic mice resulted in the development of multiple epithelial-derived tumors [113]. In humans, the *TPR–MET* translocation has been reported in both the precursor lesions of gastric cancers and in the adjacent normal mucosa, suggesting that this genetic lesion could predispose the development of gastric carcinomas [114]. These findings with TPR–MET became the starting point for an ongoing effort to uncover all the oncogenic activites of c-MET. Currently, c-MET and HGF are being studied in a wide range of different cancers [301].

As described above, c-MET signaling is an intricate and highly regulated process. During tumor growth or cancer progression, mechanisms have been identified that can result in constitutive or prolonged activation of c-MET. Data collected from *in vitro* and *in vivo* tumor models suggest that these mechanisms typically occur via three mechanisms:

- The occurrence of specific genetic lesions, including translocations, gene amplifications and activating mutations;
- Transcriptional upregulation of the c-MET protein in the absence of gene amplification;
- Ligand-dependent autocrine or paracrine mechanisms [115].

MET gene mutation

Proof-of-concept for the role of c-MET in human cancers was provided following the identification of activating point mutations in the germ line of patients with hereditary papillary renal carcinomas [116,117]. However, sporadically and spontaneously

occurring oncogenic *MET* mutations remain rare, occuring in approximately 2–3% of patients [117,118]. Activating mutations have been described mainly in non-small-cell lung cancer (NSCLC), hereditary and spontaneous renal carcinomas, hepatocellular carcinomas, gliomas, gastric cancers, squamous cell carcinomas of the head and neck, and breast carcinomas [119–124]. Potentially oncogenic point mutations that were reported in cancers include those that generate an alternative splice variant lacking exon 14, which encodes for the juxtamembrane domain of c-MET [119,125]; point mutations in the kinase domain that render the enzyme constitutively active [120]; and a mutation at Tyr-1003 that abrogates CBL binding leading to constitutive c-MET expression [70,126,127]. In contrast, several other point mutations (i.e., N375S, R988C and T1010I) have been reported as single nucleotide polymorphisms and were found to lack transforming abilities [128–130]. To date, missense mutations and single nucleotide polymorphisms have been found in the SEMA and juxtamembrane domains of *MET* (Figure 1).

MET gene amplification

The most frequent genetic alteration of *MET* is gene amplification, resulting in high c-MET protein expression and consequent activation. *MET* amplification is facilitated since it forms part of the chromosomal fragile site FRA7G [131–133]. High protein expression, detected by immunohistochemistry, as a result of *MET* amplification has been associated with poor prognosis in NSCLCs, colorectal and gastric cancers [134–138]. Reports that *MET* is more frequently amplified in metastatic compared with primary tumors suggest a role for this gene in the late phases of malignant progression [138–140]. The importance of c-MET activation by other RTKs has gained considerable interest during the last 5 years, following the report that a lung adenocarcinoma cell line sensitive to the EGFR inhibitor erlotinib developed resistance to this drug by amplification of the *MET* gene [141]. This finding is further supported by clinical evidence that lung tumors from four EGFR tyrosine kinase inhibitor (TKI) refractory patients displayed *MET* amplification as well [141]. Furthermore, cells with amplified *MET* are now sensitive to dual treatment with EGFR and MET inhibitors, suggesting that inhibition of both receptors could result in disease stabilization. In a large cohort of EGFR TKI-treated lung cancer patients who had relapsed, approximately 18% displayed *MET* amplification [135,142–144] or high HGF levels [145]. Based on this evidence, as well as evidence of c-MET–EGFR RTK cross-talk discussed earlier, two putative mechanisms have been suggested by which c-MET activation may bypass EGFR TKI sensitivity:

- c-MET autophosphorylation creates docking sites where downstream signaling proteins can transduce prosurvival signals via the MAPK and PI3K/AKT signaling pathways;
- Transphosphorylation of other ERBB receptors may amplify the protumorigenic invasive program of c-MET. Other RTKs may allow cells resistant to c-MET TKIs to bypass this inhibition using similar cross-talk mechanisms.

c-MET protein overexpression

Increased protein expression as a consequence of transcriptional upregulation in the absence of gene amplification is the most frequent cause of constitutive c-MET activation in human tumors [12] and has been reported in a growing number of carcinomas including thyroid [137,146], colorectal [139,147,148], ovarian [149] pancreatic [16,137], lung [13,150] and breast [151], to name a few. Hypoxia-induced overexpression is another method by which c-MET expression can be aberrantly increased in cancer. Hypoxia, caused by a lack of oxygen diffusion to the center of a growing tumor, has been demonstrated to activate *MET* transcription *in vitro* and *in vivo* [152]. Hypoxia activates the *MET* promoter, via the transcription factor HIF1α, which itself is regulated by the concentration of intracellular oxygen [153].

c-MET autocrine or paracrine activation

Ligand-dependent autocrine or paracrine c-MET stimulation is another mechanism of c-MET activation. HGF is expressed ubiquitously within human tissues and has been found to be frequently overexpressed in the reactive stroma of primary tumors [154]. This supports the formation of paracrine positive feedback loops, which in turn can support the dissemination of cancer cells to distant locations. The autocrine stimulation of c-MET has also been identified in cancer cells [155,156] and appears to be associated with increased aggressiveness and metastatic potential of tumor cells [17,157,158].

c-MET as a prognostic marker

Regardless of the mechanism, high levels of HGF and/or c-MET expression have been associated with poor patient outcome. Nearly half of lung adenocarcinoma patients demonstrate high expression of HGF and c-MET [15,159,160]. Such high expression patterns have been reported to correlate with increased tumor growth rate and metastasis, poor prognosis and resistance to radiotherapy [157,161,162]. High levels of HGF/c-MET in breast carcinoma has been correlated with higher

histological grade, poorer prognosis and high tumor cell proliferative index [163–165], and with a greater incidence of metastases [166,167]. In these reports, c-MET overexpression was observed in hypoxic areas and correlated directly with poorer overall survival (OS). Overall, reports tend to show that high levels of HGF and/or c-MET expression are found in a significant subset of primary patient samples and, importantly, high levels of these proteins in distant metastases are often correlated with worse prognosis.

c-MET as a therapeutic target

Due to its diverse roles in cellular processes important to oncogenesis and cancer progression, c-MET has been postulated as an important target in anticancer therapy [40,168–170]. Preclinical studies have shown that in animal models, the inhibition of c-MET impairs tumorigenic and metastatic properties of cancer cells [171–176]. As such, a few molecules targeting c-MET have recently been evaluated in clinical trials and several articles have been published on this subject [12,177,178]. c-MET inhibitors include small molecule TKIs and biological antagonists, targeting either the ligand or the receptor [12,178,179]. Mechanisms of action of these inhibitors are summarized in Figure 3.

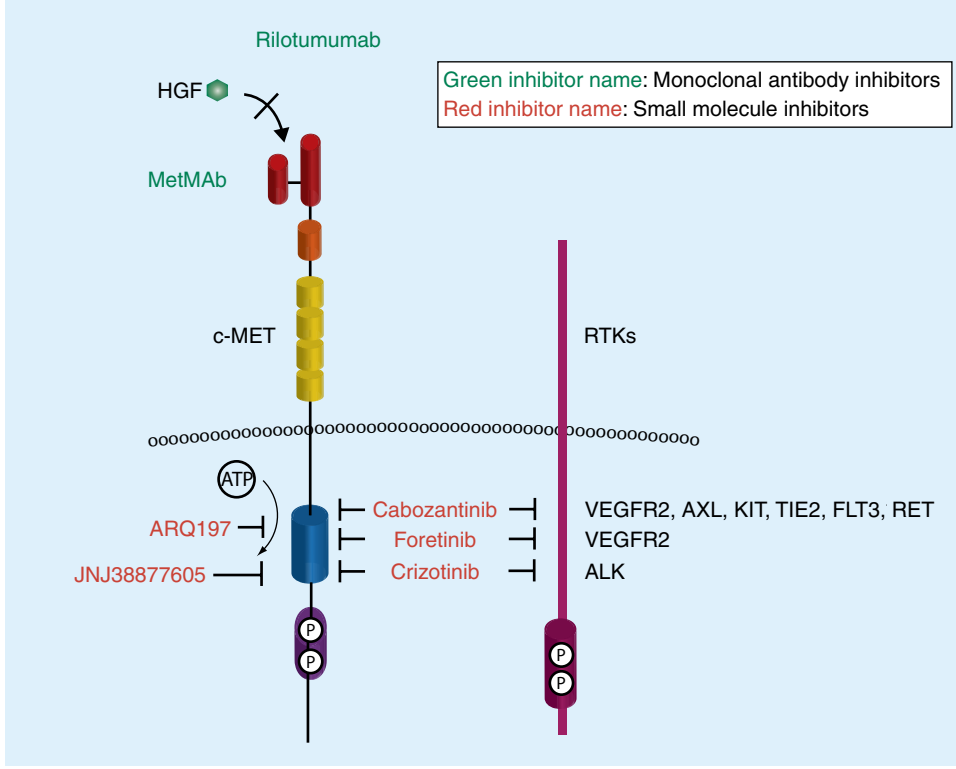

Figure 3. c-MET/HGF inhibitors in clinical trials. C-MET inhibitors currently being evaluated in clinical trials include small molecule tyrosine kinase inhibitors and biological antagonists, targeting either the ligand or the receptor. C-MET-specific inhibitors include the non-ATP competitive inhibitor tivantinib (ARQ 197), and the ATP-competitive inhibitor JNJ38877605. Other multikinase inhibitors include cabozantinib (XL184), foretinib (XL880), crizotinib (PF02341066) and dacomitinib (PF00299804). Anti-c-MET monoclonal antibodies have also displayed promising results in tumors with high HGF/c-MET levels, and include, Rilotumumab (AMG102), which is an anti-HGF monoclonal antibody that interferes with c-MET's activation by HGF, and MetMAb (OA-5D5), a human, monovalent, antagonistic anti-MET antibody.
RTK: Receptor tyrosine kinase.

Promising c-MET-specific inhibitors are currently being clinically evaluated. The most advanced in clinical trials is the non-ATP competitive c-MET inhibitor tivantinib (ARQ 197), which recently completed a Phase II clinical trial showing an increased response rate and OS when combined with erlotinib [180]. Based on these results, tivantinib has started the ATTENTION Phase III trial (randomized, double-blinded, placebo-controlled) in previously treated patients with advanced or metastatic wild-type EGFR NSCLC (NCT01377376) [302]. Prior to this study, a Phase I trial demonstrated that 27% (14 out of 51 patients) had stable disease for over 4 months [181]. However, little is known regarding the mechanism of action of this inhibitor [182,183].

Several of the other c-MET inhibitors currently in clinical trials are multikinase inhibitors, targeting several different RTKs in addition to c-MET. Cabozantinib (XL184), a multikinase inhibitor that targets c-MET, VEGFR2, AXL, KIT, TIE2, FLT3 and RET, has reached Phase II/III trials showing reduction of tumor mass in almost 60% of glioblastoma patients and an overall disease control rate of almost 50% in all of the patients who received this inhibitor in Phase II studies [184,185]. Exelixis has announced two different Phase III clinical trials to test cabozantinib: one in metastatic castration-resistant prostate cancer (registered under the name of '306) [303] and the other is the EXAM trial for medullary thyroid cancer patients (NCT00704730) [304]. Preliminary results from the latter trial demonstrate a significant improvement in median progression-free survival (PFS) by 7.2 months compared with placebo: median PFS for cabozantinib- and placebo-treated patients being 11.2 versus 4.0 months, respectively (hazard ration [HR] = 0.28). Lastly, cabozantinib is

being combined with erlotinib [186]. Several Phase II trials have been initiated for foretinib as a single agent or in combination with EGFR inhibitors in advanced or metastatic NSCLC patients who have failed chemotherapy [305] and in metastatic/recurrent triple negative (NCT01147484) [306] or ERBB2-positive breast cancer patients (NCT01138384) [307]. Lastly, the dual MET and ALK inhibitor crizotinib (PF02341066), which was recently approved for NSCLC patients with *ALK* gene rearrangement, is being tested as a single agent (NCT00585195) [308] or in combination with the irreversible pan-HER inhibitor dacomitinib (PF00299804) in Phase I/II trials involving advanced NSCLC patients (NCT01121575 and NCT00965731) [309,310].

A different class of c-MET-targeted agents includes monoclonal antibodies, which have displayed promising results in tumors with high HGF/c-MET levels. Rilotumumab (AMG102) is an anti-HGF monoclonal antibody that interferes with c-MET activation by HGF [187]. Rilotumumab is currently being evaluated in Phase I/II studies alone or in combination with the EGFR-blocking antibody panitumumab [311]. Previous studies have shown that rilotumumab decreases c-MET phosphorylation and can stabilize the progression of certain solid tumors [188,189]. Onartuzumab (also known as MetMAb or OA-5D5) is a human monovalent antagonistic anti-MET antibody [190] that has shown promising preclinical results. It was able to inhibit glioblastoma U87, as well as pancreatic BxPC3 and KP4 tumor xenograft growth by causing a decrease in cellular proliferation and motility [190,191]. A recent Phase II clinical trial involving onartuzumab in combination with erlotinib in NSCLC patients did not result in significant improvement in both PFS and OS [192]. However, patients with low c-MET expression tumors determined by immunohistochemistry, when treated with onartuzumab and erlotinib, had a worse OS than when compared with the erlotinib plus placebo arm (PFS HR = 2.01; OS HR = 3.02), while c-MET positive tumors (scoring a 2+ or 3+, using a scale of 0–3+ by immunohistochemistry) benefited from the combinational treatment (PFS HR = 0.56; OS HR = 0.55). Nonetheless, this antibody has now entered a Phase III clinical trial (MetLung) in combination with erlotinib, which will target patients with incurable NSCLC and be identified as c-MET positive (NCT01456325) [312]. So far, monoclonal antibodies in preclinical and clinical studies have only demonstrated a partial or complete response in patients (or cell lines) with high c-MET levels or an HGF/c-MET autocrine loop [188–191,193].

An important issue relevant to the development of c-MET inhibitors is the identification of molecular profile predictive of tumors that would benefit from this targeted therapy. Several studies on a large panel of cell lines demonstrated that upon treatment with a c-MET TKI, those with constitutive c-MET activation due to the presence of an autocrine loop or *MET* amplification undergo apoptosis both *in vitro* and *in vivo*. These studies identified a subset of tumors, based on genetic alterations, which appear to be dependent on sustained c-MET activity for their growth and survival, such that treatment with a single agent may inhibit tumor growth and induce cell death [125,171,174,175,193,194]. This appears to be the case in the onartuzumab trial, as a greater benefit from onartuzumab plus erlotinib compared with erlotinib alone was observed mainly in high c-MET expression patients (scoring a 2+ or 3+ on a scale of 0–3 by immunohistochemistry) [192].

Blocking of HGF or c-MET using antibodies and TKIs appears to be a promising therapeutic strategy, and one anticipates that many studies will be initiated in the years to come. All of the c-MET targeted agents discussed here exhibit the potential to reach approval to be administered, either alone or in combination with other kinase inhibitors, for the treatment of solid tumors.

Potential resistance factors to c-MET inhibitors

As with other RTK inhibitors, cancer cells and tumors treated with c-MET inhibitors eventually develop resistance [195,196]. Based on preclinical cell-line studies, three mechanisms have been hypothesized. First, cells treated with c-MET TKIs at high doses develop a dependence on EGFR signaling as a way to circumvent c-MET inhibition [197,198]. Cells harboring high *MET* copy number can undergo an oncogenic switch to ERBB dependency, similar to the oncogenic switch from EGFR to c-MET in NSCLC cells. The second mechanism may occur when c-MET dependent NSCLC and gastric cancer cell lines exposed to increasing doses of c-MET inhibitors acquire amplifications of wild-type *MET* and *KRAS*, which enables cells to overcome the inhibitory threshold of the compound to sustain high MAPK and PI3K/AKT activation [196]. Finally, the third potential mechanism of resistance reported is the acquisition of a point mutation in the kinase domain of c-MET (Y1230H) [199]. While this mutation had been previously described as a somatic mutation in hereditary and sporadic renal carcinomas [120], it may overcome the inhibitory effect of any c-MET kinase inhibitor.

In recent years, the aim of anticancer therapeutics has shifted away from personalized therapies that selectively target a single molecule, towards combinatorial therapies: that is, finding drugs or combinations of drugs that are able to inhibit multiple pathways both in cancer cells and cells of the microenvironment [195].

Clinical experience has shown that patients treated by a single-targeted therapy often develop drug resistance and relapse. In addition, we are more aware that the tumor microenvironment plays an important role in maintaining the tumor niche; therefore, combination therapies must attempt to inhibit not only neoplastic cells, but also the vessels and stromal cells (cancer-associated fibroblasts or tumor-associated macrophages) that provide them with the nutrients and growth factors critical to their survival [200]. Finally, the use of multikinase inhibitors have the potential to delay the development of resistance, since it is known that neoplastic cells are able to undergo an 'oncogenic switch' by which the cell that was originally dependent on a single oncogene can rely on the activation of alternative(s) oncogenes [195,196].

Future perspective

Over 25 years since its first discovery, much is known about the mechanisms and pathways involved in c-MET signaling. As our knowledge of these pathways grows, the c-MET receptor emerges as an important prognostic indicator and target for personalized cancer therapy. Results from early phase clinical trials are beginning to highlight the importance of HGF/c-MET signaling in cancer biology, as inhibition of c-MET receptor activity *in vivo* has shown promising results in reduction of cancer cell growth and impaired angiogenesis. Importantly, inhibition of c-MET can overcome resistance to anti-EGFR therapies and this is now under consideration for use in combination with other RTK inhibitors to treat advanced NSCLC patients. If lessons can be learned from clinical trials with EGFR inhibitors, it appears as though small-molecule TKIs may be more effective when the receptor is mutated, while inhibitory antibodies are more efficacious when the receptor protein is overexpressed. Owing to the fact that c-MET mutations are so rarely found in solid tumors, c-MET-blocking antibodies may prove to be the more promising therapeutic. If this is the case, then the challenge will then be to combine this treatment with other important cross-talk mechanisms of c-MET activation in cancer, leading to further improvements in the efficacy of novel and personalized anticancer therapeutics.

Executive summary

c-MET & cancer

- c-MET is a receptor tyrosine kinase that binds to its ligand HGF. After activation, c-MET becomes autophosphorylated on its kinase domain, leading to activation of its C-terminal tyrosines, creating a binding site for a wide range of downstream mediators.
- c-MET-pathway activation leads to phenotypes such as cell survival, transformation, motility, invasion and proliferation.
- c-MET is highly expressed in numerous cancers, most frequently by gene amplification and/or protein overexpression. High c-MET and/or HGF expression has been associated with poor prognosis.

Clinical trials with c-MET inhibitors

- c-MET inhibitors currently in clinical trials include the small molecule tyrosine kinase inhibitors tivantinib, cabozantinib, foretinib and crizotinib, while monoclonal antibodies targeting either the ligand or the receptor include rilotumumab and onartuzumab.
- Drug combination trials involving c-MET inhibitors and other targeted anticancer agents are ongoing, with the aim of delaying or preventing the onset of acquired resistance.

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