An overview of the c-MET signaling pathway

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Abstract: c-MET is a receptor tyrosine kinase that, after binding with its ligand, hepatocyte growth factor, activates a wide range of different cellular signaling pathways, including those involved in proliferation, motility, migration and invasion. Although c-MET is important in the control of tissue homeostasis under normal physiological conditions, it has also been found to be aberrantly activated in human cancers *via* mutation, amplification or protein overexpression. This paper provides an overview of the c-MET signaling pathway, including its role in the development of cancers, and provides a rationale for targeting the pathway as a possible treatment option.

Keywords: cancer, c-MET, hepatocyte growth factor (HGF), *MET*, signaling, receptor tyrosine kinase

Receptor tyrosine kinases

Receptor tyrosine kinases (RTKs) regulate many essential cellular processes in mammalian development, cell function and tissue homeostasis. However, although RTKs are important in normal physiology, dysregulation of certain RTKs has been implicated in the development and progression of many types of cancer [Krause and Van Etten, 2005]. For example, expression of the c-MET RTK and its ligand, hepatocyte growth factor (HGF), has been observed in tumor biopsies of most solid tumors and c-MET signaling has been documented in a wide range of human malignancies [Peruzzi and Bottaro, 2006; Birchmeier *et al.* 2003; Comoglio and Trusolino, 2002]. This paper provides an overview of the c-MET signaling pathway, including its role in the development of cancers, and provides a rationale for targeting the pathway as a possible treatment option.

Hepatocyte growth factor and c-MET: structure and function

The c-*MET* proto-oncogene is located on chromosome 7q21-31. Its transcription is regulated by Ets (E-twenty six), Pax3 (paired box 3), AP2 (activator protein-2) and Tcf-4 (transcription factor 4) [Boon *et al.* 2002; Epstein *et al.* 1996; Gambarotta *et al.* 1996; Boccaccio *et al.* 1994], and it is expressed as multiple mRNA transcripts of 8, 7, 4.5, 3 and 1.5 kilobases [Park *et al.* 1986]. The protein product of this gene is the c-MET tyrosine kinase. This cell surface receptor is expressed in epithelial cells of many organs, including the liver, pancreas, prostate, kidney, muscle and bone marrow, during both embryogenesis and adulthood [Comoglio *et al.* 2008].

The c-MET receptor is formed by proteolytic processing of a common precursor in the post-Golgi compartment into a single-pass, disulphide-linked α/β heterodimer (Figure 1a.) [Trusolino and Comoglio, 2002]. The extracellular portion of c-MET is composed of three domain types. The N-terminal 500 residues fold to form a large semaphorin (Sema) domain, which encompasses the whole α-subunit and part of the β-subunit. The Sema domain shares sequence homology with domains found in the semaphorin and plexin families. The PSI domain (found in plexins, semaphorins and integrins) follows the Sema domain, spans approximately 50 residues and includes four disulphide bonds. This domain is connected to the transmembrane helix *via* four immunoglobulin–plexin–transcription (IPT) domains, which are related to immunoglobulin-like domains and are found in integrins, plexins and transcription factors. 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 by two independent studies as both a motility factor and a scatter factor for hepatocytes, and this factor was later found to be the same molecule: HGF, also known as scatter factor (SF) [Weidner *et al.* 1991; Nakamura *et al.* 1989; Stoker *et al.* 1987]. HGF acts as a pleiotropic factor and cytokine, promoting cell proliferation, survival,
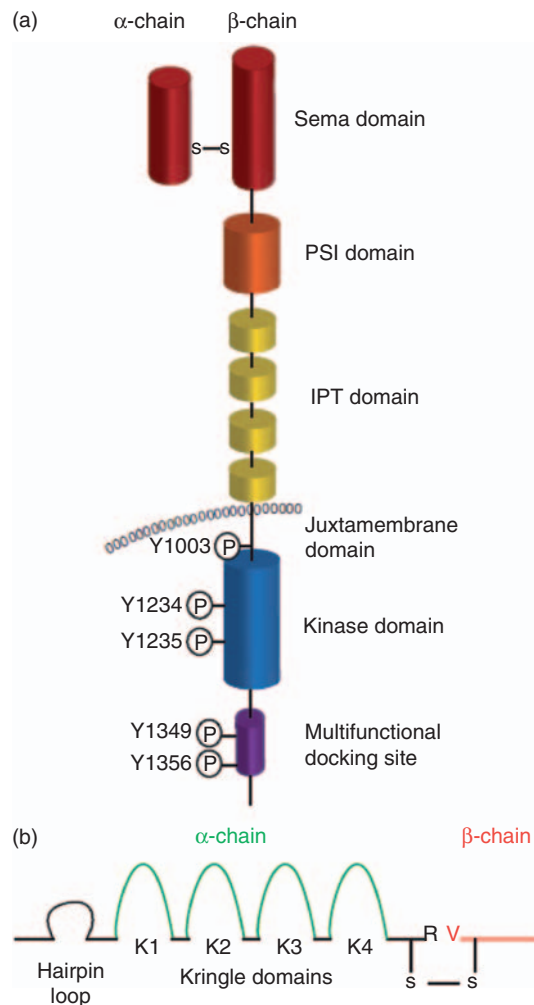
Figure 1. Domain structure of c-MET and hepatocyte growth factor (HGF). (a) The c-MET receptor is formed by proteolytic processing of a common precursor into a single-pass, disulphide-linked α/β heterodimer. The extracellular portion of c-MET is composed of three domain types. The N-terminal 500 residues fold to form a large semaphorin (Sema) domain, which encompasses the whole α-subunit and part of the β-subunit. The plexin—semaphorin—integrin (PSI) domain follows the Sema domain, spans approximately 50 residues and includes four disulphide bonds. This domain is connected to the transmembrane helix *via* four immunoglobulin—plexin—transcription (IPT) domains, which are related to immunoglobulin-like domains. Intracellularly, the c-MET receptor contains a tyrosine kinase catalytic domain flanked by distinctive juxtamembrane and carboxy-terminal sequences. This portion of c-MET contains the catalytic tyrosines Y1234 and Y1235, which positively modulate enzyme activity, while the juxtamembrane tyrosine 1003 negatively regulates c-MET by recruiting the ubiquitin ligase casitas B-lineage lymphoma (c-CBL). The multifunctional docking site in the C-terminal tail contains tyrosines Y1349 and Y1356, which recruit several transducers and adaptors when c-MET is active. (b) The c-MET ligand, hepatocyte growth factor (HGF), is secreted by mesenchymal cells as a single-chain, biologically inert precursor and is converted into its bioactive form when extracellular proteases cleave the bond between Arg494 and Val495. The mature form of HGF consists of an α- and β-chain, which are held together by a disulphide bond. 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), K1—4. The β-chain is homologous to the serine proteases of the blood-clotting cascade, but lacks any proteolytic activity. Adapted from Comoglio *et al.* [2008].

motility, scattering, differentiation and morpho-genesis [Basilico *et al.* 2008; Birchmeier *et al.* 2003; Trusolino and Comoglio, 2002]. In addition, HGF appears to play a protective role in several diseases, including liver cirrhosis [Ueki *et al.* 1999], lung fibrosis [Watanabe *et al.* 2005] and progressive nephropathies [Liu and Yang, 2006; Okada and Kalluri, 2005]. HGF is secreted by mesenchymal cells as a single-chain, biologically inert precursor and is converted into

its bioactive form when extracellular proteases cleave the bond between Arg494 and Val495. The mature form of HGF consists of an α- and β-chain, which are held together by a disulphide bond. 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). The β-chain is homologous to serine proteases of the blood-clotting cascade, but lacks proteolytic activity (Figure 1b).

Physiologically, c-MET is responsible for the cell-scattering phenotype, as first demonstrated with MDCK cells treated with HGF [Zhu *et al.* 1994]. This process involves the disruption of cadherin-based cell–cell contacts and subsequent cell motility, and is a key epithelial function in embryogenesis and wound repair [Corso *et al.* 2005]. During embryogenesis, this motility function of c-MET is crucial for the long-range migration of skeletal muscle progenitor cells. Ablation of the *MET* or *Hgf* gene in mice results in the complete absence of all muscle groups derived from these cells [Bladt *et al.* 1995]. During development, c-MET and HGF provide essential signals for survival and proliferation of hepatocytes and placental trophoblast cells; consequently, *MET* or *Hgf* knockout embryos show markedly reduced liver size. As well, altered placental development in *Hgf* and *MET* knockout mice is responsible for the death of these animals *in utero* [Schmidt *et al.* 1995; Uehara *et al.* 1995].

HGF/c-MET signaling

The complex phenotype that results from c-MET signaling involves a number of molecular events, which have been described in detail in previous reviews [Trusolino *et al.* 2010; Liu *et al.* 2008; Peruzzi and Bottaro, 2006; Birchmeier *et al.* 2003; Maulik *et al.* 2002b]. HGF binding to c-MET results in receptor homodimerization and phosphorylation of two tyrosine residues (Y1234 and Y1235) located within the catalytic loop of the tyrosine kinase domain [Rodrigues and Park, 1994]. Subsequently, tyrosines 1349 and 1356 in the carboxy-terminal tail become phosphorylated. These two tyrosines form a tandem SH2 recognition motif unique to c-MET ($Y^{1349}VHVX_3Y^{1356}VNV$) [Ponzetto *et al.* 1994]. When these tyrosines become phosphorylated, they recruit signaling effectors that include the adaptor proteins Growth factor receptor-bound protein 2 (GRB2) [Fixman *et al.* 1996], Src homology-2-containing (SHC) [Pelicci *et al.*

1995] and v-crk sarcoma virus CT10 oncogene homolog (CRK) and CRK-like (CRKL) [Sakkab *et al.* 2000; Garcia-Guzman *et al.* 1999], the effector molecules phosphatidylinositol 3-kinase (PI3K), phospholipase Cγ (PLCγ) and v-src sarcoma (Schmidt-Ruppin A-2) viral oncogene homolog (SRC) [Ponzetto *et al.* 1994], Src homology domain-containing 5' inositol phosphatase (SHIP-2) [Koch *et al.* 2005] and the transcription factor signal transducer and activator of transcription (STAT-3) [Zhang *et al.* 2002; Boccaccio *et al.* 1998] (Figure 2). In addition, unique to c-MET is its association with the adaptor protein GRB2-associated binding protein 1 (GAB1) [Weidner *et al.* 1996], a multi-adaptor protein that, once bound to and phosphorylated by c-MET, creates binding sites for more downstream adaptors. GAB1 can bind either directly to c-MET or indirectly, through GRB2. Additional tyrosines can also contribute to c-MET signaling. When Y1313 is phosphorylated, it binds and activates PI3K, which probably promotes cell viability and motility [Maulik *et al.* 2002a]. In addition, Y1365 regulates cell morphogenesis when phosphorylated [Maulik *et al.* 2002a].

The downstream response to c-MET activation relies on stereotypical signaling modulators common to many RTKs. These pathways have been reviewed in detail [Trusolino *et al.* 2010], and are summarized in Figure 2. For activation of the Mitogen activated protein kinase (MAPK) cascades, c-MET activation stimulates the activity of the rat sarcoma viral oncogene homolog (RAS) guanine nucleotide exchanger Son of Sevenless (SOS) *via* binding with SHC and GRB2 [Graziani *et al.* 1993], leading to the activation of RAS. This leads to the indirect activation of v-raf murine sarcoma viral oncogene homolog B1 (RAF) kinases, which can subsequently activate the MAPK effector kinase MEK and finally MAPK, which can then translocate to the nucleus to activate 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 [Paumelle *et al.* 2002; Fixman *et al.* 1996]. Src homology 2 domain-containing phosphatase-2 (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 [Maroun *et al.* 2003; Schaeer *et al.* 2000].
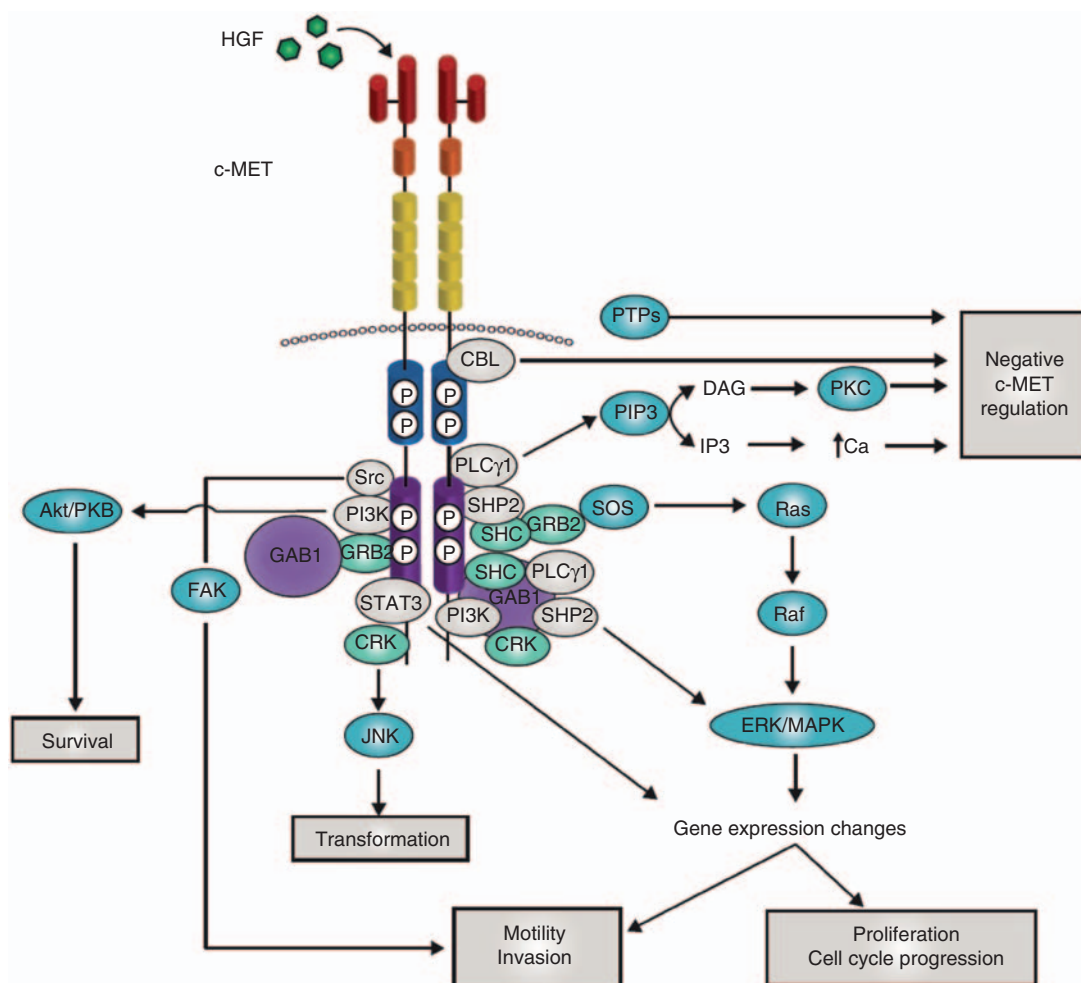
Figure 2. c-MET signaling adaptors and mediators. When the tyrosines within the multifunctional docking site become phosphorylated they recruit signaling effectors, including the adaptor proteins growth factor receptor-bound protein 2 (GRB2), src homology 2 domain-containing (SHC), v-crk sarcoma virus CT10 oncogene homolog (CRK) and CRK-like (CRKL); the effector molecules phosphatidylinositol 3-kinase (PI3K), phospholipase Cγ (PLCγ) and SRC, the src homology 2 domain-containing 5' inositol phosphatase SHIP-2, and the signal transducer and activator of transcription STAT3. In addition, unique to c-MET is its association with the adaptor protein GRB2-associated binding protein 1 (GAB1), a multi-adaptor protein that, once bound to and phosphorylated by c-MET, creates binding sites for more downstream adaptors. GAB1 can bind either directly to c-MET or indirectly, through GRB2. The downstream response to c-MET activation relies on stereotypical signaling modulators common to many receptor tyrosine kinases. For activation of the mitogen-activated protein kinase (MAPK) cascades, c-MET activation stimulates the activity of the rat sarcoma viral oncogene homolog (RAS) guanine nucleotide exchanger son of sevenless (SOS) via binding with SHC and GRB2 leading to the activation of RAS. This leads to the indirect activation of v-raf murine sarcoma viral oncogene homolog B1 (RAF) kinases, which can subsequently activate MAPK effector kinase (MEK), and finally MAPK, which can then translocate to the nucleus to activate the transcription factors responsible for regulating a large number of genes, including those involved in cell proliferation, cell motility and cell cycle progression. 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. The p85 subunit of PI3K can bind either directly to c-MET or indirectly through GAB1, which then signals through AKT/protein kinase B. This axis is primarily responsible for the cell survival response to c-MET signaling. Transformation downstream of the c-MET receptor is mediated by the phosphorylation of Janus kinase 1 (JNK), which occurs *via* binding to CRK. STAT3 has also been implicated in transformation. The direct binding of STAT3 to c-MET results in STAT3 phosphorylation, dimerization and its translocation to the nucleus. This has been shown to result in tubulogenesis and invasion. However, other reports have found that, although STAT3 is required for c-MET-mediated tumorigenesis, it has no effect on proliferation, invasion or branching morphogenesis. Cellular migration is also mediated downstream of c-MET by focal adhesion kinase (FAK), which is localized to cellular adhesion complexes. FAK is activated through phosphorylation by SRC family kinases, which have been shown to directly associate with c-MET. The c-MET–SRC–FAK interaction leads to cell migration and the promotion of anchorage-independent growth. Negative regulation of the c-MET receptor is crucial for its tightly controlled activity. The Y1003 site, located in the juxtamembrane domain, is a negative regulatory site for c-MET signaling that acts by recruiting c-CBL. Regulation of c-MET signaling is also accomplished via its binding to various protein tyrosine phosphatases (PTPs). These PTPs modulate c-MET signaling by dephosphorylation of either the tyrosines in the c-MET kinase or the docking site. Finally, binding of PLCγ to c-MET results in the activation of protein kinase C (PKC), which can then negatively regulate c-MET receptor phosphorylation and activity. Independently of PKC activation, an increase in intracellular calcium levels can also lead to negative c-MET regulation. Adapted from Trusolino *et al.* [2010] and Birchmeier *et al.* [2003]. DAG, diacylglycerol; HGF, hepatocyte growth factor; IP3, inositol triphosphate; PIP3, phosphatidylinositol (3,4,5)-triphosphate.

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/protein kinase B. This axis is primarily responsible for the cell survival response to c-MET signaling [Xiao *et al.* 2001]. Transformation downstream of the c-MET receptor is mediated by the phosphorylation of Janus kinase 1 (JNK), which occurs *via* binding to CRK [Garcia-Guzman *et al.* 1999; Rodrigues *et al.* 1997]. STAT3 has also been implicated in transformation, although its proposed mechanism is controversial. The direct binding of STAT3 to c-MET results in STAT3 phosphorylation, dimerization and its translocation to the nucleus. This has been shown to result in tubulogenesis [Boccaccio *et al.* 1998] and invasion [Syed *et al.* 2011]. However, other reports found that, although it is required for c-MET-mediated tumorigenesis, it has no effect on proliferation, invasion or branching morphogenesis [Zhang *et al.* 2002]. Therefore, the role of STAT3 in c-MET signaling is probably context- and tissue-dependent.

Cellular migration is also mediated downstream of c-MET by focal adhesion kinase (FAK), which is localized to cellular adhesion complexes. FAK is activated through phosphorylation by SRC family kinases, which have been shown to associate directly with c-MET [Ponzetto *et al.* 1994]. The c-MET–SRC–FAK interaction leads to cell migration and the promotion of anchorage-independent growth [Hui *et al.* 2009; Rahimi *et al.* 1998]. In addition, SRC activation can positively feed back on c-MET activation [Organ *et al.* 2011; Hui *et al.* 2009]. Because of this, combinatorial therapies involving both c-MET and SRC inhibitors show promise in the treatment of cancers dependent on either kinase [Sen *et al.* 2011; Bertotti *et al.* 2010; Okamoto *et al.* 2010].

Negative regulation of the c-MET receptor is crucial for its tightly controlled activity, and can occur through a number of mechanisms. The Y1003 site, located in the juxtamembrane domain, is a negative regulatory site for c-MET signaling that acts by recruiting c-CBL (casitas B-lineage lymphoma) [Petrelli *et al.* 2002; Peschard *et al.* 2001]. Regulation of c-MET signaling is also accomplished via its binding to various protein tyrosine phosphatases (PTPs), including the receptor-type PTPs density enhanced phosphatase 1 (dEP1) (or PTPrI) and leukocyte common antigen-related molecule (LAR) (or PTPrF) [Machide *et al.* 2006; Palka *et al.* 2003], and the nonreceptor PTPs PTP1B and T-cell protein tyrosine phosphatase (TCPTP) [Sangwan *et al.* 2008]. 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). Finally, binding of PLCγ to c-MET results in the activation of protein kinase C (PKC), which can then negatively regulate c-MET receptor phosphorylation and activity [Gandino *et al.* 1994; Gandino *et al.* 1990]. Independently of PKC activation, an increase in intracellular calcium levels can also lead to negative c-MET regulation [Gandino *et al.* 1991].

Although the downstream response to c-MET is common to many RTKs, the potency, endurance and specificity of c-MET-triggered pathways is secured by a network of upstream signaling co-receptors that physically associate with c-MET at the cell surface (Figure 3) [Trusolino *et al.* 2010]. c-MET membrane partners can then amplify and/or diversify c-MET-dependent biochemical inputs and translate them into meaningful (and specific) biological outcomes. 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 and moesin (ERM) family of proteins in order to recruit SOS, which then amplifies RAS-ERK signaling [Orian-Rousseau *et al.* 2007]. Recent work has also shown that intercellular adhesion molecule 1 (ICAM-1) can substitute for CD44v6 as a co-receptor for c-MET in CD44v6 knockout mice, resulting in similar c-MET pathway activation [Olaku *et al.* 2011]. As another example, c-MET binding to integrin α6β4 creates a supplementary docking platform for binding of signaling adaptors, leading to specific enhancement of PI3K, RAS and SRC activation [Trusolino *et al.* 2001; Bertotti *et al.* 2005]. In addition, the G-protein-coupled receptor (GPCR) agonists lysophosphatidic acid (LPA), bradykinin, thrombin and carbachol can induce c-MET phosphorylation [Fischer *et al.* 2004], although the functional consequences of these interactions are still unclear.

Crosstalk between c-MET and other RTKs has also been studied in great depth because of its potential importance in the development of
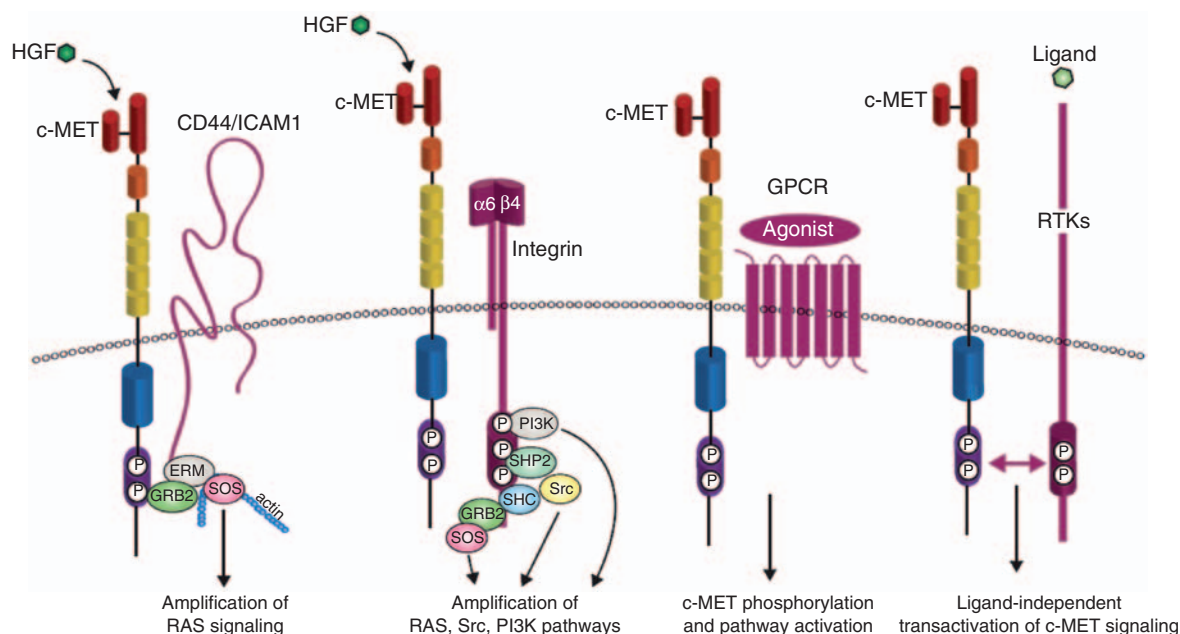
Figure 3. c-MET transactivation. The potency and endurance of c-MET-triggered pathways is secured by a network of upstream signaling co-receptors that physically associate with c-MET at the cell surface. c-MET membrane partners can then amplify and/or diversify c-MET-dependent biochemical inputs and translate them into meaningful (and specific) biological outcomes. The v6 splice variant of the hyaluronan receptor CD44 links c-MET signaling to the actin cytoskeleton via the growth factor receptor-bound protein 2 (GRB2) and the ezrin, radixin, moesin (ERM) family of proteins in order to recruit son of sevenless (SOS), which then amplifies RAS-ERK signaling. Intercellular adhesion molecule 1 (ICAM-1) can substitute for CD44v6 as a co-receptor for c-MET in CD44v6 knockout mice, resulting in similar c-MET pathway activation. c-MET binding to integrin α6β4 creates a supplementary docking platform for the binding of signaling adaptors, leading to specific enhancement of phosphatidylinositol 3-kinase (PI3K), RAS and SRC activation. c-MET can also be activated by G-protein coupled receptors (GPCRs), although the functional outcome of this interaction is not well characterized. Crosstalk between c-MET and other receptor tyrosine kinases (RTKs) has also been studied in great depth because of its potential importance in the development of resistance to cancer therapeutics. Examples of these RTKs include the semaphorin receptors, the epidermal growth factor receptor (EGFR) family of receptors, the recepteur d'origine nantais (RON), platelet-derived growth factor receptor (PDGFR) and Axl; the list continues to grow. Adapted from Trusolino *et al.* [2010] and Corso *et al.* [2005] HGF, hepatocyte growth factor; SHC, src homolgy 2 domain-containing; SHP2, src homology 2 domain-containing phosphatase 2.

resistance to cancer therapeutics [Lai *et al.* 2009]. For instance, several members of the family of semaphorin receptors, including the plexins and neuropilins, can transactivate c-MET in the absence of HGF when stimulated by their semaphorin ligands [Sierra *et al.* 2008; Hu *et al.* 2007; Conrotto *et al.* 2004]. c-MET has also been shown by multiple studies to interact directly with the epidermal growth factor receptor (EGFR), allowing activation of c-MET after stimulation of cells with the EGFR ligands EGF or transforming growth factor (TGF-α) [Jo *et al.* 2000]. 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 [Puri and Salgia, 2008]. Evidence also exists for c-MET interaction with the other EGFR family members ERBB2 and ERBB3 (for erythroblastic leukemia viral oncogene homologs B2 and B3), causing transactivation of both receptors [Bachleitner-Hofmann *et al.* 2008; Khoury *et al.* 2005]. Interaction of c-MET with the closely related RON (recepteur d'origine nantais) receptor has also been shown to cause transphosphorylation of the c-MET receptor in the absence of HGF [Follenzi *et al.* 2000]. 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 [Benvenuti *et al.* 2011]. Recently, transactivation between c-Met and both platelet-derived growth factor receptor (PDGFR) and Axl was found to play a role in bladder cancer [Yeh *et al.* 2011]. The list of cell surface receptors that play a role in c-MET signaling is growing constantly, and highlights the

importance of personally targeted cancer therapies, depending on the expression of these RTKs in specific patients.

The c-MET receptor relies on its multitude of signaling adaptors and cell surface co-receptors to mediate biological responses unique to the receptor. Recent large-scale phosphoproteomic studies have provided even more insight into the intricacies of the HGF/c-MET signaling axis [Organ *et al.* 2011; Hammond *et al.* 2010; Guo *et al.* 2008]. Although these studies identified the highly conserved, core elements in c-MET signaling, they also identified tissue-specific differences, in addition to activation- compared with inhibition-specific differences, in downstream mediators of c-MET. Although much work has been done since the discovery of the c-*MET* oncogene to map out the details of c-MET signaling, this suggests that our understanding of the greater c-MET network remains incomplete.

HGF/c-MET signaling in cancer
As described above, c-MET signaling is an intricate and highly regulated process. Mechanisms operating during tumor growth or cancer progression 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 typically take place by means of three mechanisms: the occurrence of specific genetic lesions, including translocations, gene amplifications and activating mutations; by transcriptional upregulation of the c-MET protein in the absence of gene amplification; or *via* ligand-dependent autocrine or paracrine mechanisms [Danilkovitch-Miagkova and Zbar, 2002].

c-*MET* was originally identified as an oncogene in the 1980s [Cooper *et al.* 1984], isolated first from a human osteosarcoma cell line treated with the carcinogen *N*-methyl-*N*-nitro-*N*-nitrosoguanidine. The c-MET identified in this cell line contained a chromosomal rearrangement that fused the tyrosine kinase domain of the c-*MET* proto-oncogene to an upstream translocating promoter region (TPR). This rearrangement caused constitutive dimerization and therefore activation of the encoded protein [Park *et al.* 1986]. Expression of TPR-MET in transgenic mice resulted in the development of multiple epithelial-derived tumors [Liang *et al.* 1996]. In humans, the TPR-MET translocation has been found in both the precursor lesions of gastric cancers and in the adjacent normal mucosa,

suggesting that this genetic lesion can predispose to the development of gastric carcinomas [Soman *et al.* 1991].

Amplification of the c-*MET* gene, with consequent protein overexpression and constitutive kinase activation, has been reported in a number of human primary tumors. These include gastric and oesophageal carcinomas [Miller *et al.* 2006; Hara *et al.* 1998; Kuniyasu *et al.* 1992; Houldsworth *et al.* 1990], medulloblastomas [Tong *et al.* 2004], and liver metastases from colon carcinoma [Di Renzo *et al.* 1995c]. This last finding suggests that *MET* gene amplification can be acquired during the course of tumor progression. Interestingly, recent research has shown that non-small cell lung carcinomas with acquired resistance to EGFR inhibitors tend to show amplifications in *MET* [Bean *et al.* 2007; Engelman *et al.* 2007]. This suggests that combined treatment with EGFR and c-MET inhibitors could be necessary in a subset of patients to circumvent the onset of resistance to these drugs.

The most convincing evidence that implicates c-MET in human cancers is provided by the activating mutations that were discovered in the c-MET kinase domain in both sporadic and inherited forms of human renal papillary carcinomas [Olivero *et al.* 1999; Schmidt *et al.* 1999]. Activating kinase domain mutations have subsequently been identified in a small number of other cancers. Mutations have also been identified in the c-CBL binding site of the juxtamembrane domain and in the HGF-binding region of the Sema domain [Forbes *et al.* 2008]. In hereditary cancers, heterozygous mutations are usually accompanied by trisomy of the whole chromosome 7, suggesting that when only a single allele is mutated the mutation must be present in multiple copies to produce the full transformed phenotype [Schmidt *et al.* 1997].

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 [Comoglio *et al.* 2008], and has been reported in an ever growing number of carcinomas, including thyroid [Di Renzo *et al.* 1992; Di Renzo *et al.* 1995b], colorectal [Hiscox *et al.* 1997; Di Renzo *et al.* 1995a; Liu *et al.* 1992], ovarian [Di Renzo *et al.* 1994], pancreatic [Di Renzo *et al.* 1995b; Furukawa *et al.* 1995], lung

[Nakamura *et al.* 2008; Tsao *et al.* 1998] and breast [Lengyel *et al.* 2005], to name a few. Hypoxia, caused by lack of oxygen diffusion to the centre of a growing tumor, is one mechanism that has been demonstrated to activate c-MET transcription *in vitro* and *in vivo* [Pennacchietti *et al.* 2003]. Hypoxia activates the *c-MET* promoter, via the transcription factor hypoxia inducible factor 1α (HIF1α), which itself is regulated by the concentration of intracellular oxygen [Kitajima *et al.* 2008].

Although c-MET activation via a ligand-dependent autocrine or paracrine loop will be fully discussed elsewhere in this supplement, we will touch on it briefly here. HGF is expressed ubiquitously within the body and has been found to be frequently overexpressed in the reactive stroma of primary tumors [Matsumoto and Nakamura, 2006]. 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 [Rahimi *et al.* 1996; Rong and Vande Woude, 1994], and appears to be indicative of increased aggressiveness of tumors along with poor prognostic signs in cancer patients [Navab *et al.* 2009; Vadnais *et al.* 2002; Tuck *et al.* 1996].

c-MET as a target for therapeutic inhibition

Although the development of c-MET inhibitors will be discussed elsewhere in this supplement, here we consider the dual role c-MET plays in both the development and progression of cancers, and how each could be targeted by c-MET inhibitors.

Some tumors appear to be dependent on (or 'addicted' to) sustained c-MET activity for their growth and survival, and this is often associated with *MET* gene amplification. This phenomenon is known as 'oncogene addiction' and applies to all settings where cancer cells appear to be dependent on a single overactive oncogene for their proliferation and survival [Sharma *et al.* 2007; Sharma and Settleman, 2007]. Oncogene addiction was identified after studies using EGFR tyrosine kinase inhibitors demonstrated that these inhibitors were efficacious only in a small subset of tumors which exhibited genetic alterations of the receptor itself [Sharma *et al.* 2007]. Although this c-MET-addicted phenotype has only recently been (yet consistently) described in cultured cells from gastric and non-small cell lung carcinomas, it continues to strongly suggest that amplification of the *MET* gene might be a genetic predictor of therapeutic responsiveness [Lutterbach *et al.* 2007; Smolen *et al.* 2006].

'Oncogene expedience' is a tumor-specific term that describes the scattering, invasion and survival of cancer cells associated with metastatic spreading [Comoglio *et al.* 2008]. In contrast to oncogene addiction, the inappropriate activation of c-MET resulting in oncogene expedience is the consequence rather than the cause of the transformed phenotype. Thus, activation of c-MET is a secondary event in various types of tumor, exacerbating the malignant properties of already transformed cells. In these cases, aberrant c-MET activation occurs through a number of possible routes; these include transcriptional upregulation by other oncogenes [Abounader *et al.* 2004; Ivan *et al.* 1997], environmental conditions such as hypoxia [Pennacchietti *et al.* 2003] and agents secreted by reactive stroma such as inflammatory cytokines, proangiogenic factors and HGF itself [Bhowmick *et al.* 2004; Boccaccio *et al.* 1994].

As *MET* is a necessary oncogene for a number of neoplasms, targeted therapies against c-MET could be effective as a front-line intervention to treat a limited subset of c-MET-addicted tumors and subsequent c-MET-addicted metastases [Comoglio *et al.* 2008]. In addition, as *MET* also acts as an adjuvant prometastatic gene for many neoplasms, targeted therapies against c-MET could also be used as a secondary approach to hamper the progression of a much wider spectrum of advanced cancers that rely on c-MET activation for metastatic spreading.

Summary and conclusions

The HGF/c-MET pathway comprises a complex and unique signaling network and plays a pivotal role in both normal development and cancer progression. c-MET controls multiple biological functions, including proliferation, survival, motility and invasion, which, when dysregulated by aberrant c-MET activation, can lead to both tumor growth and metastatic progression of cancer cells. Consequently, c-MET is a versatile candidate for targeted therapeutic intervention.

Acknowledgement

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