Targeting MET in cancer: rationale and progress

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Abstract | Uncontrolled cell survival, growth, angiogenesis and metastasis are essential hallmarks of cancer. Genetic and biochemical data have demonstrated that the growth and motility factor hepatocyte growth factor/scatter factor (HGF/SF) and its receptor, the tyrosine kinase MET, have a causal role in all of these processes, thus providing a strong rationale for targeting these molecules in cancer. Parallel progress in understanding the structure and function of HGF/SF, MET and associated signalling components has led to the successful development of blocking antibodies and a large number of small-molecule MET kinase inhibitors. In this Review, we discuss these advances, as well as results from recent clinical studies that demonstrate that inhibiting MET signalling in several types of solid human tumours has major therapeutic value.

Clastogenic carcinogen
A chemical agent that can cause cancer as a result of its ability to induce chromosome breaks, which results in the loss or rearrangement of parts of one or more chromosomes.

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MET and its physiological ligand hepatocyte growth factor/scatter factor (HGF/SF) were discovered in the mid-1980s as a result of three independent lines of research (TIMELINE). A transforming MET fusion protein, translocated promoter region (TPR)–MET, was first identified in a human osteogenic sarcoma cell line as an active oncogene[1], and the proto-oncogene was later found to encode the receptor tyrosine kinase (RTK) MET[2]. Originally named after the clastogenic carcinogen that is responsible for generating TPR-MET (*N*-methyl-*N*′-nitroso-guanidine), the demonstration of a role in metastasis suggested renaming the RTK MET for metastasis[3]. In other studies, a liver mitogen (HGF)[4–7] and a fibroblast-derived epithelial motility factor, scatter factor (SF)[8,9], were independently characterized but were then found to be the same protein, referred to as HGF/SF[10,11]. In 1991, molecular biological and biochemical experiments identified HGF/SF as the MET ligand[12], a conclusion that was confirmed by targeted deletion of *Hgf* and *Met* alleles in mice[13–15]. Analysis of these mutant mice highlighted the essential physiological roles of the proteins encoded by these genes in survival, growth and migration of several cell types and tissues[13–15].

A striking feature of the HGF/SF–MET signalling system is the diversity of cellular responses that follow MET activation, the basis of which lies in the activation of distinct signalling pathways downstream of MET and its associated docking protein growth factor receptor-bound protein 2 (GRB2)-associated binding protein 1 (GAB1)[16,17], and their cooperation with other signalling systems[18,19].

Numerous discoveries have brought into focus the role of HGF/SF and MET in cancer (TIMELINE). In addition to the large number of different cancer types in which aberrant HGF/SF–MET expression is found (see the HGF/SF - MET and cancer online table (see Further information)), the large numbers of experimental studies and clinical investigations that demonstrate activating MET kinase mutations in patients with renal carcinomas[20] have provided powerful and comprehensive evidence for a role in human cancer and a rationale for the development of MET inhibitors[21]. The roles of HGF/SF–MET in cancer and the progress in the development of inhibitors for therapy constitute the main focus of this Review.

The regulation of HGF/SF and MET signalling

Our understanding of the structure of HGF/SF and MET, as well as MET signalling, has advanced considerably in recent years. Binding of HGF/SF to MET activates various signalling cascades that induce survival, as well as mitogenic and motogenic responses, and major advances have been made in the biochemical and genetic analysis of the crosstalk of MET with other signalling systems and their role in cancer.

HGF/SF and MET activation. HGF/SF is a complex, multidomain protein (FIG. 1a) that is related to the blood proteinase precursor plasminogen, and, in addition to transcriptional regulation, a key post-translational step in the regulation of HGF/SF–MET signalling is

Coagulation cascade
An ordered sequence of chemical reactions triggered by tissue components after tissue damage and catalysed by enzymes present in serum that ultimately causes the formation of a blood clot.

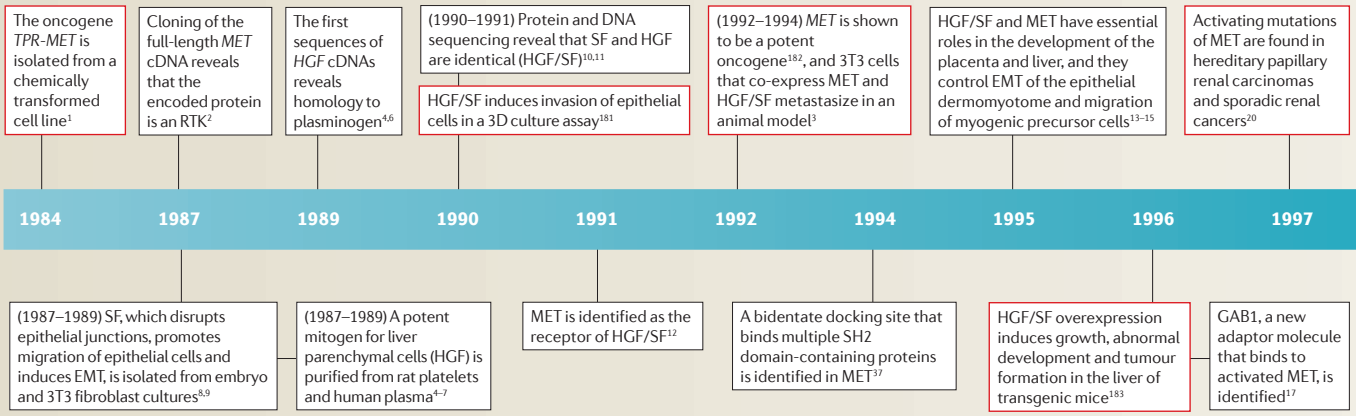
At a glance

- The growth and motility factor hepatocyte growth factor/scatter factor (HGF/SF) and its receptor tyrosine kinase MET, the product of the *MET* proto-oncogene, provide essential signals for survival and long-distance migration of epithelial and myogenic precursor cells during embryogenesis. Cancer cells hijack HGF/SF–MET for invasion and metastasis, hence these molecules have emerged as key targets for cancer therapy.
- Aberrant MET activation occurs in many types of cancer, and results from multiple mechanisms. Many carcinomas overexpress MET and the surrounding stroma overexpresses HGF/SF. Furthermore, certain patients with renal papillary, hepatocellular or gastric carcinomas carry point mutations in *MET*. These mutations have proved important in demonstrating a causal role of aberrant MET signalling in human cancer.
- The intracellular signalling cascades activated by MET include the PI3K–AKT, RAC1–cell division control protein 42 (CDC42), RAP1 and RAS–MAPK pathways. An intricate network of cross-signalling involving the MET–epidermal growth factor receptor (EGFR), MET–vascular endothelial growth factor receptor (VEGFR) and MET–WNT pathways has also emerged in the past few years. This signalling network has major implications for therapy.
- Structural studies of HGF/SF, the MET ectodomain and the pathways involved in activation of the precursor form of HGF/SF (pro-HGF/SF) have yielded important results and new opportunities for therapeutic intervention, namely specific inhibitors of the major HGF/SF activators, HGF/SF fragments with antagonistic activity — such as NK4 — and HGF/SF and MET antibodies.
- Parallel efforts in the structural analysis of the MET kinase have led to extensive progress in the development of MET kinase inhibitors for cancer therapy, and three major classes of inhibitors have emerged from this work that differ in their binding mode, activity on MET kinase mutants and enzyme specificity.
- A number of recent clinical trials have demonstrated strong activity of MET inhibitors in patients with a variety of advanced or metastatic tumours, including non-small-cell lung cancer (NSCLC), and breast, prostate, liver and renal cancer. MET inhibitors have also displayed clinical benefits in patients with NSCLC and patients with breast cancer who had developed resistance to EGFR therapy. These recent data clearly indicate that HGF/SF–MET therapeutics may have potential in several groups of cancer patients either alone or in combination with inhibitors of other signalling pathways.

the proteolytic activation of pro-HGF/SF to the active ligand. Activation of pro-HGF/SF causes both global[22] and local[23] structural rearrangements and is effected by three serine proteinases: the soluble HGF activator (HGFA), as well as the type II transmembrane enzymes matriptase (also known as ST14) and hepsin[24]. Matriptase and hepsin are expressed on the surface of MET-expressing target cells; whereas, HGFA is a soluble proteinase that is activated by thrombin, which provides an important link between the coagulation cascade and the tissue-regenerative responses that are controlled by HGF/SF–MET[25]. Activation of HGF/SF is finely tuned by the expression of at least two inhibitors, which are known as HGF activator inhibitor 1 (HAI1; also known as SPINT1) and HAI2 (also known as SPINT2)[26,27]. Elevated expression of matriptase[28] and/or hepsin[29] induces cancer cell invasion and metastasis, as does decreased expression of HAI1 and/or HAI2 (REF. 30). Therefore, membrane-bound HGF/SF activators and their inhibitors are targets for therapeutic intervention (discussed below).

There are crystal structures available of several fragments of HGF/SF (N-terminal and kringle domain 1 (NK1)[31,32], NK2 (REF. 33) and the serine proteinase

Timeline | **Milestones of MET and HGF/SF discoveries**



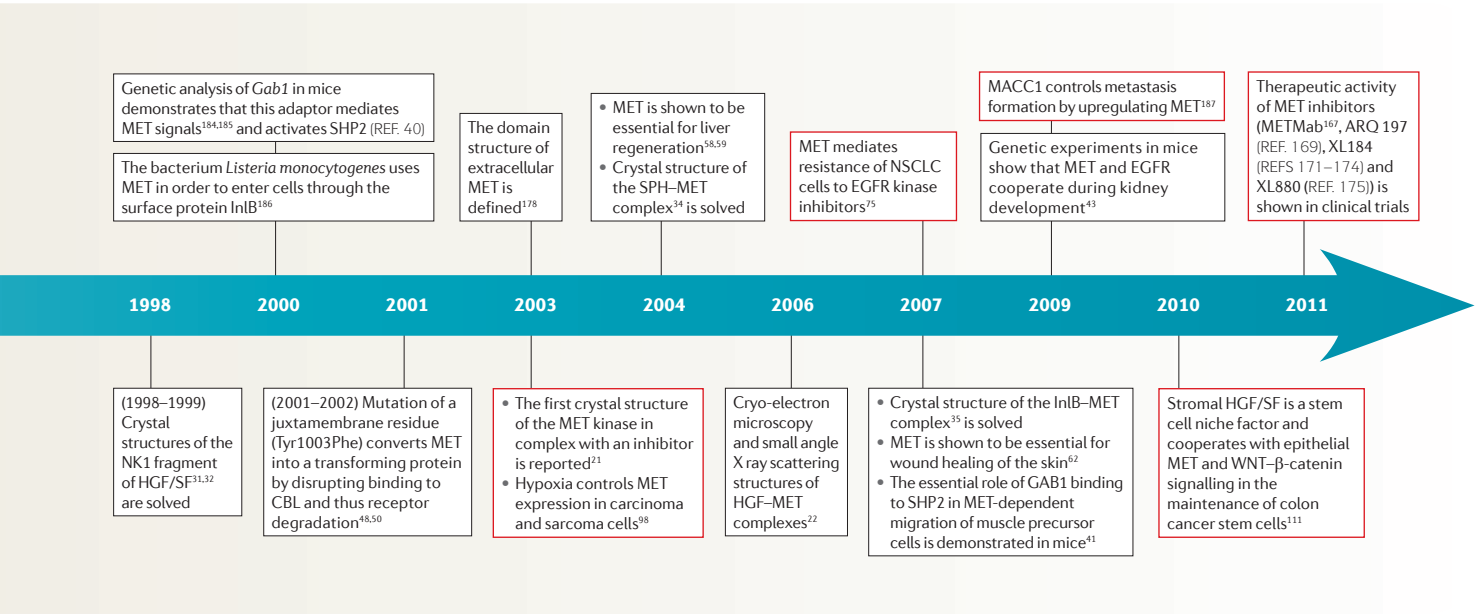
Discoveries related to cancer are outlined in red. 3D, three-dimensional; EGFR, epidermal growth factor receptor; EMT, epithelial-to-mesenchymal transition; GAB1, GRB2-associated-binding protein 1; HGF, hepatocyte growth factor; InlB, Internalin B; MACC1, metastasis-associated gene in colon cancer 1; NK1, N terminal and kringle domain 1; NSCLC, non-small-cell lung cancer; RTK, receptor tyrosine kinase; SF, scatter factor; SH2, SRC homology 2; SHP2, SRC homology 2 domain-containing phosphatase 2; SPH, serine proteinase homology; *TPR*, translocated promoter region.

homology (SPH) domain[23]), as well as fragments of the MET ectodomain in complex with the SPH domain of HGF/SF[34] (FIG. 1b) and in complex with Internalin B[34,35] (InlB) (FIG. 1c), which is a protein expressed by the bacterium *Listeria monocytogenes* and which is responsible for bacterial internalization in hepatocytes and macrophages through the MET receptor. The SPH domain binds the large, amino-terminal domain of MET[34] (the SEMA domain (FIG. 1b)). By contrast, InlB binds the first of four immunoglobulin-like (Ig) domains that are present in the extracellular portion of MET[35] (FIG. 1c). Low-resolution small angle X-ray scattering (SAXS) models of the HGF/SF–MET complex[22] and analysis of InlB-MET crystal structures[36] have established that minimal, signalling-competent MET complexes have 2:2 stoichiometry, with a ligand dimer at the centre of the structure and two MET molecules at the periphery. High-resolution structures of the catalytic domain of MET, which is cytoplasmic, alone or in complex with inhibitors, are available and are discussed below.

Basic mechanisms of MET signalling. Ligand-induced MET dimerization activates the tyrosine kinase by phosphorylation of tyrosine residues (Tyr1230, Tyr1234 and Tyr1235) in the kinase domain, which leads to autophosphorylation of the carboxy-terminal bidentate substrate-binding site (Tyr1349 and Tyr1356) of MET[16,17,37]. Various cytoplasmic effector proteins, including GAB1, GRB2, phospholipase C (PLC) and SRC are directly recruited to this site, and these proteins become frequently phosphorylated on tyrosine residues (reviewed in REFS 16,18) (FIG. 2). Phosphorylated GAB1 bound to MET at the plasma membrane can attract further docking molecules and enzymes such as SRC homology 2 domain-containing phosphatase 2 (SHP2; also known as PTPN11), PI3K, CRK-like protein (CRKL) and others[17,38–40] that together activate various downstream signalling cascades. MET signalling, which is mainly mediated by the RAS–MAPK and PI3K–AKT pathways, affects gene expression and cell cycle progression through the binding of transcription factors, such as the ETS family[16,18] (FIG. 2). Cytoplasmic signalling cascades mediated by PI3K–AKT and the GTPases RAC1 or cell division control protein 42 (CDC42) modulate cell survival and elicit cytoskeletal changes. Signals to the plasma membrane control cell migration and cell adhesion mainly through the RAP1 and RAC1–CDC42 pathways, which affect integrins and cadherins (FIG. 2).

Genetic experiments in mice have provided important insights into the roles of the different branches of MET signalling and have shed light on the relevance of various downstream molecules *in vivo*. A crucial role of the ERK–MAPK branch in MET signalling has been confirmed in mice that carry specific mutations in GAB1 that prevent binding of the protein tyrosine phosphatase SHP2 or of PI3K[41]. Recruitment of SHP2 to GAB1 and ERK–MAPK signalling is essential for embryonic survival, myogenic precursor cell migration and liver growth; all of these processes are controlled by HGF/SF and MET during development[16] (TIMELINE). In humans, activating mutations of *PTPN11*, the gene that encodes SHP2, are associated with a number of malignancies, most prominently juvenile myelomonocytic leukaemia (JMML)[42].

Several types of signal cooperation and crosstalk between MET and other receptor pathways have been unveiled in recent years, and a recent study has demonstrated cooperative signalling between MET and the epidermal growth factor receptor (EGFR) during kidney development[43] (TIMELINE), providing genetic evidence for the role of HGF/SF in kidney-branching morphogenesis that was inferred from earlier experiments with cell and organ cultures[44,45]. The absence of MET during renal development caused reduced branching of the ureteric bud and a decreased number of nephrons, and the defect was particularly severe in mice in which both MET and



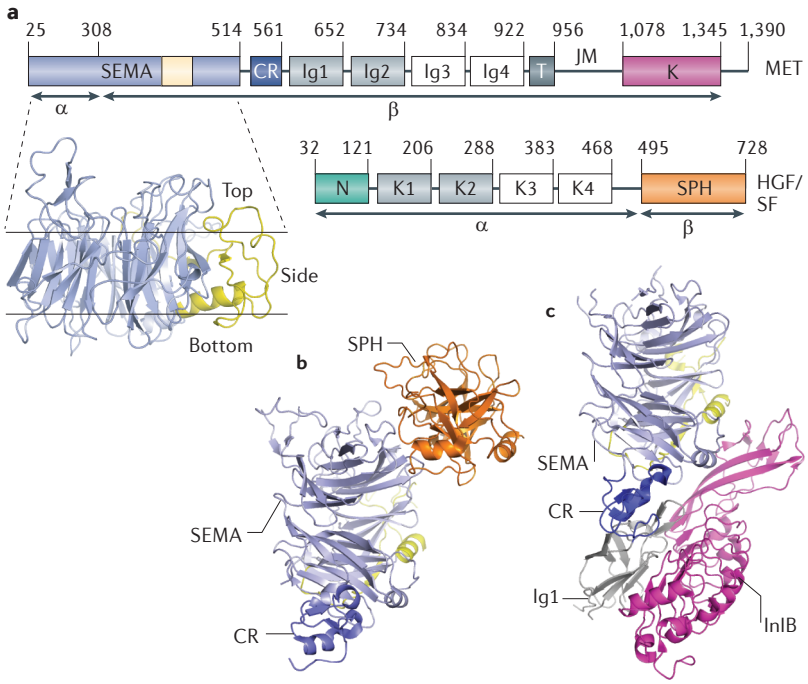


Figure 1 | **The multidomain structure of MET and HGF/SF. a** | MET is synthesized as a single chain precursor and cleaved by furin during transit through the endoplasmic reticulum[177], thus yielding a smaller, amino-terminal α-chain and a larger β-chain. The MET ectodomain consists of a large N-terminal SEMA domain, which adopts a seven-bladed β-propeller fold and a stalk structure consisting of four immunoglobulin-like (Ig) domains[178]. The SEMA domain and the stalk structure are separated by a small cystine-rich (CR) domain. The transmembrane (T), the long juxtamembrane (JM) sequence, the kinase (K) domain and a carboxy-terminal sequence that contains essential motifs for downstream signalling are also shown. The SEMA domain is a structural variant of the β-propeller, a large protein domain with an irregular cylindrical shape that consists of a variable number of antiparallel β-sheets (or blades) each formed by four β-strands (named A, B, C and D). These blades are arranged radially around a central cavity, and there are seven of these in the MET β-propeller. The face of the domain that displays loops connecting β-strands B–C and D–A is called the 'top face'; whereas, the face that displays loops connecting β-strands A–B and C–D is known as the 'bottom face'. Hepatocyte growth factor/scatter factor (HGF/SF) is composed of six domains: an N-terminal (N) domain, four copies of the kringle domain (K1–4) and a C-terminal serine proteinase homology (SPH) domain that is structurally related to the catalytic domain of serine proteinases but that is enzymatically inactive. Mature, biologically active HGF/SF is a two-chain (α–β) protein that is produced by site-specific proteolysis in the extracellular space from single-chain, pro-HGF/SF by the serine proteinases matriptase, pepsin and HGF-activator. HGF/SF contains two MET-binding sites: one in the NK1 fragment and one in the SPH domain[179]. **b** | The crystal structure of an SPH–MET complex is shown: the SPH domain of HGF/SF binds to an area of the SEMA domain within the MET α-chain (protein databank (PDB) ID: 1SHY[34]). **c** | The crystal structure of an Internalin B (InlB)–MET complex is shown: InlB primarily binds to the Ig1 domain of the MET stalk[35]. Structures were drawn using PyMOL[180].

EGFR signalling was impaired[43]. Crosstalk between MET and other signalling systems (such as transforming growth factor-β (TGFβ), WNT and others) has emerged as a major mechanism in human cancer and is discussed below.

MET ubiquitylation, endocytosis and shedding. On ligand activation, MET — like other RTKs — is internalized through endocytosis. The internalized receptor is then either degraded or recycled to the plasma membrane. Derailed receptor trafficking and degradation, as well as unbalanced recycling, can cause sustained signalling and can contribute to cell transformation, tumorigenesis and metastasis[46].

MET endocytosis and degradation are initiated by ligand-dependent phosphorylation of the receptor, which is then internalized primarily by clathrin-coated pits and vesicles. The internalized receptor is delivered to endosomal compartments and remains capable of signalling during vesicle trafficking. Subsequently, the receptor is either degraded or recycled. MET mutations that increase endocytosis and/or recycling activity and that decrease degradtion result in enhanced anchorage-independent growth, tumorigenesis and experimental metastasis *in vivo*[47]. The ubiquitin E3 ligase CBL contains a phosphotyrosine-binding module that recognizes the phosphorylated Tyr1003 residue in the juxtamembrane domain of MET[48] and induces degradation (TIMELINE). CBL also contains a RING finger domain that engages E2 protein ubiquitin ligases to mediate ubiquitylation of MET, which might occur at the cell membrane or in the early endocytic compartment. Ubiquitylated MET is degraded in a late endosomal or lysosomal compartment in a proteasome-dependent manner[49,50]. Mutation or deletion of the CBL-binding site converts MET into a transforming protein. Such receptor variants are still internalized on ligand activation, but they escape degradation owing to a change in endosomal sorting[48]. Endosomal sorting is regulated by adaptors that recognize and bind ubiquitylated proteins, among them hepatocyte growth factor-regulated tyrosine kinase substrate (HRS; also known as HGS), which is a MET substrate that is involved in endosomal sorting of ubiquitylated MET[51]. Several mechanisms that affect RTK internalization and trafficking have been reported to be altered in cancer cells (see REF. 46 for a recent review) but their role in aberrant MET activity requires further analysis.

Certain cancer cells express alternatively spliced *MET* mRNAs that encode a receptor without the juxtamembrane CBL-binding site or with mutations in the juxtamembrane domain that interfere with CBL binding[52]. Owing to the inability to recruit the CBL E3 ubiquitin ligase, receptor downregulation is impaired[48,53]. Aberrant endocytosis in cancer cells and the resulting escape from degradation results in MET overexpression[46].

Another mechanism that leads to downregulation of MET is regulated proteolysis and shedding of the extracellular domain. Shedding is mediated by members of the a disintegrin and metalloproteinase (ADAM) family and results in the formation of a soluble MET ectodomain and a membrane-anchored cytoplasmic tail. The surface-associated cytoplasmic tail undergoes proteolysis by γ-secretase and is rapidly cleared by proteasome-mediated degradation[54].

Physiology of HGF/SF and MET

Recent genetic studies in mice have demonstrated that HGF/SF–MET signalling is essential for regeneration in liver and skin. These normal functions have served as a paradigm for understanding the roles of HGF/SF and MET in cancer and are discussed below.

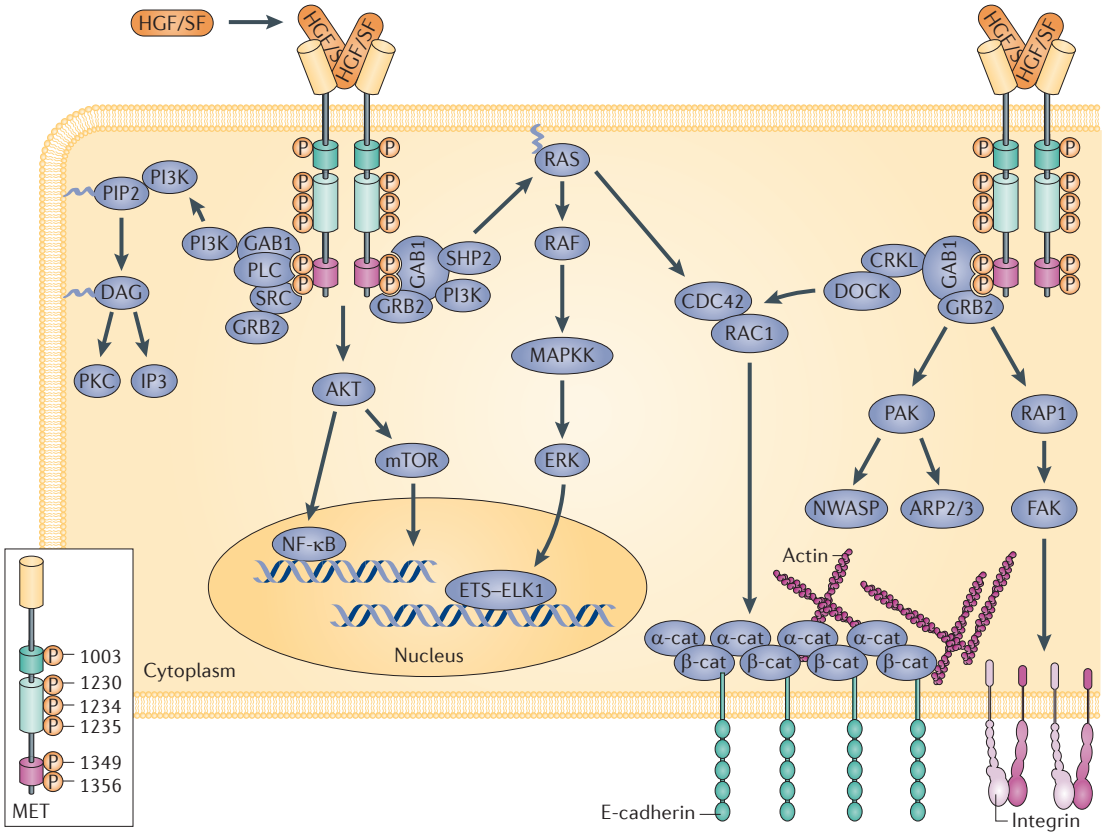


Figure 2 | **Signalling pathways activated by HGF/SF and MET.** Hepatocyte growth factor/scatter factor (HGF/SF) induces dimerization and activation of MET at the plasma membrane. The cytoplasmic tyrosine phosphorylation (P) sites of MET are indicated: Tyr1003 is in the juxtamembrane CBL-binding site (shown in green), Tyr1230, Tyr1234 and Tyr1235 are in the active site of the kinase (shown in light green), and Tyr1349 and Tyr1356 are in the bidentate docking site (shown in pink). Various cytoplasmic effector molecules such as growth factor receptor-bound protein 2 (GRB2), GRB2-associated-binding protein 1 (GAB1), phospholipase C (PLC) and SRC are recruited to the bidentate docking site. Tyrosine-phosphorylated GAB1 that is bound to MET can attract further docking proteins, including the tyrosine phosphatase SRC homology 2 domain-containing phosphatase 2 (SHP2), PI3K and others, which, together with the direct MET binders, activate various downstream signalling cascades. Signalling by the RAS–MAPK and PI3K–AKT pathways reaches the nucleus to affect gene expression and cell cycle progression. Cytoplasmic signalling cascades that are mediated by RAC1–cell division control protein 42 (CDC42) and p21-activated kinase (PAK) elicit cytoskeletal changes. Signals through the RAP1 and RAC1–CDC42 pathways reach the plasma membrane and control cadherin and integrin adhesion molecules and thereby affect cell migration. Signalling to membrane-bound lipids and protein kinase C (PKC) is also shown. These signalling pathways control cell survival and cell migration. α-cat, α-catenin; β-cat, β-catenin; ARP, actin-related protein; CRKL, CRK-like protein; DAG, diacylglycerol; DOCK, dedicator of cytokinesis; FAK, focal adhesion kinase; IP3, inositol trisphosphate; NF-κB, nuclear factor-κB; NWASP, neural Wiskott–Aldrich syndrome protein; PIP2, phosphatidylinositol 4,5-bisphosphate.

HGF/SF and MET in EMT and cell migration during embryogenesis. During development, MET controls the epithelial-to-mesenchymal transition (EMT) of myogenic progenitor cells that are released from the epithelial dermomyotome. These cells migrate in a MET- and GAB1-dependent manner over long distances in the embryo[15,55]. MET-dependent EMT and long-distance migration of tumour cells also have major roles in invasion and metastasis.

MET in organ regeneration. Distinct cellular mechanisms are used for regeneration. Stem cells can provide a source, but, in certain tissues, terminally differentiated cells can re-enter the cell cycle and sustain regeneration. It has been argued that cancer resembles a persistent regeneration process that is unable to define its end point (tumours have been referred to as "wounds that do not heal" (REF. 56)). Loss of liver mass can be induced in rodents by administering hepatotoxic chemicals or by surgical removal of up to two-thirds of the liver. Shortly after partial hepatectomy, HGF/SF is mobilized from the extracellular matrix, resulting in MET activation in hepatocytes, which leads to DNA synthesis and cytokinesis[57]. Conditional ablation of *Met* in hepatocytes in mice interferes with hepatocyte re-entry into S phase and cell cycle progression after partial hepatectomy, resulting in impaired proliferation and incomplete liver regeneration[58,59].

In the skin, stem cell populations generate different epidermal cell types during normal turnover and wound repair[60,61], and a recent study showed that MET

Myogenic progenitor cells
Progenitor cells that have the potential to differentiate into skeletal muscle.

Epithelial dermomyotome
A transient epithelial structure of the embryo that will give rise to skeletal muscle, dermis and other cell types in later development.

Keratinocytes
Epithelial cells of the skin and its appendages, such as hair and skin glands.

Autocrine signalling
A type of cell signalling in which the same cell produces both the chemical messenger (a hormone, growth factor or cytokine) and the membrane receptor that triggers the biological response to the messenger.

is essential for wound repair[62]. In mice with conditional ablation of *Met* in keratinocytes, only cells that had escaped recombination and that continued to express a functional MET[62] could contribute to regeneration. This result was unexpected because growth factors of the EGF and fibroblast growth factor (FGF) families are also involved in re-epithelialization, but cannot compensate for a lack of HGF/SF–MET signalling in the skin *in vivo*. During the repair of skin wounds HGF/SF and MET are co-expressed in keratinocytes, which implies that autocrine signalling occurs. Upregulated HGF/SF levels were also reported after injury to other epithelial organs, such as the kidney and lung, as well as skeletal muscle and heart[63].

How HGF/SF and MET can cause cancer

The tight regulation of HGF/SF and MET signalling that is observed in development and regeneration is lost in cancer at multiple levels. These changes often involve transcriptional deregulation, but a number of other mechanisms, including inadequate degradation, receptor crosstalk or synergies in downstream signalling, have also been observed. The association of HGF/SF–MET alterations with different types of cancer can be found in a searchable, fully referenced table (see the HGF/SF - MET and cancer online table; see Further information).

Genetic abnormalities that cause aberrant HGF/SF–MET signalling. Activating point mutations of *MET* occur in sporadic and inherited human renal carcinomas, hepatocellular carcinomas and several other cancer types[20,64]. Most of these mutations are located in the kinase domain and are homologous to cancer-inducing mutations that occur in other RTKs (such as EGFR, RET and KIT). When used to replace endogenous *Met* in the mouse germ line, these mutations cause a variety of tumours, including sarcomas, lymphomas and carcinomas. When expressed in the mammary gland, they induce basal-like breast carcinomas[65,66]. Thus, these studies constitute proof of concept that aberrant MET signalling can cause human cancer. Activating mutations of *MET* are clonally selected for during the metastasis of human head and neck cancers[67], as their frequency increased from 2% in the primary tumours to 50% in the metastases, and this constitutes additional proof of principle that, at least in this type of tumour, aberrant MET is associated with progression and metastasis. Finally, in certain human gastric and colorectal carcinomas, as well as in other tumours[68–71], amplification of *MET* (on chromosome 7q31) can occur.

Crosstalk between MET and other signalling pathways. Functional crosstalk of MET with EGFR, ERBB2 or insulin-like growth factor 1 receptor (IGF1R) has been reported in several systems[72,73] and has emerged as a major mechanism for cancer progression and resistance to therapy. Even in cells that express moderate levels of EGFR and MET, EGFR stimulation results in MET phosphorylation and activation[74]. Conversely, *MET* amplification can activate ERBB3–PI3K–AKT signalling in lung cancer cells that carry EGFR mutants that are resistant to EGFR kinase inhibitors[75], but resistance can be prevented by combined inhibition of EGFR and MET, as shown in human lung, pancreatic and breast tumour xenografts (see, for example, REFS 76,77). The semaphorin 4D receptor also controls cell migration by coupling with MET[78,79].

Crosstalk between MET and developmental signalling pathways, such as WNT–β-catenin and TGFβ–bone morphogenetic protein (BMP), has also been demonstrated. Mutation or overexpression of key components of the WNT–β-catenin pathway can cause cancer[80]. *MET* is a direct transcriptional target of WNT–β-catenin in colon cancer cell lines and other tissues[81] (FIG. 3); conversely, MET and integrin α3β1 signalling regulate the transcription of *WNT7B* in the kidney[82]. Moreover, HGF/SF induces the nuclear translocation of β-catenin–TCF and the transcription of their target genes in liver and bladder cancer cells[83], as well as the tyrosine phosphorylation of BCL92 (also known as BCL9L) in colon cancer cells[84].

An intricate interaction between TGFβ and MET signalling has been discovered by genetic experiments in mice[85]. Following mutation of TGFβ receptor II (*Tgfbr2*) in mesenchymal cells, epithelial tumours developed in the fore-stomach and the mammary gland as a result of the upregulation of stromal HGF/SF and MET activation in epithelial cells. Further functional links of MET have been uncovered with tetraspanins and the tumour suppressors INK4A and ARF, which are encoded by the *CDKN2A* locus. The tetraspanins kangai 1 (KAI1; also known as CD82) and CD151 can attenuate integrin-mediated adhesion and MET signalling in cancer cells by inhibiting SRC or by preventing the binding of GRB2 and PI3K to MET[86,87]. Finally, genetic and biochemical experiments have defined a functional link between MET, INK4A and ARF in the origin of rhabdomyosarcoma, a tumour that occurs with high penetrance and short latency in *Cdkn2a*$^{-/-}$ mice that overexpress HGF/SF[88].

HGF/SF and MET in angiogenesis. Angiogenesis and lymphangiogenesis are important processes in tumour formation and metastasis. The vascular endothelial growth factor (VEGF) and VEGF receptor (VEGFR) families have a prime role in both processes but HGF/SF–MET signalling is a potent inducer of endothelial cell growth and promotes angiogenesis and lymphangiogenesis *in vitro* and *in vivo*[89–91]. Furthermore, MET signalling can induce VEGFA expression and angiogenesis through common signalling intermediates such as SRC homology 2 domain-containing proteins (SHCs). Thrombospondin 1 (TSP1; also known as THBS1) is a negative regulator of angiogenesis that is suppressed by HGF/SF; by 'turning on' VEGFA and 'turning off' TSP1, HGF/SF–MET functions as a potent regulator of the angiogenic switch[92]. HGF/SF–MET and VEGF–VEGFR2 cooperate in inducing angiogenesis *in vitro* and *in vivo*. MET and VEGFR do not physically associate or trans-phosphorylate each other but they synergistically activate common signalling intermediates: ERK–MAPK, AKT and focal adhesion kinase (FAK)[93]. In line with these results, MET kinase inhibitors and a peptide

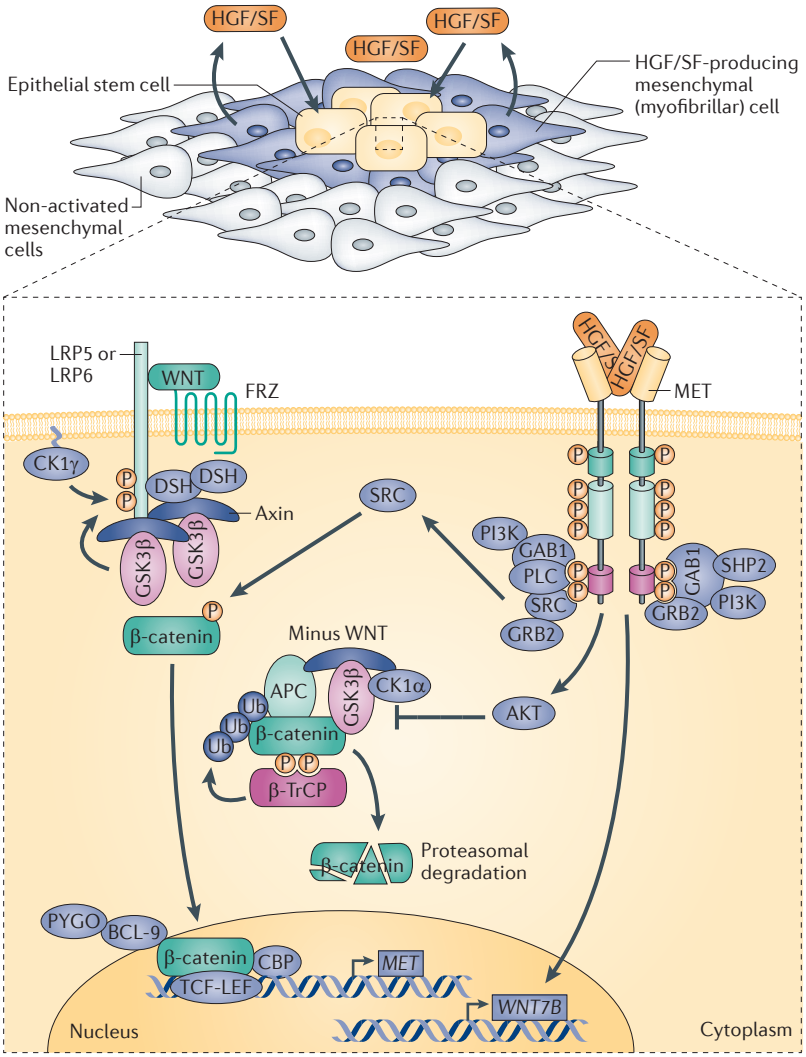


Figure 3 | **Cooperation between the HGF and WNT–β-catenin pathways.** A recent report has shown that interaction of stroma-derived hepatocyte growth factor/scatter factor (HGF/SF) controls the maintenance of stem cell-like properties of colon cancer cells, which is a function of WNT–β-catenin signalling[111]. A stem cell niche (top of the figure) contains epithelial (cancer) stem cells (shown in yellow) that are surrounded by mesenchymal (myofibrillar) niche cells (shown in blue), which secrete HGF/SF. Multiple mechanisms have been reported to allow interactions between MET and WNT–β-catenin signalling in epithelial cells, of which a few are shown here. MET can contribute to the transcriptional activation of WNT ligands, such as *WNT7B*. MET can also induce the activation of β-catenin–TCF–LEF-target genes; for example, through direct or indirect (SRC) tyrosine phosphorylation (P) and nuclear targeting of β-catenin, or by inhibition of the β-catenin degradation complex by AKT phosphorylation of glycogen synthase kinase-3β (GSK3β). β-TrCP, β-transducin repeat-containing protein; APC, adenomatous polyposis coli; CBP, CREB-binding protein; CK1, casein kinase 1; DSH, disheveled; FRZ, frizzled; GAB1, GRB2-associated-binding protein 1; GRB2, growth factor receptor-bound protein 2; LRP, low-density lipoprotein receptor-related protein; PLC, phospholipase C; PYGO, pygopus.

that contained the MET bidentate docking site blocked cancer growth and decreased the number of blood vessels in experimental tumours[94,95].

A further interesting aspect of MET biology in tumours that has emerged in recent years is the regulation of MET expression and activity by hypoxia. Hypoxia induces the expression of the transcription factor hypoxia-inducible factor 1α (HIF1α), and HIF (which is comprised, in this case, of HIF1α and HIF1β (also known as ARNT))-dependent expression of MET occurs in several types of carcinoma cells[96–99]. As inhibitors of angiogenesis reduce tumour vascularization, thus causing tumour hypoxia, these studies raised the possibility that anti-angiogenesis therapy alone may reduce tumour mass but may also promote MET-dependent spreading of cancer cells, and so these observations argue for combination therapies that target both angiogenesis and HGF/SF–MET. Preclinical studies with low-molecular-mass compounds that inhibit both VEGFR2 and MET kinases have validated this concept in mouse xenograft models[100,101], and these inhibitors may prove valuable in controlling metastatic cancer[102] by concurrently blocking angiogenesis and invasion.

HGF/SF and MET signalling in metastasis. The ability of HGF/SF–MET to induce metastasis in different organs has been shown experimentally with xenografts of tumour cells that are transfected with HGF/SF or MET[3,103], as well as in transgenic mice that overexpress HGF/SF or MET[104–106] (TIMELINE). A role of MET in metastatic progression has also been established in patients with head and neck cancer[3] (discussed above). The bidentate docking site of MET is essential for the role of MET in metastasis, because single point mutations at this site have been shown to prevent experimental metastases induced by TPR–MET *in vivo* in mice[107]. RAS–MAPK and RAC1 signalling are important in the early steps of metastasis[108,109] (FIG. 2), and HGF/SF–MET controls RAS and RAC1 activity[110]. Last, MET and WNT signalling affect metastasis independently, but they functionally interact in colon cancer[111].

HGF/SF and MET signalling in stem and cancer stem cells. Several tumours contain stem cells, known as cancer stem cells or cancer-initiating cells, which constitute a variable proportion of the tumour cell population that effectively reconstitutes the whole tumour after transplantation[112]. The presence of these cells, therefore, has implications for tumour therapy, although their actual role in progression and metastasis is debated[113].

Developmental signalling pathways have crucial roles in the generation and maintenance of stem cells and cancer stem cells[114–117], and a role for HGF/SF and MET in mesenchymal and haematopoietic progenitor and stem cells[118,119,120] has recently been demonstrated. HGF/SF is involved in the mobilization of cardiac stem cells after myocardial infarction[121] and it has been implicated in the activation of satellite cells, which are the stem cells of adult muscle[122]. The developing liver harbours bipotent hepatic stem or progenitor cells, which could be enriched in the presence of HGF/SF[123]. Further, HGF/SF–MET signalling also has important roles in stem or progenitor cell functions in both the developing and the adult pancreas[124].

A recent report has demonstrated that HGF/SF–MET signalling is essential for the maintenance of colon cancer stem cells, as these cells depend on mesenchyme (myofibroblast)-derived HGF/SF for

WNT–β-catenin-dependent transcription and stemness[111] (FIG. 3). These findings are important because, although the role of WNT–β-catenin signalling in cancer stem cells is well known, that of HGF/SF–MET has only just emerged[117,125]. There may be additional tumour types in which the WNT and MET pathways cooperate in maintaining a cancer stem cell compartment. For example, in human breast cancer metastases to the bone, bone-derived or autocrine HGF/SF activates MET–SRC–WNT signalling[126]. Intratumoral MET and stromal HGF/SF affect growth and the prognosis of patients with non-small-cell lung cancer (NSCLC)[127]. In multiple myeloma, HGF/SF–MET and WNT are aberrantly activated and interference with either pathway inhibits the growth of multiple myeloma cells[128,129].

HGF/SF and MET inhibitors for cancer therapy

An increased understanding of the structure–function relationship of ligand, receptor and activators has enabled considerable progress in the development of HGF/SF–MET inhibitors for cancer therapy. The first three classes of inhibitors are discussed below. Inhibitors of HGF/SF activators, HGF/SF inhibitors and MET antagonists are protein therapeutics that function outside target cells. The kinase inhibitors function inside the cell and have constituted, so far, the largest effort within the pharmaceutical industry towards MET-based therapies. Inhibitors of the downstream components of MET signalling, such as inhibitors of RAS, RAF1, SRC, SHP2, MAPKs, AKT and others, are not discussed in this Review.

Inhibitors of HGF/SF activators and HGF/SF. Crystallographic and functional studies by scientists at Genentech, USA, have shown that the first Kunitz domain (KD1) of HAI1 inhibits the activity of the catalytic domain of HGFA, blocking access to pro-HGF/SF[130]. The specificity of KD1 mirrors that of the HAI1 ectodomain, and pegylated KD1 was shown to inhibit the invasion and metastasis of human prostatic cancer cells that overexpressed hepsin in severe combined immunodeficient (SCID) mice[131]. HGFA antibodies that bind either the substrate-binding domain (Fab58 (REF. 132)) or outside the catalytic cleft (Fab40 (REF. 133)), as well as anti-matriptase antibodies (FabE2 (REF. 134)), have also been developed (FIG. 4a).

In a separate approach, Vande Woude and colleagues[135] have demonstrated that antibodies directed towards HGF/SF inhibit the growth of cancer cell lines that are dependent on HGF/SF–MET signalling[135]. These early studies relied on mixtures of antibodies directed against two or more epitopes, but subsequent work has led to the isolation of individual monoclonal antibodies that can block HGF/SF binding to MET. One of these, AMG102, binds the SPH domain[136] (FIG. 4b).

MET antagonists. Truncated splice variants of HGF/SF have formed a strong basis for developing MET antagonists (FIG. 4c). NK1, the shortest splice variant of HGF/SF, has agonistic activity *in vivo*[137] and dimerizes in solution in the presence of heparin, but it can be converted into a receptor antagonist by the mutation of residues at the dimer interface, such as Tyr124 and Asn127 (REFS 138,139). NK2, the most abundant alternative splice variant of HGF/SF, has partial agonistic and antagonistic activity *in vivo*[140], and mutation of an unpaired cysteine (Cys214) yields a variant with receptor antagonistic activity[33]. Finally NK4, a fragment that corresponds to the α-chain of HGF/SF (FIG. 1a), has been extensively characterized as a receptor antagonist by Nakamura, Matsumoto and colleagues[141]. In addition to MET antagonistic activity, NK4 has broad anti-angiogenic activities against HGF/SF-, VEGF- or bFGF (also known as FGF2)-induced angiogenesis[142]; however, NK4 is more difficult to produce than NK1 and NK2 and may require delivery via gene therapy.

Several MET antibodies with antagonistic activity are now available (FIG. 4c). METMab (also known as onartuzumab) is a monovalent antibody developed at Genentech that binds the SEMA domain of MET[143] and that displays potent antagonistic activity[144]. METMab may act as a classic receptor antagonist by competing for the binding of HGF/SF to MET. The MET antibody DN-30 causes MET activation and shedding through ADAM10 (REFS 145,146). Conversion of the intact IgG into a monovalent form abolished agonistic activity and yielded a bona fide antagonist[147]. A MET antibody with antagonistic activity in a bivalent format (11E1) has also been described[148]. The mechanism for the antagonistic activity of 11E1 is unclear but is probably different from those of METMab and DN-30.

MET kinase inhibitors. Impressive numbers of MET kinase inhibitors have been developed over the past 10 years. Compounds for which structural data have been made available (see the MET inhibitors online table; see Further information) are discussed below (see REF. 149 for a recent review). The catalytic domain of MET has the typical architecture of other protein kinases in which an N-terminal lobe (N) with a predominant β-structure is connected by a short linker to an α-helical C-terminal lobe (C). Structures of the auto-inhibited[150] and catalytically active form of the MET kinase[151] are available and, in line with results from studies on other protein kinases, the switch from the inactive to the active conformation is associated with major structural rearrangements (FIG. 5a). In the inactive conformation, the activation loop blocks access of ATP to the enzyme but on activation the loop is extruded (FIG. 5b). ATP binds in a pocket between the N and C lobes and makes extensive hydrogen and ion bonds with residues in the linker (Pro1158 and Met1160), the nucleotide-binding loop (Gly1087 and His1088), the catalytic loop (Asp1204, Arg1208 and Asn1209) and the activation loop (Asp1222)[152] (FIG. 5c).

Superimposed structures of the ATP–MET kinase complex and 25 crystal structures of inhibitor–MET kinase complexes show that inhibitors can be clustered in three groups that differ in their mode of binding (FIG. 5d) (see the MET inhibitors online table; see Further information). Type I compounds and the binding of one of these (PF-02341066 (also known as crizotinib);

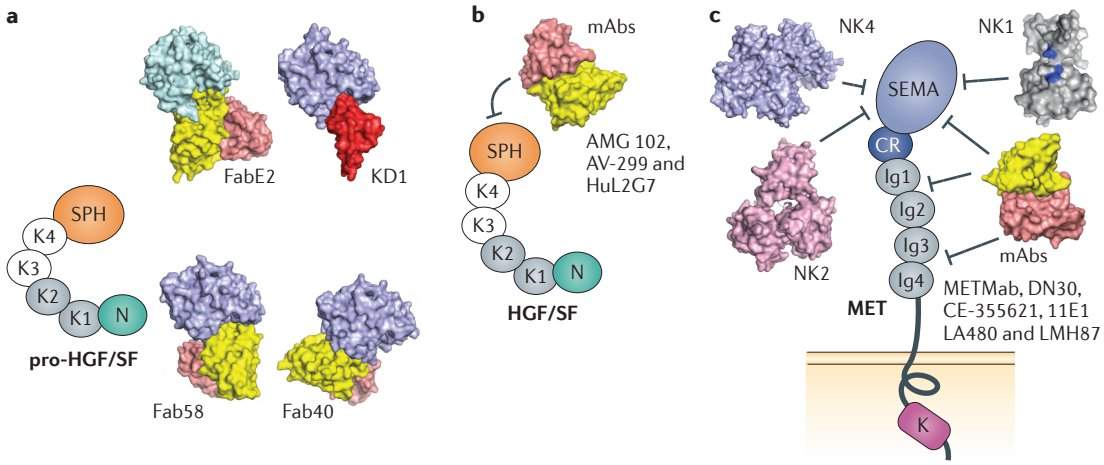


Figure 4 | **Extracellular inhibitors of HGF/SF and MET.** Representative examples of several classes of extracellular hepatocyte growth factor/scatter factor (HGF/SF) and MET inhibitors are shown. **a** | Inhibitors of pro-HGF/SF convertases include the HGF activator (HGFA)-specific Kunitz domain inhibitor KD1, the HGFA antibodies Fab40 and Fab58 and the matriptase antibody FabE2 (protein databank (PDB) IDs: 1YC0, 2R0K, 3K2U and 3BN9, respectively). **b** | Inhibitors of HGF/SF include several monoclonal antibodies (mAbs), including AMG102, AV299 (also known as ficlatuzumab) and HuL2G7. **c** | MET antagonists include several engineered fragments of HGF/SF, namely NK1 linker mutants (Tyr124Ala and Asn127Ala), the NK2 mutant Cys214Ala and NK4, as well as MET antibodies. The structures of NK2 and the NK1 monomer are from PDB IDs 3HN4 and 1NK1, respectively. Antibodies are shown as Fv models (VH is shown in yellow and VL is shown in pink) using PDB ID 1HAW as a template. NK4 is also shown as a model using the 3HN4 structure as a template. Structures and models were drawn with PyMOL[180].

protein databank (PDB) ID: 2WGJ[153]) are shown in FIG. 5d,e. These compounds occupy the ATP-binding pocket, are competitive inhibitors of ATP binding and typically form hydrogen bonds to backbone atoms of Met1160 and Asp1222, and π stacking interactions with Tyr1230 of the activation loop. Most type I compounds display preferential binding to the inactive conformation of the enzyme and have limited activity against the Tyr1230H mutation that is present in certain human tumours. However, there are type I compounds, for example MK-2461, that have a different set of contacts and a strong binding preference for the active form of the kinase[151].

Type II inhibitors (FIG. 5d) also occupy the ATP-binding pocket but also extend into a second pocket that is formed when the side chain of Asp1222, a residue of the activation loop that coordinates a Mg^{2+} ion bound to ATP during catalysis, instead points away from the ATP-binding pocket. The resulting, inactive 'DFG out' conformation that is adopted by residues Asp1222, Phe1223 and Gly1224 enables the binding of type II inhibitors (FIG. 5f) (such as compound BMS-777607 (PDB ID: 3F82)[154]). A smaller number of type III compounds (FIG. 5d) occupy the ATP-binding pocket and extend into a hydrophobic cavity that is formed by the displacement of the αC helix rather than into the pocket that is formed by the DFG out conformation (such as compound MT3 (PDB ID: 3EFJ[155]) (FIG. 5g). Whereas the majority of MET kinase inhibitors that are under development can be clustered into these three main types, there are exceptions. For example, ARQ 197 (also known as tivantinib), like type I inhibitors, inhibits ATP binding to the MET kinase in a non-competitive manner[156], binds the ATP binding cleft and makes canonical contacts with Met1160 but it also occupies a small hydrophobic pocket located between Phe1089 of the glycine-rich loop and Phe1223 (REF. 157).

The different binding modes of the available MET inhibitors have implications for specificity and activity. Although the body of data available is very large, it remains incomplete. As a result, the activity of the MET inhibitors against kinases other than *in vitro* kinase platforms or a limited set of kinase mutants has not been extensively studied and the activity profile of individual inhibitors may change as additional data are obtained. It is also clear that even small modifications can have a profound effect on both potency and/or specificity and, as a great deal of work on the MET kinase inhibitors is still in progress, the activity of several final drugs might display significantly improved profiles compared with those of the lead compounds that have been initially reported.

For example, type I inhibitors have generally been described as specific for the MET kinase (see the MET inhibitors online table; see Further information). However, PF-02341066 has strong activity against anaplastic lymphoma kinase (ALK) and has recently demonstrated impressive therapeutic activity in a group of patients with NSCLC carrying *EML4–ALK* fusions[158]. Among the type II inhibitors are compounds that have been described as specific (for example, L8V) but also others that inhibit multiple RTKs. For example, BMS-777607 has strong activity against MET, RON (also known as MST1R), AXL (also known as UFO) and TYRO3, and XL880 (also known as GSK1363089 and foretinib) inhibits MET, AXL, VEGFR2, platelet-derived growth factor receptor-β (PDGFRβ) and TIE2 (also known as TEK) (see the MET inhibitors online

π stacking interactions
A chemical interaction between aromatic rings that is commonly seen in DNA and RNA structures, nucleoprotein complexes and between complexes of small organic compounds with proteins. The interaction is mediated by π orbitals, and the two rings are piled (stacked).

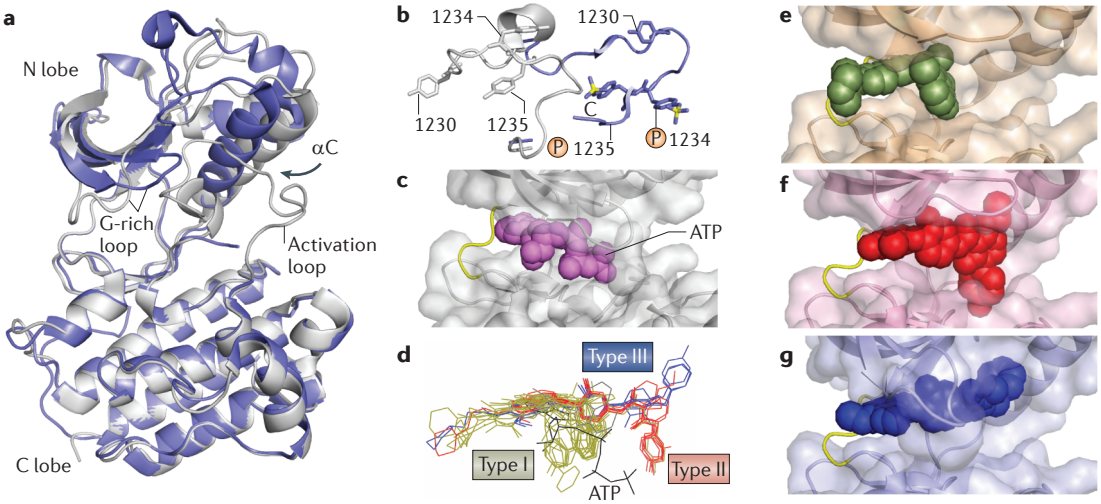


Figure 5 | **MET kinase inhibitors.** Superimposed structures of the inactive (protein databank (PDB) ID: 2G15; shown in grey) and the active (PDB ID: 3Q6U; shown in dark blue) structures of the MET kinase are shown (part **a**). The activation loop in 3Q6U is absent because it is disordered in the structure. Superimposed structures of the activation loops of inactive and active forms of the MET kinase are shown (part **b**). The inactive conformation (shown in grey) of the activation loop is from PDB ID 2G15, the active conformation (shown in dark blue) is from the structure of an analogue of MK-2461 in complex with the MET kinase (PDB ID: 3Q6W). Binding of ATP to the MET kinase (PDB ID: 3DQC) is shown (part **c**). Superimposed structures of the MET kinase inhibitors for which crystal structures have been determined (see the MET inhibitors online table; see Further information) are shown (part **d**). For reference, ATP is shown in black. Type I inhibitors are shown in green, type II inhibitors are shown in red and type III inhibitors are shown in blue. The compound ARQ 197 does not cluster well into these three main types of inhibitor and is shown in grey. Examples (parts **e**, **f** and **g**) of binding of type I, type II and type III inhibitors to the MET kinase are shown. The type I inhibitor is PF-02341066 (PDB ID: 2WGJ) (part **e**). The type II inhibitor is BMS-777607 (PDB ID: 3F82) (part **f**). The type III inhibitor is MT3 (PDB ID: 3EFJ) (part **g**). Structures were drawn with PyMOL[180]. P, phosphorylation.

table; see Further information). Type III inhibitors have been described as selective, but a derivative of MT4 has much more potent activity against RON than the lead compound, thus confirming that medicinal chemistry can reshape both potency and specificity.

Targeting HGF/SF–MET in cancer

Patient stratification. The most notable advances in cancer therapy that have occurred in the past decade — for example, with tumours carrying BCR–ABL or EML4–ALK fusion genes[158,159] — have resulted from three crucial factors: a genetic defect yielding a single target for therapy and the availability of an effective inhibitor and effective methods for the identification of tumours carrying the relevant genetic defect. In the case of HGF/SF–MET, the role of aberrant signalling in cancer is clear, and effective therapeutics are now available, but methods for assessing the level of HGF/SF–MET expression and activity have not been extensively validated and deployed. Thus, patient stratification according to HGF/SF–MET expression or MET phosphorylation needs further development and is not currently an important component of study design in the numerous clinical trials that are in progress (FIG. 6a,b) (see the Clinical Trials Involving HGF/SF-MET Inhibitors online table; see Further information). Here, we argue for patient stratification as an essential component for therapeutic success and suggest that antibody-based analysis of HGF/SF–MET expression levels[160] and/or receptor phosphorylation[161] may constitute valid strategies.

MET signalling crosstalk and therapy. In recent years signalling crosstalk has evolved from a loose biochemical concept to one with a rigorous genetic foundation[43,85] and major clinical relevance, as demonstrated by the findings of studies with MET and EGFR in NSCLC[75,76] (discussed above). This mechanism is also active in a subset of breast cancers[162] and might be at work in other tumours, as revealed by preclinical studies with human tumour xenografts[163]. Conversely, the treatment of tumour cells with MET kinase inhibitors may lead to the selection of tumour cell populations that escape growth inhibition via the EGFR or SRC kinases[164–166]. The implications of these findings for therapy are clear and argue for a shift from monotherapy to combination (multi-target) therapies in which both the signalling pathway primarily responsible for the cancer phenotype and the 'rescue pathways' are targeted concurrently (FIG. 6c).

Anti-angiogenesis therapy and MET activation. Anti-angiogenesis therapies have been shown to impair the growth of a number of experimental and human tumours and are currently used in metastatic colon cancer and NSCLC; the rationale for combining anti-angiogenesis therapies with inhibitors of MET is discussed above. Concurrent inhibition of VEGFR and MET can be achieved either by combining specific VEGF–VEGFR and MET inhibitors or by dual or multi-specificity kinase inhibitors that inhibit both MET and VEGFR2, as has been shown in human tumour

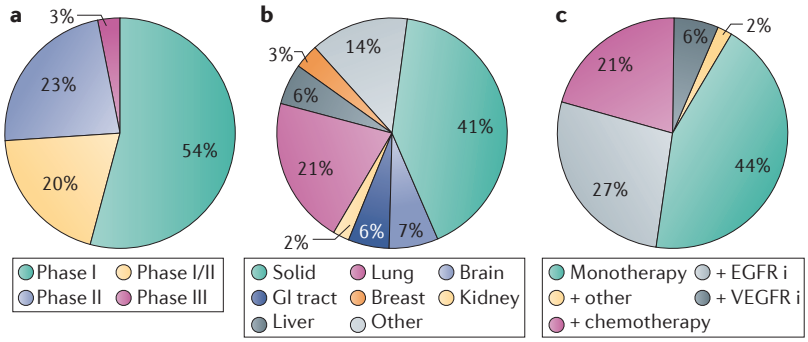


Figure 6 | **Clinical trials with HGF/SF–MET inhibitors.** The figure illustrates data from 96 clinical studies involving antibodies to hepatocyte growth factor/scatter factor (HGF/SF) or MET and small-molecule inhibitors of the MET kinase listed in the US National Institutes of Health registry of Clinical Trials (see the ClinicalTrials.gov website and the Clinical Trials Involving HGF/SF-MET Inhibitors online table; see Further information). **a** | The distribution according to study type and stage (96 trials) is shown. 54% of these trials are Phase I studies primarily focusing on drug dosage and safety; whereas, 46% are Phase I/II, Phase II and Phase III trials addressing clinical efficacy. **b** | The distribution according to tumour type (84 trials) is shown. These 84 trials involve cancer patients, of which 41% had advanced stage multiple solid tumours; whereas, 59% had specific tumour types. Among the 59%, the studies on lung tumours constitute the largest group (21%), followed by brain tumours (7%) and tumours of the gastrointestinal (GI) tract (6%) and liver (6%). **c** | The distribution according to therapeutic strategy (monotherapy versus combined therapy) is shown. Of 44 efficacy studies (Phase I/II, Phase II and Phase III), 41% involve HGF/SF–MET monotherapies, 21% involve an HGF/SF–MET drug combined with chemotherapy, and 27% and 6% involve an HGF/SF-MET drug combined with inhibitors of epidermal growth factor receptor (EGFR i) or vascular endothelial growth factor receptor (VEGFR i), respectively. Note that monotherapy includes not only specific HGF/SF–MET inhibitors but also agents with multiple targets.

xenograft models[163] (see the Clinical Trials Involving HGF/SF-MET Inhibitors online table; see Further information).

Early results from clinical trials. The vast majority of the clinical trials that aim to define the efficacy of HGF/SF–MET therapeutics are currently in progress but initial results from several studies have been made available. Striking results with the MET antibody METMab in combination with an EGFR inhibitor (erlotinib) have been reported in patients with NSCLC[167]. As determined retrospectively by immunohistochemistry, METMab increased progression-free survival (PFS) in patients with high levels of MET expression compared with the group receiving erlotinib alone; however, patients with low or no MET expression experienced decreased PFS[167]. Improvement in overall survival has also been reported in a different patient group — specifically, patients with advanced gastric adenocarcinoma in which treatment with the HGF/SF monoclonal antibody AMG102 (also known as rilotumumab) combined with chemotherapy was compared with chemotherapy alone[168]. Even in this study, the best response was observed in patients expressing a high level of MET in the tumour[168]. Thus, both the study with METMab in NSCLC and the study with AMG102 in gastric cancer highlight an essential requirement for patient stratification to ensure clinical benefit.

A large number of kinase inhibitors are now in clinical trials (FIG. 6c) (see the Clinical Trials Involving HGF/SF-MET Inhibitors online table; see Further information). A Phase II study with ARQ 197 in patients with NSCLC has shown a clear trend of improved PFS and overall survival in patients treated with the inhibitor plus erlotinib compared with patients who received erlotinib and a placebo[169]; a trial with this drug combination has now advanced to a Phase III study. In other clinical trials, treatment with ARQ 197 alone also inhibited the growth of hepatocellular and pancreatic carcinomas, as well as tumours driven by microphthalmia-associated transcription factor (MITF)[170]. A recent report has documented striking activity of the MET and ALK inhibitor PF-02341066 in patients with NSCLC carrying an EML4–ALK fusion[158]. The EML4–ALK fusion protein occurs in 2–7% of patients with NSCLC, and PF-02341066 induced a major therapeutic response in this patient group compared with standard chemotherapy[158]. The bulk of the therapeutic effect of PF-02341066 in patients with NSCLC carrying the EML4–ALK fusion protein is most probably due to inhibition of ALK[158], but the drug is also a potent MET kinase inhibitor and it would be interesting, therefore, to further analyse the patient response on the basis of the level of MET expression in the tumour.

Studies with the multi-target MET inhibitor XL184 (also known as cabozantinib) have shown significant activity against a number of solid tumours, including breast cancer, NSCLC, melanoma and liver cancer[171]. Ovarian cancer[172] displayed notable responses to XL184, but the most remarkable response was seen in both soft tissue and bone metastatic lesions in patients with metastatic castration-resistant prostate cancer (CRPC)[173]. The success of XL184 against CRPC primary and metastatic tumours marks a turning point for MET kinase inhibitors and their power to change terminal cancer prognoses. XL184 also showed activity against medullary thyroid cancer[174] and the range of applications for this drug may further expand.

Finally, the multi-target MET inhibitor XL880 has been reported to cause tumour reduction in patients with breast cancer with resistance to inhibitors of EGFR (such as erlotinib) or EGFR and ERBB2 (such as lapatinib)[175], a result that mirrors those obtained with MET and EGFR inhibitors in NSCLC.

Conclusions and perspectives

The availability of a wealth of HGF/SF–MET inhibitors with a range of potencies and specificities has provided a strong basis for assessing the therapeutic value of HGF/SF–MET inhibition in human cancer, and initial results from clinical studies have demonstrated therapeutic benefits in patients with a variety of advanced or metastatic tumours, including NSCLC, and breast, prostate, liver and renal cancer. These results have enabled the progression of several compounds to Phase III trials, and larger studies and rigorous patient stratification procedures will further clarify the therapeutic value and long-term safety of HGF/SF–MET inhibitors in cancer patients.

With the exception of biological agents such as METMab, and the low-molecular-mass compound ARQ 197, the first group of therapeutics to reach Phase II and Phase III studies predominantly included inhibitors with multiple specificity that, in addition to MET,

Progression-free survival
(PFS). A statistical parameter that measures the time — for example, after diagnosis and/or treatment — in which the disease remains stable (progression free). It can also be expressed as the proportion of patients whose disease has remained stable after diagnosis and/or treatment at a specified time.

Overall survival
A statistical parameter that measures the survival time of a patient or a patient group after diagnosis and/or treatment, regardless of the cause of death. It can also be expressed as the proportion of patients who remain alive at a specified time.

target other RTKs involved in cancer, such as VEGFR and RET. This makes it currently difficult to define the contribution of MET inhibition to the overall therapeutic response but comparisons of results with more specific kinase inhibitors or biological molecules is likely to define the clinical benefit derived from targeting MET in the future. Whether the emergence of resistance to MET kinase inhibitors will constitute a serious limitation for this class of therapeutics is currently difficult to assess. Resistance can rapidly develop with cancer cell lines in culture through multiple mechanisms[164–166], but patient data are clearly required to define the potential effect on therapeutic outcome. Resistance to kinase inhibitors can also be circumvented by combining different types of inhibitors, as demonstrated recently for BCR–ABL[176], or by shifting to the use of MET antagonists.

Even at this early stage of clinical investigation, however, it is safe to conclude that inhibition of HGF/SF–MET signalling in cancer has evolved during the past decade from a concept built on strong experimental foundations (activity on cells and mouse models of disease) to one with considerable scope for the control of human cancer.

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Competing interests statement
The authors declare no competing financial interests.

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AMG102 | ARQ 197 | BMS-777607 | erlotinib | lapatinib | METMab | PF-02341066 | XL184 | XL880

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