

## Targeting the c-Met Signaling Pathway in Cancer

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**Abstract** On binding to the cell surface receptor tyrosine kinase (TK) known as c-Met, hepatocyte growth factor (HGF) stimulates mitogenesis, motogenesis, and morphogenesis in a wide range of cellular targets including, epithelial and endothelial cells, hematopoietic cells, neurons, melanocytes, and hepatocytes. These pleiotropic actions are fundamentally important during development, homeostasis, and tissue regeneration. HGF signaling also contributes to oncogenesis and tumor progression in several human cancers and promotes aggressive cellular invasiveness that is strongly linked to tumor metastasis. Our present understanding of c-Met oncogenic signaling supports at least three avenues of pathway selective anticancer drug development: antagonism of ligand/receptor interaction, inhibition of TK catalytic activity, and blockade of intracellular receptor/effector interactions. Potent and selective preclinical drug candidates have been developed using all three strategies, and human clinical trials in two of the three areas are now under way.

## Background

The *MET* oncogene was isolated from a human osteogenic sarcoma cell line that had been chemically mutagenized *in vitro*. Transforming activity was due to a DNA rearrangement where sequences from the translocated promoter region (*TPR*) locus on chromosome 1 were fused to sequences from the *MET* locus on chromosome 7 (*TPR-MET*), a rearrangement that was later found in patients with gastric carcinoma (1, 2). Isolation of the full-length *MET* proto-oncogene coding sequence revealed structural features of a membrane spanning receptor tyrosine kinase (TK; ref. 1). The identification of hepatocyte growth factor (HGF) as the natural ligand for the c-Met receptor protein and the identity of scatter factor (SF) and HGF united a collection of findings showing that a single receptor transduced multiple biological activities, including motility, proliferation, survival, and morphogenesis (3–6). Both HGF/SF and c-Met proteins are processed proteolytically from single-chain precursors into mature disulfide-linked heterodimers. Both are widely expressed early in development; deletion of either gene causes lethal disruptions to embryogenesis; and widespread expression persists throughout adulthood (3, 4, 6). Both *MET*

and *HGF/SF* genes are up-regulated after kidney, liver, or heart injury, suggestive of a general homeostatic mechanism of protection against tissue damage and promotion of tissue repair and regeneration (7–11).

Upon HGF/SF binding, c-Met autophosphorylation occurs on two tyrosine residues (Y1234 and Y1235) within the activation loop of the TK domain, which regulate kinase activity. Phosphorylation on two tyrosine residues near the COOH terminus (Y1349 and Y1356) forms a multifunctional docking site that recruits intracellular adapters via Src homology-2 domains and other recognition motifs, leading to downstream signaling (4, 6). An intact multifunctional docking site is required to mediate transformation and induce a metastatic phenotype (6). Among the most widely studied adapter proteins and direct kinase substrates in this pathway are growth factor receptor-bound protein 2 (Grb2), Gab1, phosphatidylinositol 3-kinase (PI3K), phospholipase C- $\gamma$ , Shc, Src, Shp2, Ship1, and signal transducer and activator of transcription 3 (4, 6). Gab1 and Grb2 are considered critical effectors and are among those that interact directly with the receptor; through these, a larger network of adaptor proteins are involved in signaling, presumably contributing to the pleiotropic biological effects elicited by HGF/SF binding. In particular, the direct binding of Grb2 to the c-Met docking site through Y1356 links the receptor to the Ras/mitogen-activated protein kinase pathway regulating cell cycle progression (4). Gab1 is recruited to c-Met through direct binding and indirectly via Grb2, initiating morphogenesis in several epithelial and vascular endothelial cell types (5, 12). Gab1 tyrosyl phosphorylation by the c-Met TK leads to the recruitment of PT3K, which also binds c-Met directly through its p85 subunit, contributing to cell cycle progression, protection from apoptosis, and increased cell motility (5). Among the many genes up-regulated by pathway activation relevant to cancer are those encoding proteases that regulate HGF/SF and c-Met processing and extracellular matrix remodeling, as well as *MET* itself, creating the potential for c-Met overexpression in otherwise normal target cells through persistent ligand stimulation (4).

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## Oncogenic c-Met Signaling

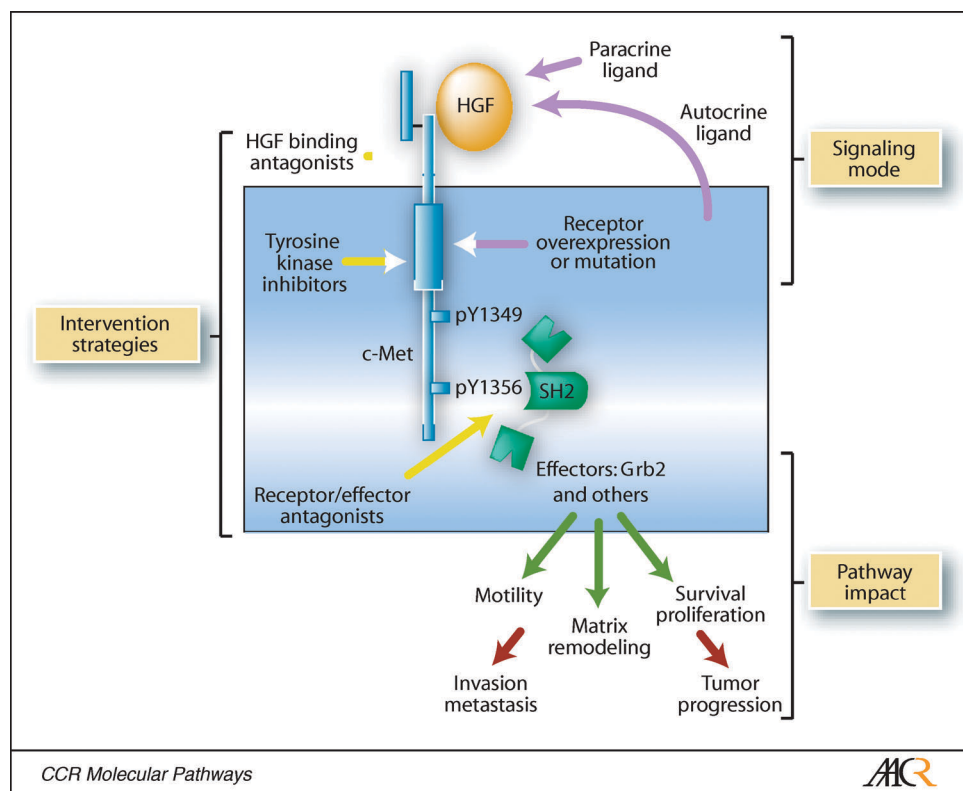
c-Met signaling is implicated in a wide variety of human malignancies, including colon, gastric, bladder, breast, ovarian, pancreatic, kidney, liver, lung, head and neck, thyroid, and prostate cancers as well as sarcomas, hematologic malignancies, melanoma, and central nervous system tumors (3, 6, 13, 14). Through paracrine signaling, overexpression of ligand and/or receptor, autocrine loop formation and/or receptor mutation, and gene rearrangement and/or amplification, this signaling pathway can enhance tumor cell proliferation, survival, motility, and invasion. Inappropriate c-Met signaling in disease can resemble developmental transitions between epithelial and mesenchymal cell types normally regulated by HGF/SF. Tumors of epithelial origin frequently display c-Met overexpression and paracrine delivery of HGF/SF results in dysregulated signaling, whereas cells of mesenchymal origin that normally express HGF/SF often acquire c-Met expression, and several sarcomas and central nervous system tumors display autocrine c-Met signaling (3, 14). Importantly, the c-Met pathway activates a program of cell dissociation and motility coupled with increased protease production that has been shown to promote cellular invasion through extracellular matrices and that closely resembles tumor metastasis *in vivo* (3). In addition, pathway activation in vascular cells stimulates tumor angiogenesis, facilitating tumor growth for cancers that are growth limited by hypoxia and promoting tumor metastasis. Hypoxia alone up-regulates c-Met expression and enhances HGF/SF signaling in cultured cells and mouse tumor models (15).

Inherited missense mutations in *MET* were first found in individuals with hereditary papillary renal carcinoma type 1;

similar somatic mutations were also found in a small subset (13%) of sporadic papillary renal carcinoma tumor samples (16–19). The biochemical and biological effect of these *MET* mutants have been investigated in several model systems, confirming their suspected oncogenic potential (20–26). Trisomy of chromosome 7, which contains both *MET* and *HGF/SF* genes, occurs in 95% of sporadic papillary renal carcinoma (27); a detailed study of trisomy 7 in hereditary papillary renal carcinoma revealed nonrandom duplication of the mutant *MET* allele in 100% of tumor samples (28). Somatic *MET* mutations have since been found in several other human cancers, including gastric and liver cancer (29, 30), small cell and non-small cell lung cancers (31–33), and metastases of head and neck squamous cell carcinoma (34, 35). Unlike renal carcinoma, where mutations are typically confined to exons encoding the TK domain, these mutations encompass other receptor regions, most notably, the juxtamembrane region, where missense and deletion mutations that delay c-Met down-regulation occur with significant frequency (~12%) in lung cancer tumors (33). Overall, *MET* mutation occurs at a lower frequency than most other mechanisms of pathway activation in tumors; nonetheless, mutations provide strong direct evidence of the pathway's oncogenic potential and a means to identify patient subpopulations that might benefit most from c-Met-targeted therapy.

## Cancer Drug Development Targeting the c-Met Pathway

Our present understanding of oncogenesis mediated by c-Met signaling supports at least three avenues of therapeutic development: antagonism of ligand/receptor interaction,



**Fig. 1.** c-Met-mediated oncogenic signaling. Activation of c-Met-mediated oncogenic signaling occurs most commonly through aberrant paracrine HGF stimulation and consequent receptor overexpression or through autocrine HGF production, receptor mutation, or gene amplification or rearrangement. Increased cell proliferation, survival, motility, and extracellular matrix degradation resulting from pathway activation contributes to tumor growth, invasiveness, and metastasis. At least three routes of pathway intervention have been followed as selective anticancer drug development strategies: antagonism of ligand binding, inhibition of TK catalytic function, and blockade of interactions between activated receptors and downstream intracellular effectors.

inhibition of TK catalytic activity, and blockade of receptor/effector interactions (Fig. 1). In addition, combinations of conventional and c-Met-targeted therapies may offer promise for specific cancers (36).

Antagonism of ligand binding is a logical therapeutic strategy for a majority of carcinomas, where paracrine HGF/SF signaling and c-Met overexpression result in aberrant pathway activation, and for melanoma, glioblastoma, and several sarcomas, where autocrine HGF/SF signaling drives tumor progression. A collection of structure/function studies, including the early discovery that a naturally occurring truncated HGF/SF variant (HGF/NK2) was a specific competitive mitogenic antagonist, led the development of HGF/NK4, a larger, more antagonistic HGF/SF fragment (37, 38), and to an uncleavable form of pro-HGF/SF (39), both of which block tumor growth and metastasis in animal models. Similarly, the early development of a c-Met ectodomain/IgG fusion protein with HGF/SF-neutralizing activity preceded the engineering of a soluble c-Met ectodomain fragments with pathway neutralizing and anti-tumor activities (40, 41). Neutralizing mouse monoclonal antibodies against human HGF/SF have also been shown to be effective antitumor agents in animal models (42–44). The recent development of a fully human monoclonal antibody with HGF/SF-neutralizing and antitumor properties and its introduction into phase 1 human clinical trials is an important step forward (45, 46).

Recent successes in the treatment of chronic myeloid leukemia, gastrointestinal stromal tumors, and other cancers using TK inhibitors strongly supports the potential efficacy of this therapeutic strategy in targeting c-Met. Early work with the staurosporine-like alkaloid K252a showed that it could inhibit c-Met autophosphorylation and mitogen-activated protein kinase and Akt activation and revert the transforming potential of the *TPR-MET* oncogene (47). Recently, much more selective synthetic inhibitors of c-Met ATP binding, effective in the nanomolar concentration range in cultured cells, have been developed and tested in various model systems (13, 48–54). Of these, the novel indolinone compounds SU11274 and PHA665752 displayed a minimum of 50-fold selectivity for c-Met relative to several other TKs and potentially blocked HGF stimulated activities in cultured cells and tumorigenicity in well-characterized c-Met-driven xenograft models (13). Analysis of SU11274 using cells expressing hereditary papillary renal carcinoma-associated *MET* mutants revealed interesting differences in sensitivity (51), and gastric cancer cells with *MET* gene amplification displayed significantly increased sensitivity to PHA665752 (54), strongly reinforcing the concept that knowledge of genetic alterations should help predict the efficacy of c-Met TK inhibitors for specific patient groups. Not surprisingly, the number of pharmaceutical and biotechnology companies that have

announced drug development programs targeting the c-Met TK has grown considerably in the last 3 years (55–57). Although it is anticipated that combinations of pathway selective therapies may eventually be needed for many complex cancer types, single-agent clinical trials targeting cancers where the pathway is an established contributor to disease progression will probably set the stage for selecting which drugs to combine as well as appropriate patient populations for more advanced trials.

The requirement of the COOH-terminal docking site for wild-type or mutant c-Met-transforming activity in cultured cells (22, 23) and the known roles of intracellular effectors including Gab1, PI3K, Grb2, Shc, and signal transducer and activator of transcription 3 in cell transformation (4, 6) suggest that targeting one or more of these interactions could effectively disrupt c-Met-driven oncogenesis. Knowledge of the unique structure of the Grb2 Src homology-2 domain provided the basis for the development of small synthetic Grb2 selective binding antagonists (58). Further refinement of these early structures have yielded compounds that block HGF/SF-stimulated cell motility, matrix invasion, and morphogenesis in normal and tumor-derived cultured cells and vascular endothelial cells, at low nanomolar concentrations (59). Several agents targeting TK effectors, including signal transducer and activator of transcription 3, Akt, and PI3K, are also under development, although their basic and preclinical development has not focused on c-Met oncogenic signaling. Beyond effector targeting, compounds that block HSP90/client interactions, such as geldanamycin (60), also potentially block c-Met oncogenic signaling (61), so potentially, in fact, as to suggest that other mechanisms of drug action may be involved (62). Phase 1 and 2 clinical trials of geldanamycin-related compounds are under way for a variety of cancers where the c-Met pathway is active (63). Combining agents such as geldanamycin that attenuate the supply of new receptors to the cell surface with inhibitors of other specific receptor functions, could lower the effective dose of each, reducing the likelihood of drug toxicity and the selection pressure for drug-resistant mutations.

Extensive evidence that c-Met signaling is involved in the progression and spread of several human cancers and a refined understanding of its molecular basis have facilitated the development of a variety of pathway antagonists with clinical potential. As drug development progresses, there will be new challenges to accurately identify patients most likely to benefit from c-Met-directed therapeutics, to assess drug activities in tumor tissues, and to understand the potential toxicity of long-term c-Met pathway blockade. Armed with knowledge of the genetic, biochemical, and physiologic correlates of oncogenic signal transduction, clearly distinguished from those of development and adult homeostasis, our greater goal will surely be *MET*.

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