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Perspective

Targeting *MET* in cancer therapy

Hong-Nan Mo, Peng Liu*

Department of Medical Oncology, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100021, China

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Abstract

MET encodes a receptor tyrosine kinase c-MET for hepatocyte growth factor (HGF). The specific combination of c-MET and HGF activates downstream signaling pathways to trigger cell migration, proliferation, and angiogenesis. *MET* exon 14 alterations and *MET* gene amplification play a critical role in the origin of cancer. Several monoclonal antibodies and small-molecule inhibitors of c-MET have been evaluated in clinical trials. In patients with advanced non-small cell lung cancer, cabozantinib and crizotinib showed clear efficacy with a generally tolerable adverse events profile. In gastrointestinal cancers, most phase III trials of MET inhibitors showed negative results. In hepatocellular carcinoma, based on the encouraging results of some phase II studies, a series of phase III trials are currently recruiting patients to access the efficacy and safety of *MET* inhibitors.

Keywords: Proto-oncogene protein c-MET; Antineoplastic agents; Protein kinase inhibitors; Molecular targeted therapy

Introduction

MET, also known as the N-methyl-N′-nitroso-guanidine human osteosarcoma transforming gene, is a proto-oncogene encoding a receptor tyrosine kinase c-MET for hepatocyte growth factor (HGF).[1,2] The binding of HGF results in c-MET dimerization and autophosphorylation, which in turn activates the mitogen-activated protein kinase (MAPK), phosphatidylinositol 3-kinase (PI3K), v-src avian sarcoma (Schmidt-Ruppin A-2) viral oncogene homolog (SRC), and signal transducer and activator of transcription (STAT) signaling pathways.[3] c-MET activation is normally essential for cell morphogenesis, scattering and motility, proliferation, and protection from apoptosis.[3] The *MET* pathway plays an important role in wound healing, post-injury response, and degenerative diseases such as renal and lung fibrosis.[4]

Aberrant *MET* expression is widely observed in various malignancies, particularly non-small cell lung cancer (NSCLC), gastrointestinal (GI) cancer, and hepatocellular carcinoma (HCC).[5−8] *MET*-receptor overexpression, genomic amplification, mutation, or alternative splicing results in cellular deregulation of

* Corresponding author.

E-mail address: 13910216310@163.com (P. Liu).

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MET.[9] Several agents targeting *MET* have been examined in clinical trials, but the results range from relatively high response rates to prominent failure. This review summarizes *MET* pathway dysregulation in cancers and the use of *MET* inhibitors to treat advanced cancers.

c-MET pathway

The *MET* gene is located on chromosome 7q21–q31 and is approximately 125 kb long with 21 exons. c-MET is a heterodimer composed of a 50-kDa highly glycosylated alpha-chain subunit and 145-kDa beta-chain.[10] This transmembrane protein consists of a large extracellular region, membrane-spanning segment, and intracellular tyrosine kinase domain.[11] c-MET is the only known high-affinity receptor for HGF and is widely expressed in cells of epithelial-endothelial origin, including liver cells, fibroblasts, hematopoietic cells, and keratinocytes.[12]

HGF, also known as scatter factor, was initially identified as a growth factor for hepatocytes and fibroblast-derived cell motility factor.[13] HGF forms a heterodimer consisting of a 69-kDa alpha-chain subunit and 34-kDa beta-chain, linked by a disulfide bond. HGF can induce cell dissociation and movement, promote mitosis, and induce morphogenesis of epithelial cells. In addition, it can stimulate the growth of vascular endothelial cells and increase extracellular matrix protein hydrolysis.

The specific combination of c-MET and HGF induces a conformational change in the c-MET receptor protein, and its intracellular protein tyrosine kinase domain is activated by autophosphorylation. The downstream MAPK, PI3K, SRC, and STAT signaling pathways are successively phosphorylated and activated.[14] The waterfall-like phosphorylation reactions amplify the signal step-by-step. Eventually, the c-MET pathway triggers a variety of cellular responses, including cell migration, mitogenesis, morphogenesis, proliferation, and angiogenesis.[4]

In some NSCLCs, the c-MET pathway is thought to be the primary driving mechanism, particularly *MET* exon 14 (METex14) alterations and *MET* gene amplification. METex14 alterations are detected in approximately 3–4% of lung adenocarcinomas and 20–30% of pulmonary sarcomatoid carcinomas.[15] These alterations result in decreased degradation of c-MET, sustained *MET* overexpression, and oncogenesis. Next-generation sequencing is the most frequently used tool for diagnostic testing of METex14 alterations.[16,17] The prevalence of *MET* amplification in NSCLC ranges from 1% to 5%. The fluorescence *in situ* hybridization can be used to determine the ratio of MET to the centromeric portion of chromosome 7 (CEP7) to distinguish between polysomy and true *MET* amplification (MET/CEP7 ratio > 5).

As *MET* mutations are exceedingly rare in GI cancers, *MET* is mainly activated by receptor overexpression or genomic up-regulation.[8] *MET* amplification appears to be rare in GI cancers, with reported incidences of 0–5%.[18]

c-MET signaling promotes hepatocyte proliferation and regeneration, suggesting a potential tumor-promoting role in HCC.[19,20] c-MET transcription and expression is increased in 30–100% of HCC compared to the surrounding tissue, while HGF expression is decreased in tumors compared to that in the surrounding liver tissue.[7,21]

The c-MET pathway exhibits significant cross-talk with other signaling pathways. Interactions between MET and HER2 family members have emerged as a major mechanism of tumor progression and treatment resistance. MET signaling has also been shown to interact with the vascular endothelial growth factor (VEGF) and VEGF receptor (VEGFR) pathways.[22] *MET* activation increases VEGF-A expression to promote angiogenesis and endothelial cell growth.

c-MET deregulation plays important roles in tumor formation, growth, maintenance, and invasion. It has implicated in several cancers, including lung, colorectal, liver, and gastric carcinoma. Therefore, c-MET has become an attractive target for cancer treatment and drug development.

Inhibit *MET* for malignancy

Currently, there are three main methods for inhibiting the kinase activity of c-MET: preventing the extracellular combination of c-MET and HGF with neutralizing antibodies or biological antagonists; preventing phosphorylation of tyrosine in the kinase domain using small-molecule inhibitors; blocking c-MET kinase-dependent signaling through relevant signal transducers or downstream signaling components.

Several small-molecule inhibitors and monoclonal antibodies of c-MET have been evaluated in preclinical studies. Crizotinib is a dual c-MET and anaplastic lymphoma kinase (ALK) inhibitor that has been approved for treating ALK-positive NSCLC.[23] Cabozantinib is a multikinase inhibitor that targets c-MET, VEGFR2, AXL, KIT, TIE2, FLT3, and RET.[24] Tivantinib is a non-adenosine triphosphate (ATP) competitive c-MET inhibitor.[25] Foretinib is a multikinase inhibitor of