MET Receptor Tyrosine Kinase

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Abstract

MET receptor tyrosine kinase (RTK) and its ligand hepatocyte growth factor (HGF) have become important therapeutic target in oncology, especially lung cancer. MET RTK is involved in cancer cell growth/survival, motility/migration, invasion/metastasis, and in angiogenesis. MET can be overexpressed in lung cancer, sometimes mutated, and sometimes amplified. Not only can MET be overexpressed, there are subsets of lung cancer tumors that have HGF overexpression. The mutations of MET can occur in the semaphorin and/or juxtamembrane domain in a majority of times. Amplification of MET can occur de novo in primary/metastatic tumors, as well arise in the context of therapeutic inhibition. There are a number of clinical inhibitors that have been developed against MET/HGF. Small molecule inhibitors such as XL184 and PF02341066 have come to clinical fruition, as well as antibodies against MET (such as MetMAb). These inhibitors will be discussed.

BACKGROUND

The c-MET (hereafter referred as MET) receptor tyrosine kinase (RTK) was originally identified as the cellular homologue of the TPR-MET oncoprotein(1). MET can be overexpressed in a number of malignancies, sometimes mutated (germline mutations/single nucleotide polymorphisms (SNPs) or somatic mutations), or sometimes even amplified. MET, located on chromosome 7 (7q21–q31), encodes for a single precursor that is post-transcriptionally digested and glycosylated, forming a 50 kDa extracellular α-chain and a transmembrane 140 kDa ß-chain, which are then linked by disulfide bonds. The ligand for MET has been identified as hepatocyte growth factor (HGF). The MET Sema domain folds into a seven ß-propeller structure, where blades 2 and 3 bottom face bind to HGF ß-chain active site region.

Ligation of the MET receptor by HGF leads to receptor dimerization and activation of its intrinsic tyrosine kinase, followed by internalization into clathrin-coated vesicles, delivery to sorting endosomes, and degradation via the lysosomal pathway. Phosphorylation of MET at Y1230, Y1234 and Y1235 in the activation loop of the tyrosine kinase domain correlates with increased tyrosine kinase activity. MET activation can lead to autophosphorylation or phosphorylation of downstream intermediates and activation of signaling pathways. Also, Y1003 within the juxtamembrane domain recruits c-Cbl (E3-ubiquitin ligase) when phosphorylated. A large number of downstream targets have been defined for MET. As an example, in small cell lung cancer (SCLC), activation of MET with HGF leads to phosphorylation/activation of several pathways involving cell proliferation/survival (ERK1/2, AKT), cell cycle (RB), and cytoskeletal proteins (paxillin, FAK)(2).
Expression of MET and phospho-MET has been studied for a number of tumors. In a recent systematic study of a number of solid tumors, for lung cancer, 28% (1/40) of tumor tissues had no expression (0), whereas 33% (13/40) had 1+, 35% (14/40) had 2+, and 5% (2/40) had 3+ c-MET expression. Forty percent (16/40) of lung cancer tissues overexpressed c-MET. In lung cancer, 73% expressed phospho-MET (1+, 14/40; 2+, 13/40; 3+, 2/40) while 27% (11/40) did not(3).

Missense mutations of MET have been reported in a variety of cancers, with the initial ones identified in the cytoplasmic activation-loop tyrosine kinase domain. Identification of activating mutations of MET in hereditary papillary renal carcinomas provided the first direct evidence linking MET directly to human oncogenesis. Germline missense mutations in the TK domain are detected in the majority of hereditary papillary renal cell carcinomas (HPRCC); somatic mutations have been found in some sporadic papillary renal carcinomas(4). TK domain mutations can occur in other tumor types such as head and neck cancer(5) and glioblastomas (6). A number of tumors have been investigated for MET mutations(3). These mutations could potentially be germline (including non-synonymous SNPs, however, referred here as germline) or somatic. The relative role of germline mutations in non-HPRCC tumors is beginning to be defined. A large number of these solid tumors do not have mutations in the TK domain, but there are mutations in the JM and semaphorin Sema domain. JM domains of RTKs are thought to be key regulators of catalytic functions.

We have shown specific JM mutations of MET in various tumors (such as SCLC, non-SCLC (NSCLC), malignant pleural mesothelioma, melanoma, head and neck cancer, and pancreatic cancer(7,8)). We further showed in a study of 127 adenocarcinoma NSCLC tumors that there were mutations of MET at R988C, T1010I, and S1058P. These JM domain mutations of MET led to enhanced tumorigenicity, increased cell motility, altered cellular architecture, increased MET phosphorylation, and downstream signal molecule phosphorylation, and stronger response to therapeutic inhibition with small molecule inhibitors(9). It is possible that these variations may affect lung cancer risk in carriers.

There are also clusters of mutations within the Sema domain for certain tumors, alter the binding to HGF, and appear to be activating mutations. The Sema domain is conserved among all semaphorins and is also found in the plexins and MET. In MET, the Sema domain is encoded by exon 2, and binds specifically to HGF. The extracellular ligand-binding domain in the MET ectodomain was identified as adopting a seven-blade β-propeller fold for the Sema domain of MET, homologous to the β-propeller fold template seen in the N-terminal domain of αv-integrin(6).

MET can also be amplified in lung cancers. In de novo lung cancers, approximately 11% of tumors can be amplified for MET(10). MET can also be amplified in resistance to therapy.

**SUMMARY OF PRESENTATIONS**

Several MET inhibitors are currently under evaluation (in vitro cell lines, in vivo mouse models, and clinically). These inhibitors also include: PF2341066, XL880, XL184, ARQ197, and SGX523. Many of these inhibitors not only have activity against MET, but also against other kinases. As more inhibitors are brought to clinical fruition, differentiation will need to be made from specific MET inhibitor to a MET inhibitor with additional other kinase inhibitory activity. Importantly, as many tumors may not respond to inhibition of just one pathway, combinational strategies against MET and cytotoxic chemotherapies/and or radiation therapy will need to be implemented. Not only are there small molecule inhibitors against MET, there are also antibodies against MET (pre-clinically and clinically). Most recently there is MetMAb (anti-MET antibody) in a Phase I clinical trial.
At the Santa Monica Conference, three inhibitors against MET were presented. They are summarized as below.

**XL184**

XL184 is a small molecule inhibitor that can target MET, VEGFR2, and RET. A phase I clinical trial is nearing completion with XL184. The majority of side effects were diarrhea, nausea, fatigue, liver function abnormalities, and skin changes. Pre-clinically, XL184 can resensitize gefitinib-resistant cells in vitro. In vivo, there can also be synergism between XL184 and erlotinib. Based on this, a Phase I/II clinical trial with XL184 and erlotinib has been instituted.

**PFO2341066**

PFO2341066 is a small molecule inhibitor that can target MET as well as ALK. Also, a phase I clinical trial is ongoing currently. The maximum tolerated dose was 250 mg bid. Three DLTs were observed: grade 3 increase in ALT (1 patient at 200 mg qd) and grade 3 fatigue (2 pts at 300 mg bid). The most common adverse events were nausea, emesis, fatigue and diarrhea. Further phase II clinical trials are planned.

**MetMAb**

MetMAb antibody is an anti-MET monovalent antibody that is antagonistic. In an ongoing phase I clinical trial, MetMAb is given every 3 weeks, and cohorts of 3 testing 1, 4, 10, 20, and 30 mg/kg. A single DLT of pyrexia (4mg/kg) was observed. Common drug-related side effects (≥ 10%) included grades 1-2 fatigue (33%) and grades 1-2 nausea and vomiting (14% each). The recommended dose of MetMAb is 15 mg/kg IV every 3 weeks. Currently, in a phase II study, there is comparison of erlotinib with MetMAb versus erlotinib with placebo in second/third line non-small cell lung cancer.

**FUTURE DIRECTIONS**

MET/HGF pathway is important in a large number of biological and biochemical functions for cancer cells. There are a number of inhibitor strategies currently being utilized pre-clinically and clinically. Some MET/HGF inhibitors have already entered into phase I and/or phase II clinical trials. As we learn more about targeted therapies and combination with standard or other novel therapies, further clinical trials will be designed.

**Acknowledgments**

Supported in part by NIH/National Cancer Institute, V-Foundation (Guy Geleerd Memorial Foundation), Kate McMullen Foundation, Respiratory Health Association of Chicago, and Mesothelioma Applied Research Foundation (Jeffrey P. Hayes Memorial Grant).

**REFERENCES**


