c-Met Inhibition

Ravi Salgia, MD, PhD
Associate Professor of Medicine
Director, Thoracic Oncology Research Program
Department of Medicine
Section of Hematology/Oncology
University of Chicago

H&O What is c-Met?

RS c-Met is a receptor tyrosine kinase localized on chromosome 7. This kinase was originally discovered in the context of a chemical carcinogen for an osteosarcoma cell line. The fusion of the Met locus on chromosome 7 with the Tpr locus on chromosome 1 creates the Tpr-Met oncogene.

Once the Tpr-Met fusion was identified, the original c-Met was cloned and found to be a receptor tyrosine kinase. This enzyme is expressed in embryonic development and also in many cancers.

c-Met has an external extracellular domain that includes an extracellular semaphorin, or ligand-binding domain. The ligand for c-Met is known as hepatocyte growth factor and also as scatter factor. Other domains for c-Met include the external integrin-like domains as well as transmembrane (TM) and juxtamembrane (JM) domains. The TM and JM domains are quite important in the regulatory function of the receptor itself. c-Met's tyrosine kinase domain is the adenosine triphosphate–binding domain and has enzymatic function.

H&O What happens in the cell when c-Met becomes activated?

RS Many tyrosines within the intracytoplasmic domain become phosphorylated or activated when ligand binding with hepatocyte growth factor occurs. In addition, there are tyrosines that then become docking sites for other adapter molecules and signal transduction molecules, which affect cell signaling as well as the biologic function of the cell.

Normally, activated c-Met is important in cell motility, migration, proliferation, growth, and in angiogenic functions. c-Met has also been found to be overexpressed, either through amplification or other mechanisms, in many solid tumors, and c-Met can also potentially be mutated.

H&O Could you describe the mutations of c-Met that have been identified?

RS Germline mutations of c-Met in the tyrosine kinase domain were initially identified in hereditary papillary renal cell carcinoma. Similar mutations have since been identified in head and neck cancers, glioblastoma multiforme, and hepatocellular carcinoma.

Several years ago, our group sought to determine whether mutations of c-Met existed in solid tumors in domains other than the tyrosine kinase and found somatic and germline mutations of c-Met in lung cancer in the JM and semaphorin domains. Currently, we are investigating what role these mutations might have in the pathogenesis of lung cancer. We have also found similar mutations in mesothelioma. It may be that the JM domain is a negative regulator of the tyrosine kinase domain and when mutations arise, the tyrosine kinase domain becomes activated. We have previously shown that JM domain mutations activate cancer cell motility and migration. The functionality of the semaphorin domain mutations is not yet understood but most likely involves responsiveness to its ligand.

If c-Met is found to be important in tumors—and research findings thus far indicate that this is the case—then it may prove to be an effective therapeutic target.

H&O Have any agents been developed?

RS Several inhibitors of the tyrosine kinase function of c-Met are in preclinical and clinical development. Ongoing trials are evaluating the compounds XL184 (Exelixis) and PF02341066 (Pfizer). These are small-molecule inhibitors that target the tyrosine kinase domain, and XL184 is also an angiogenic inhibitor. Amgen has developed an antibody directed against hepatocyte growth factor that is being studied in phase I trials. There are many other agents that are in preclinical studies and hopefully will come to clinical fruition. Also, there are multityrosine kinase inhibitors that also inhibit c-Met.

H&O How is c-Met targeted by these agents?

RS There are different approaches that can be taken to inhibiting c-Met. The tyrosine kinase domain or tyrosine kinase function can be inhibited. Alternatively, antibodies against either the receptor or the ligand can be developed. An important component of clinical studies would be to determine whether there are any population subgroups in which these agents might be comparatively more effective. For example, there may be a group of patients with activating mutations or overexpression of the receptor or ligand. These are key pharmacodynamic parameters that may indicate potential greater efficacy for c-Met inhibitors.

H&O You mentioned two different functions of XL184. Is it common for an agent to have multiple functions?

RS Yes. An anticancer therapeutic can be a specific inhibitor or a specific pathway, or it can target multiple pathways. Both strategies are valid and there is interest in both types of agents among academic researchers and pharmaceutical companies.

H&O What might be the role of c-Met in lung cancer?

RS From the experience with non–small cell lung cancer, we know that the epidermal growth factor receptor (EGFR) is an important target, and several EGFR inhibitors have been developed, such as gefitinib (Iressa, AstraZeneca), erlotinib (Tarceva, OSI/Genentech), and cetuximab (Erbitux, ImClone/Bristol-Myers Squibb). These agents have been found to be effective in approximately 10–15% of patients, particularly in the setting of relapsed or refractory disease. Thus more strategies are needed for developing novel therapeutics for 85–90% of patients. c-Met is overexpressed in approximately 60–70% of lung cancers, and so this is a logical target for the development of treatments for this disease.

H&O Are there any data so far regarding the efficacy of c-Met inhibitors in the treatment of lung cancer or other malignancies?

RS It is still too early to determine the benefit of the c-Met inhibitors that are in development. In early-phase trials, it is not always possible to study surrogate markers or pre- and post-therapy biopsies, so it is not possible to verify the efficacy of the agents.

H&O Might these agents be effective in combination with other novel agents or chemotherapy?

RS Yes, and this is an important direction for future research. These agents may be effective as monotherapy. However, the efficacy may be increased when given in combination with cytotoxic chemotherapy, radiation therapy, or other novel targeted agents. We have found that there is synergism between the mTOR (mammalian target of rapamycin) pathway and c-Met inhibition. These are promising strategies that need to be considered for future preclinical and clinical research.

Suggested Reading

Jagadeeswaran R, Ma PC, Seiwert TY, et al. Functional analysis of c-Met/hepatocyte growth factor pathway in malignant pleural mesothelioma. *Cancer Res.* 2006;66:352-361.

Christensen JG, Burrows J, Salgia R. c-Met as a target for human cancer and characterization of inhibitors for therapeutic intervention. *Cancer Lett.* 2005;225;1-16.

Ma PC, Jagadeeswaran R, Jagadeesh S, et al. Functional expression and mutations of c-MET and its therapeutic inhibition with SU11279 and small interfering RNA in non–small cell lung cancer. *Cancer Res*. 2005;65:1479-1488.

Ma PC, Schaefer E, Christensen JG, Salgia R. A selective small molecule c-Met inhibitor, PHA665752, cooperates with rapamycin. *Clin Cancer Res.* 2005;11:2312-2319.

Peruzzi B, Bottaro DP. Targeting the c-Met signaling pathway in cancer. *Clin Cancer Res.* 2006;12:3657-3660.

Sattler M, Ma PC, Salgia R. Therapeutic targeting of the receptor tyrosine kinase Met. *Cancer Treat Res*. 2004;119:121-138.