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# The Met receptor tyrosine kinase: A key player in oncogenesis and drug resistance

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ABSTRACT

The Met receptor tyrosine kinase (RTK) is an attractive oncology therapeutic target. Met and its ligand, HGF, play a central role in signaling pathways that are exploited during the oncogenic process, including regulation of cell proliferation, invasion, angiogenesis, and cancer stem cell regulation. Elevated Met and HGF as well as numerous Met genetic alterations have been reported in human cancers and correlate with poor outcome. Alterations of pathways that regulate Met, such as the ubiquitin ligase c-Cbl are also likely to activate Met in the oncogenic setting. Moreover, interactive crosstalk between Met and other receptors such as EGFR, HER2 and VEGFR, underlies a key role for Met in resistance to other RTK-targeted therapies. A large body of preclinical and clinical data exists that supports the use of either antibodies or small molecule inhibitors that target Met or HGF as oncology therapeutics. The prognostic potential of Met expression has been suggested from studies in numerous cancers including lung, renal, liver, head and neck, stomach, and breast. Clinical trials using Met inhibitors indicate that the level of Met expression is a determinant of trial outcome, a finding that is actively under investigation in multiple clinical scenarios. Research in Met prognostics and predictors of drug response is now shifting toward more sophisticated methodologies suitable for development as validated and effective biomarkers that can be partnered with therapeutics to improve patient survival.



**Contents**



*Abbreviations:* ALK, Anaplastic lymphoma kinase; AML, Acute myeloid leukemia; Bid, Twice daily; CI, Confidence interval; CRPC, Castration-resistant prostate cancer; CSC, Cancer stem cell; DCR, Disease control rate; EGFR, Epidermal growth factor receptor; EMT, Epithelial–mesenchymal transition; ERK/MAPK, Extracellular signal-regulated kinase/Mitogen-activated protein kinase; FGFR, Fibroblast growth factor receptor; FISH, Fluorescent in situ hybridization; Gab1, Grb2-associated binding protein; Grb2, Growth factor receptor-bound protein; HCC, Hepatocellular carcinoma; HER2, Human epidermal growth factor receptor 2; HGF/SF, Hepatocyte growth factor/scatter factor; HNSCC, Head and neck squamous cell carcinoma; HR, Hazard ratio; IHC, Immunohistochemistry; MIT, Microphthalmia transcription factor-associated tumor; MITF, Microphthalmia transcription factor; MTC, Medullary thyroid carcinoma; NSCLC, Non-small cell lung cancer; ORR, Overall response rate; OS, Overall survival; PCR, Polymerase chain reaction; PDGFR, Platelet-derived growth factor receptor; PET, Positron emission tomography; PFS, Progression-free survival; PI3K, Phosphatidylinositol 3′ kinase; PR, Partial response; PTP1B, Protein tyrosine phosphatase 1B; Qd, Once daily; RCC, Renal cell carcinoma; RNA, Ribonucleic acid; RTK, Receptor tyrosine kinase; SD, Stable disease; SEMA, Semaphorin; TPR, Translocated promoter region; VEGF, Vascular endothelial growth factor; VEGFR, Vascular endothelial growth factor receptor.

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## 1. Introduction

The practice of oncology is undergoing a paradigm shift toward precision medicine. Understanding of the molecular pathways involved in cancer has been exploited to develop treatments tailored to the molecular profile of the individual patient. Receptor tyrosine kinases (RTKs) are ideal targets for this approach as they are frequently key drivers of tumorigenesis. Of particular interest is the Met RTK which plays a central role in epithelial tissue remodeling and morphogenesis and is deregulated in cancer. Met was identified as a prognostic marker in many cancers including lung, renal, liver, head and neck, stomach and breast, and elucidation of the oncogenic potential of Met led to the development of therapeutic agents targeting receptor activation, thereby delaying tumor progression and improving clinical outcomes in patients. However, challenges remain as to the identification of tumors most likely to respond to Met activity blockade. Thus, focusing on the development of validated biomarkers to drive utilization and effectiveness of Met-based interventions in cancer management is an unmet need. This review discusses the current status of Met prognostic and therapeutic research in oncology.

## 2. Biology of the Met receptor

### 2.1. Structure and expression patterns in normal state

Met belongs to a family of RTKs that share sequence and structural homology and includes Ron, the receptor for macrophage stimulating protein, and Sea, a Ron homologue expressed in chicken tissues (Huff et al., 1993; Gaudino et al., 1994). The high affinity ligand of Met is the hepatocyte growth factor/scatter factor (HGF/SF), a plasminogen-related growth factor involved in epithelial tissue remodeling and cell migration (Bottaro, 1991; Naldini et al., 1991a,b). While HGF is expressed by cells of mesenchymal origin, Met is predominantly expressed in cells of epithelial origin, as well as in endothelial cells, neuronal cells, melanocytes, hematopoietic progenitors, and also B cells and antigen-presenting dendritic cells (Beilmann et al., 1997; van der Voort et al., 1997; Organ & Tsao, 2011).

The Met receptor is a 190 kDa glycoprotein heterodimer consisting of an amino-terminal extracellular 45 kDa α-chain and a membrane spanning 145 kDa β subunit (Fig. 1). The β subunit is composed of extracellular semaphorin (SEMA) and immunoglobulin-like (Ig-like) domains separated by a Plexin, Semaphorin and Integrin cysteine-rich (PSI) domain (Gherardi et al., 2012). The SEMA–PSI domain was shown to provide a binding site for the α-chain of the ligand HGF (Merchant et al., 2013). The Met transmembrane domain is followed by a juxtamembrane domain containing a key tyrosine residue (Y1003) involved in Met downregulation and an intracellular portion containing the catalytic kinase domain (Peschard et al., 2001). A carboxy-terminal multisubstrate docking site recruits signaling adaptors and effectors following receptor activation (Gherardi et al., 2012).

### 2.2. Hepatocyte growth factor/Met mediated signaling

#### 2.2.1. Met signaling

Met-mediated signaling has recently been reviewed in detail (Trusolino et al., 2010; Organ & Tsao, 2011). Briefly, under normal circumstances ligand-mediated homodimerization/oligomerization results in autophosphorylation of kinase domain tyrosine residues Y1234 and

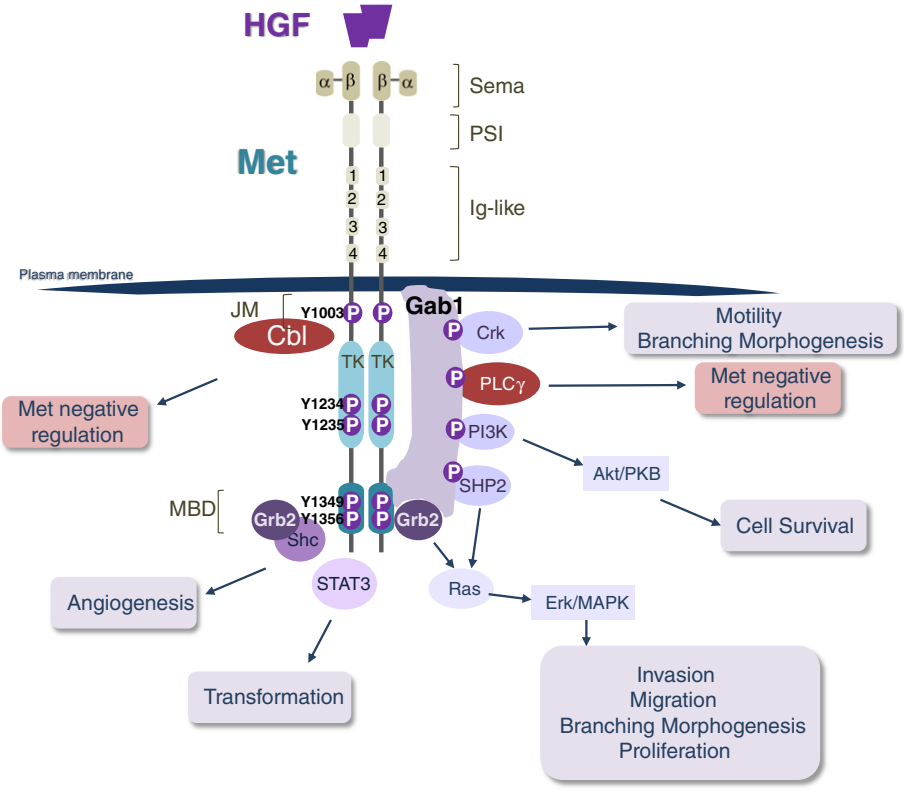


**Fig. 1.** HGF/Met mediated signaling and biological activities. Following HGF-mediated dimerization and autophosphorylation of the Met receptor, signaling proteins are recruited to the carboxy-terminal docking site, either directly or indirectly through Grb2 and Gab 1. This leads to activation of downstream pathways such as Erk/MAPK and Akt/PKB, and translates into biological responses such as cell transformation, survival, migration, dispersal, proliferation, and angiogenesis. Cbl: (*Casitas B-lineage Lymphoma*) E3 ubiquitin-protein ligase; Crk: (*CT10 regulator of kinase*) adaptor protein; Gab1: Grb2-associated binding protein; Grb2: growth factor receptor-bound protein 2; PI3K: phosphatidylinositol 3′ kinase; PLCγ: phospholipase C γ; Ras: (*Rat sarcoma*) small GTPase; SHIP1: Src homology 2-containing inositol 5-phosphatase 1; Shc: Src homology 2 domain-containing protein; SHP2: Src homology domain 2 (SH2)-containing tyrosine phosphatase; Src: tyrosine-protein kinase CSK; STAT3: signal transducer and activator of transcription 3. Ig-like 1–4: immunoglobulin-like domains 1–4.