Drug-mediated inhibition of MET activation

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This is just an excerpt of a full-length report for this pathway. To access the complete report, please download it at the Reactome Textbook.

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https://reactome.org
Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

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Literature references


Reactome database release: 82

This document contains 1 pathway and 2 reactions (see Table of Contents)
MET receptor tyrosine kinase (RTK) is a proto-oncogene that is frequently aberrantly activated in cancer through gene amplification and/or activating mutations that result in hypersensitivity to HGF stimulation or HGF-independent activation. Oncogenic MET activation can occur as a primary mechanism of malignant transformation or be selected secondarily, as a mechanism of resistance to therapeutics that target related RTKs, such as EGFR. MET targeted anti-cancer therapeutics, either recombinant monoclonal antibodies (MAbs) or small tyrosine kinase inhibitors (TKIs), have shown promise as a first-line agents for the treatment of solid tumors with primary MET activation or as second-line agents for the treatment of solid tumors with acquired MET-mediated resistance to other RTK-targeted therapies (reviewed in Comoglio et al. 2018).

**Literature references**


**Editions**

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Recombinant monoclonal anti-MET therapeutic antibodies are emerging as promising targeted therapeutics for the treatment of MET-driven cancers (reviewed in Comoglio et al. 2018).

Onartuzumab (also known as MetMAb), is an E. coli-derived humanized monovalent (one-armed) antibody that binds to MET and inhibits binding of HGF alpha chain to MET, thus preventing HGF-mediated activation of MET signaling. Onartuzumab does not display HGF agonism which is characteristic of some bivalent MET antibodies (Merchant et al. 2013).

Emibetuzumab (also known as LY2875358) is a humanized bivalent anti-MET monoclonal antibody which inhibits binding of HGF to MET and prevents HGF-mediated MET activation without exhibiting HGF agonism. In addition, emibetuzumab induces MET internalization and degradation, which further interferes with MET signaling (Liu et al. 2014).

ARGX-111 is an engineered anti-MET monoclonal antibody which competes with HGF for MET binding, acting as an HGF antagonist, inhibits HGF-induced MET activation, and engages natural killer cells to kill MET-expressing cancer cells, exhibiting enhanced antibody-dependent cellular toxicity (Hultberg et al. 2015).

SAIT301 is a bivalent recombinant anti-MET monoclonal antibody that likely acts as an HGF antagonist, but detailed studies are lacking. SAIT301 is thus annotated as a candidate HGF antagonist. SAIT301 inhibits activation of MET signaling by HGF and induces MET degradation that is independent of the MET E3 ubiquitin ligase CBL (Lee, Kim et al. 2014; Lee, Kang et al. 2014).

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Several tyrosine kinase inhibitors (TKIs) have MET as their primary target. The majority of these TKIs act by competing with ATP for binding to the ATP binding pocket in the catalytic cleft of MET, thus inhibiting HGF-induced trans autophosphorylation and activation of MET homodimers, but some do not compete with ATP binding and instead act as allosteric inhibitors. In addition, several TKIs designed for other tyrosine kinases bind MET as their non primary target (reviewed in Comoglio et al. 2018).

TKIs whose primary target is MET are:

- **AMG-337**: an ATP competitive inhibitor, highly specific for MET (Hughes et al. 2016);
- **amuvatinib** (also known as MP470): an ATP competitive inhibitor of MET, KIT and AXL (Mahadevan et al. 2007); inhibits MET trans-autophosphorylation in response to HGF stimulation (Phillip et al. 2013); annotated as a candidate MET inhibitor due to insufficient availability of experimental data;
- **BMS-777607**: an ATP competitive MET inhibitor (Schroeder et al. 2009); also inhibits MST1R (also known as RON) (Zeng et al. 2014);
- **cabozantinib** (also known as XL184): an ATP competitive inhibitor of MET, KDR, KIT, RET, AXL, TEK and FLT3 (Yakes et al. 2011), acts by inhibiting trans-autophosphorylation of MET (Yakes et al. 2011, Xiang et al. 2014), thus interfering with HGF induced cell migration (Yakes et al. 2011); can increase the efficacy of other anti cancer drugs by inhibiting the action of the ATP dependent xenobiotic transporter ABCG2 (Zhang et al. 2017);
- **capmatinib** (also known as IN280): an ATP competitive reversible inhibitor of MET (Liu et al. 2011);
- **crizotinib** (also known as PF-2341066): an ATP competitive MET inhibitor (Zou et al. 2007)
- **foretinib** (also known as XL2880 and GSK1363089): an ATP competitive inhibitor of MET; also inhibits KDR, KIT, MST1R, FLT1, FLT4, AXL and TEK (Qian et al. 2009, Kataoka et al. 2012);
- **glesatinib** (also known as MGCD265): does not compete with ATP, but inhibits HGF dependent MET trans-autophosphorylation; is effective against MET exon 14 mutants that are resistant to ATP competitive inhibitors (Engstrom et al. 2017);
- **golvatinib** (also known as E7050): a dual inhibitor of MET and KDR (Nakagawa et al. 2010)
MK-2461: an ATP competitive MET inhibitor; does not prevent HGF induced trans-autophosphorylation of the MET kinase activation loop, but prevents trans-autophosphorylation of the juxtamembrane domain and C terminal docking sites of MET (Pan et al. 2010); besides inhibiting MET, MK-2461 shows a similar potency against MST1R (RON) and FLT1 receptor tyrosine kinases (RTKs), and 8- to 30-fold lower potency against RTKs FGFR1, FGFR2, FGFR3, PDGFRB, KDR, FLT3, FLT4, NTRK1 (TRKA) and NTRK2 (TRKB);

OMO-1, annotated as a candidate due to insufficient published evidence; OMO-1 is an ATP competitive MET inhibitor (Libouban et al. 2018 - conference abstract, no data shown) that interferes with MET trans-autophosphorylation in response to HGF stimulation (Steenbrugge et al. 2021);

PHA-665752: an ATP competitive inhibitor of MET, inhibits HGF induced trans-autophosphorylation of MET and downstream cell proliferation and motility (Christensen et al. 2003);

savolitinib (also known as volitinib or AZD6094): an ATP competitive MET inhibitor (Jia et al. 2014, Gavine et al. 2015);

SGX-523: an ATP competitive, highly selective MET inhibitor; stabilizes MET in a unique inactive conformation, inaccessible to other protein kinases; abrogates HGF induced MET trans-autophosphorylation (Buchanan et al. 2009);

SU11274: an ATP competitive, selective MET inhibitor (50 times higher affinity for MET than other tested RTKs) (Sattler et al. 2003);

tepotinib: an ATP competitive MET inhibitor (Zhang et al. 2019);

tivantinib (also known as ARQ-197) is annotated as a candidate MET inhibitor because of contradicting evidence; it was initially found that tivantinib does not compete with ATP and acts as an allosteric inhibitor, diminishing trans-autophosphorylation of ligand-activated MET dimers (Munshi et al. 2010), but this could not be reproduced by Basilico et al. 2013; the study by Basilico et al. 2013. indicated that tivantinib displays a nonspecific, MET-independent cytotoxic effect by perturbing microtubule dynamics (Basilico et al. 2013); tivantinib is subject to multi drug resistance-related export via ATP-dependent xenobiotic transporter ABCG2 (Wu et al. 2020).

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