Signaling by MET

Birchmeier, W., Heynen, G., Orlic-Milacic, M.

European Bioinformatics Institute, New York University Langone Medical Center, Ontario Institute for Cancer Research, Oregon Health and Science University.

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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.

The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

Literature references


Reactome database release: 72

This document contains 9 pathways (see Table of Contents)

Activation of PLC gamma 1 (PLCG1) signaling by MET remains unclear. It has been reported that PLCG1 can bind to MET directly (Ponzetto et al. 1994) or be recruited by phosphorylated GAB1 (Gual et al. 2000). Tyrosine residue Y307 of GAB1 that serves as docking sites for PLCG1 may be phosphorylated either by activated MET (Watanabe et al. 2006) or SRC (Chan et al. 2010). Another PLCG1 docking site on GAB1, tyrosine residue Y373, was reported as the SRC target, while the kinase for the main PLCG1 docking site, Y407 of GAB1, is not known (Chan et al. 2010).

Considerable progress has recently been made in the development of HGF-MET inhibitors in cancer therapy. These include inhibitors of HGF activators, HGF inhibitors and MET antagonists, which are protein therapeutics that act outside the cell. Kinase inhibitors function inside the cell and have constituted the largest effort towards MET-based therapeutics (Gherardi et al. 2012).

Pathogenic bacteria of the species Listeria monocytogenes, exploit MET receptor as an entryway to host cells (Shen et al. 2000, Veiga and Cossart 2005, Neimann et al. 2007).


Literature references


Hepatocyte growth factor (HGF), the ligand for MET receptor tyrosine kinase (RTK), is secreted into the extracellular matrix (ECM) as an inactive single chain precursor (pro-HGF). The biologically active HGF is the heterodimer of alpha and beta chains that are produced via proteolytic cleavage of pro-HGF by the plasma membrane bound serine protease Hepsin (HPN) (Kirchhofer et al. 2005, Owen et al. 2010) or the ECM-associated serine protease Hepatocyte growth factor activator (HGFAC, commonly known as HGFA) (Shia et al. 2005). HGF binds to the extracellular SEMA and PSI domains of MET RTK, inducing a conformational change that enables MET dimerization or oligomerization (Kirchhofer et al. 2004, Stamos et al. 2004, Hays and Watowich 2004, Gherardi et al. 2006). MET dimers trans-autophosphorylate on tyrosine residues in the activation loop, leading to increased kinase activity, and on tyrosine residues at the cytoplasmic tail that serve as docking sites for adapter proteins involved in MET signal transduction (Ferracini et al. 1991, Longati et al. 1994, Rodrigues and Park 1994, Ponzetto et al. 1994).

CD44v6 was implicated as a MET co-receptor, but its role has been disputed (Orian-Rousseau et al. 2002, Dortet et al. 2010, Olaku et al. 2011, Hasenauer et al. 2013, Elliot et al. 2014).

**Literature references**


**Editions**

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PTPN11 (SHP2) may contribute to activation of RAS signaling downstream of MET (Schaeper et al. 2000, Furcht et al. 2014).

Sustained activation of MAPK1 (ERK2) and MAPK3 (ERK1) downstream of MET-activated RAS may require MET endocytosis and signaling from endosomes (Peschard et al. 2001, Hammond et al. 2001, Petrelli et al. 2002, Kermorgant and Parker 2008).

Binding of MET to MUC20 or RANBP10 interferes with RAS activation (Higuchi et al. 2004, Wang et al. 2004).

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MET binds and phosphorylates the adapter protein GAB1, thus creating a docking site for the regulatory subunit PIK3R1 of the PI3K complex. Recruitment of PI3K to MET-bound phosphorylated GAB1 results in PI3K activation, production of PIP3, and stimulation of downstream AKT signaling (Rodrigues et al. 2000, Schaeper et al. 2000).

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PTPN11 (SHP2), recruited to activated MET receptor through GAB1, is phosphorylated in response to HGF treatment, although phosphorylation sites and direct MET involvement have not been examined (Schaeper et al. 2000, Duan et al. 2006). Phosphorylation of PTPN11 in response to HGF treatment is required for the recruitment and activation of sphingosine kinase SPHK1, which may play a role in HGF-induced cell scattering (Duan et al. 2006). While PTPN11 promotes MAPK3/1 (ERK1/2) signaling downstream of MET, it can also dephosphorylate MET on unidentified tyrosine residues (Furcht et al. 2014).

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MET promotes cell motility

Location: Signaling by MET

Stable identifier: R-HSA-8875878


Literature references


## Editions

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**MET activates STAT3**

**Location:** Signaling by MET

**Stable identifier:** R-HSA-8875791

The STAT3 transcription factor binds to activated MET through phosphorylated tyrosine residue Y1356 of MET. STAT3 may also bind to activated MET indirectly through GAB1, but this interaction has not been studied in detail. Activated MET induces phosphorylation of STAT3 at Y705, triggering STAT3 dimerization and nuclear translocation (Schaper et al. 1997, Boccaccio et al. 1998, Zhang et al. 2002, Cramer et al. 2005). Endocytosis of MET and interaction with STAT3 at endosomes may be required for sustained STAT3 phosphorylation in response to HGF stimulation (Kermorgant and Parker 2008). Activated SRC may also contribute to phosphorylation of STAT3 at Y705. STAT3 may promote HGF transcription in a SRC-dependent way, but this autocrine HGF loop may be limited to breast cancer cells (Wojcik et al. 2006, Sam et al. 2007). MET-mediated activation of STAT3 is implicated in anchorage independent cell growth and invasiveness downstream of HGF (Zhang et al. 2002, Cramer et al. 2005). MET can also interact with STAT1A, STAT1B and STAT5, but the biological importance of these interactions is not known (Runge et al. 1999).

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Activated MET receptor is subject to recycling from the plasma membrane through the endosomal compartment and back to the plasma membrane (Peschard et al. 2001, Hammond et al. 2001, Petrelli et al. 2002). In the recycling process, activated MET receptor is endocytosed, and the GGA3 protein directs it, via a largely unknown mechanism, through the RAB4 positive endosomal compartments back to the plasma membrane (Parachoniak et al. 2011). Endosomal signaling by MET during the recycling process appears to play an important role in sustained activation of ERK1/ERK2 (MAPK3/MAPK1) and STAT3 downstream of MET (Kermorgant and Parker 2008).

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Negative regulation of MET activity

Location: Signaling by MET

Stable identifier: R-HSA-6807004

Signaling by MET receptor is negatively regulated mainly by MET receptor dephosphorylation or MET receptor degradation. Protein tyrosine phosphatase PTPRJ dephosphorylates MET tyrosine residue Y1349, thus removing the docking site for the GAB1 adapter (Palka et al. 2003). Protein tyrosine phosphatases PTPN1 and PTPN2 dephosphorylate MET tyrosines Y1234 and Y1235 in the kinase activation loop, thus attenuating catalytic activity of MET (Sangwan et al. 2008). The E3 ubiquitin ligase CBL promotes ubiquitination of the activated MET receptor and subsequent MET degradation. CBL contains a RING finger domain that engages E2 protein ubiquitin ligases to mediate ubiquitination of MET, which may occur at the cell membrane or in the early endocytic compartment. Ubiquitinated MET is degraded in a late endosomal or lysosomal compartment in a proteasome-dependent manner. The involvement of proteasome in MET degradation seems to be indirect, through an effect on MET endocytic trafficking (Jeffers et al. 1997, Peschard et al. 2001, Hammond et al. 2001, Petrelli et al. 2002). LRIG1 promotes lysosome-dependent degradation of MET in the absence of HGF-mediated activation (Lee et al. 2014, Oh et al. 2014).

MET-mediated activation of RAS signaling is inhibited by MET receptor binding to MUC20 (Higuchi et al. 2004) or RANBP10 (Wang et al. 2004).

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Table of Contents

Introduction 1

Met Signaling 2

- MET Receptor Activation 4
- MET activates RAS signaling 6
- MET activates PI3K/AKT signaling 8
- MET activates PTPN11 9
- MET promotes cell motility 10
- MET activates STAT3 12
- MET receptor recycling 14
- Negative regulation of MET activity 16

Table of Contents 18