MET Receptor Activation

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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.

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Literature references


Reactome database release: 69

This document contains 1 pathway and 5 reactions (see Table of Contents)
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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Hepsin (HPN, aka TMPRSS1) is a cell surface-expressed chymotrypsin-like serine protease and a member of the family of type II transmembrane serine proteases (TTSP). The HPN zymogen is activated autocatalytically by cleavage at Arg162-Ile163, forming a heterodimeric enzyme (Tsuji et al. 1991, Torres-Rosado et al. 1993). HPN plays an essential role in cell growth and maintenance of cell morphology and is highly upregulated in prostate cancer and promotes tumor progression and metastasis (Klezovitch et al. 2004). Located on the cell surface, HPN can activate fibrinolytic enzymes, matrix metalloproteases and latent forms of growth factors, such as hepatocyte growth factor (HGF). HGF is a pleiotropic factor and activates hepatocyte growth factor receptor (MET). HGF is secreted into the extracellular matrix as an inactive single chain precursor (pro-HGF (32-728)) and requires cleavage at Arg494–Val495 to form the biologically active alpha-beta heterodimer (Hartmann et al. 1992, Kirchhofer et al. 2005). The Kunitz-type protease inhibitors 1 and 2 (SPINT1 and 2, aka HAI1 and 2) are inhibitors of HPN activity (Kawaguchi et al. 1997, Shimomoura et al. 1997, Kirchhofer et al. 2005).

Followed by: HGF dimer binds MET

Literature references


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HGFAC cleaves pro-HGF to form HGF dimer

Location: MET Receptor Activation

Stable identifier: R-HSA-6800299

Type: transition

Compartments: extracellular region, plasma membrane

HGF is a pleiotropic factor and activates hepatocyte growth factor receptor (MET), a proto-oncogenic receptor tyrosine kinase. HGF is secreted into the extracellular matrix as an inactive single chain precursor (pro-HGF (32-728)) and requires cleavage at Arg494–Val495 to form the biologically active alpha-beta heterodimer. Hepatocyte growth factor activator (HGFAC, commonly known as HGFA) is a serine protease that converts HGF into its active form (Shia et al. 2005). The Kunitz-type protease inhibitor 1 (SPINT1, aka HAI1) is an inhibitor of HGFAC activity (Shia et al. 2005).

Followed by: HGF dimer binds MET

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HGF dimer binds MET

Location: MET Receptor Activation

Stable identifier: R-HSA-6800298

Type: binding

Compartments: extracellular region, plasma membrane

Hepatocyte growth factor (HGF) is a pleiotropic factor and activates hepatocyte growth factor receptor (MET). HGF is secreted into the extracellular matrix as an inactive single chain precursor (pro-HGF (32-728)) and requires cleavage to form the biologically active alpha-beta heterodimer. HGF/MET signalling plays an important role in normal development and in tumor growth and metastasis (Rong et al. 1994, Schmidt et al. 1995, Uehara et al. 1995, Bladt et al. 1995, Schmidt et al. 1997, Pennacchietti et al. 2003, Stamos et al. 2004). HGF binds the SEMA and PSI domain of the MET receptor (Kirchhofer et al. 2004).

Preceded by: HGFAC cleaves pro-HGF to form HGF dimer, HPN heterodimer cleaves pro-HGF to form HGF dimer

Followed by: MET receptor dimerizes

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MET receptor dimerizes

Location: MET Receptor Activation

Stable identifier: R-HSA-6806957

Type: binding

Compartments: plasma membrane

Upon ligand binding, MET receptor forms homodimers. Interaction between beta chains of two MET-bound HGF heterodimers may promote dimer formation (Stamos et al. 2004, Gherardi et al. 2006). Ligand bound MET dimers can further oligomerize (Hays and Watowich 2004).

Preceded by: HGF dimer binds MET

Followed by: MET dimers autophosphorylate

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The activated MET receptor autophosphorylates on four tyrosine residues. Two tyrosines, Y1234 and Y1235 are located in the kinase domain of MET and their phosphorylation increases the catalytic activity of MET. Y1235 is the major phosphorylation site (Ferracini et al. 1991, Longati et al. 1994, Rodrigues and Park 1994). The other two MET tyrosines that undergo autophosphorylation are Y1349 and Y1356. These two tyrosines are at the C-terminus of MET and serve as docking sites for binding of MET effectors (Ponzetto et al. 1994, Weidner et al. 1995). It is uncertain whether tyrosine residue Y1365 is also autophosphorylated.

Preceded by: MET receptor dimerizes

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