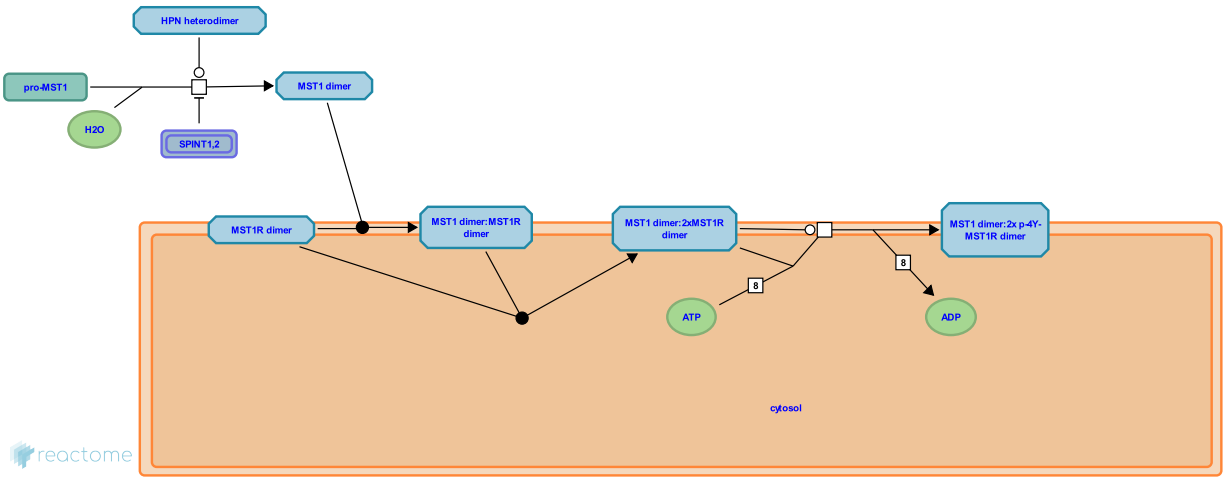
Signaling by MST1



D'Eustachio, P., Jassal, B.

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

19/01/2022

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

Fabregat, A., Sidiropoulos, K., Viteri, G., Forner, O., Marin-Garcia, P., Arnau, V. et al. (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC bioinformatics, 18*, 142. ↗

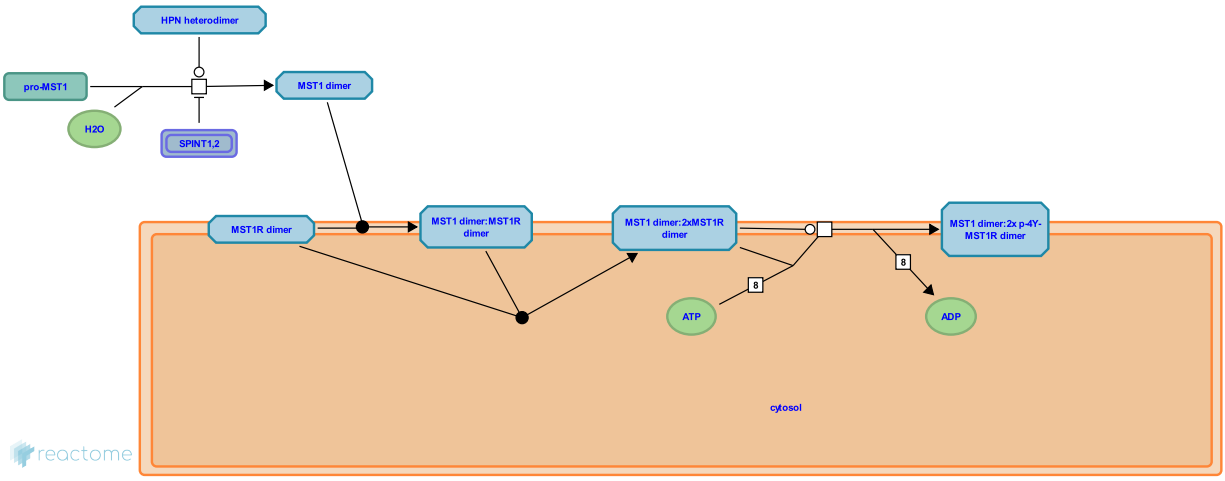
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Signaling by MST1 ↗

Stable identifier: R-HSA-8852405



Inflammatory mediators such as growth factors produced by macrophages play an important role in the inflammatory response occurring during bacterial infection, tissue injury and immune responses. Many growth factors and their receptor-type protein tyrosine kinases (RTKs) play a critical role in inflammation, wound healing and tissue remodelling. The growth factor hepatocyte growth factor-like protein (MST1, also known as macrophage-stimulating protein, MSP) binds to a specific receptor, macrophage-stimulating protein receptor (MST1R, also known as RON, recepteur d'origine nantais). MST1 belongs to the kringle protein family, which includes HGF and plasminogen. It is produced by the liver and circulates in the blood as a biologically-inactive single chain precursor (pro-MST1). Proteolytic cleavage of pro-MST1 into the biologically-active MST1 dimer is necessary for receptor binding. Cleavage occurs during blood coagulation and at inflammatory sites, the resultant MST1 dimer then binds MST1R receptors on local macrophages. MST1R is ubiquitously expressed but mainly in epithelial cells.

MST1 binding to MST1R promotes receptor homodimerisation which in turn allows autophosphorylation of two tyrosine residues within the catalytic site which regulates kinase activity and allows phosphorylation of the carboxy-terminal binding site of the receptor. The docking site is essential for downstream signaling through direct and indirect binding of SH2 domain-containing adaptor proteins such as GRB2, PI3K, and SRC. MST1/MST1R signaling plays a dual role in regulating inflammation; initially stimulating chemotaxis and phagocytosis (macrophage activation) and then exerts broad inhibitory effects on macrophages, limiting the extent of inflammtory responses (Wang et al. 2002). MST1R is upregulated in many epithelial cancers where it is thought to play a role in the progression of these types of cancer (Kretschmann et al. 2010).

Literature references

Chen, YQ., Wang, MH., Zhou, YQ. (2002). Macrophage-stimulating protein and RON receptor tyrosine kinase: potential regulators of macrophage inflammatory activities. *Scand. J. Immunol., 56*, 545-53. ↗

Kretschmann, KL., Buys, SS., Eyob, H., Welm, AL. (2010). The macrophage stimulating protein/Ron pathway as a potential therapeutic target to impede multiple mechanisms involved in breast cancer progression. *Curr Drug Targets, 11*, 1157-68. ↗

Editions

2016-01-11	Reviewed	D'Eustachio, P.
2016-01-18	Authored, Edited	Jassal, B.

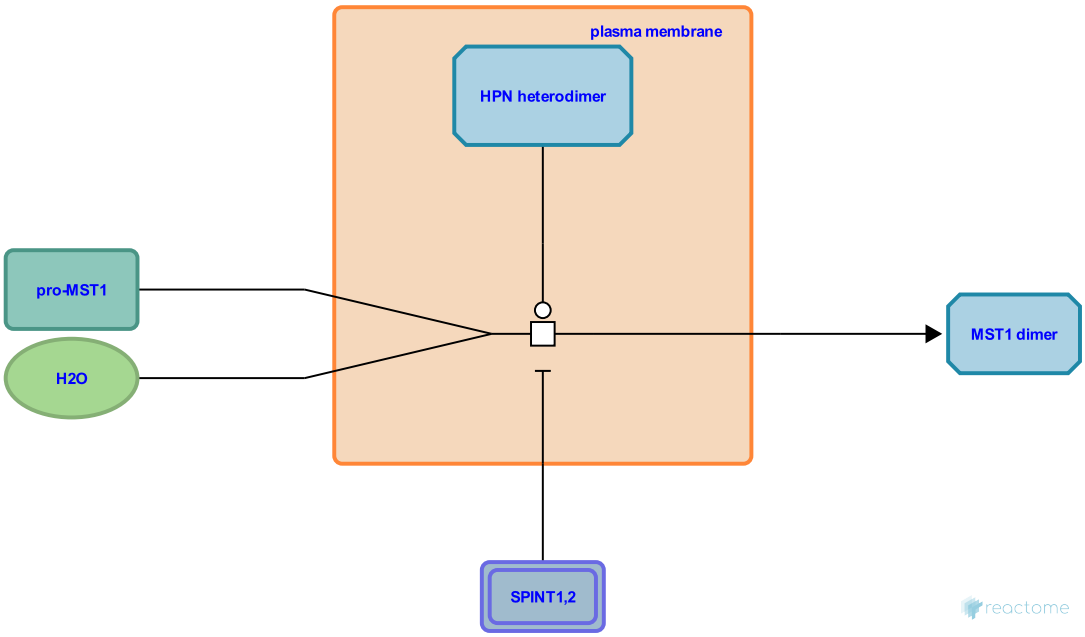
HPN heterodimer cleaves pro-MST1 to form MST1 dimer ↗

Location: Signaling by MST1

Stable identifier: R-HSA-6800198

Type: transition

Compartments: plasma membrane, extracellular region



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. Located on the cell surface, HPN can activate fibrinolytic enzymes, matrix metalloproteases and latent forms of growth factors such as hepatocyte growth factor-like protein (MST1, aka macrophage stimulatory protein, MSP). MST1 is a plasminogen-related growth factor and ligand for the receptor tyrosine kinase (MST1R, RON). The MST1/MST1R (MSP/RON) signaling system promotes wound healing and invasive tumor growth and suppresses proinflammatory immune response. For MST1 to bind MST1R, the inactive single-chain form (pro-MST1) must be cleaved into the disulfide-linked alpha-beta heterodimer by HPN (Ganesan et al. 2011). The Kunitz-type protease inhibitors 1 and 2 (SPINT1 and 2, aka HAI1 and 2) are inhibitors of HPN activity (Kirchhofer et al. 2005).

The non-synonymous coding variant in MST1 (R689C) has been associated with genetic susceptibility to both Crohn's disease and ulcerative colitis, two major types of inflammatory bowel disease (IBD). The R689C variant reduces the amount of circulating MST1 thereby reducing MST1R activity and down-regulation of the MST1/MST1R signaling pathway (McGovern et al. 2010, Gorlatova et al. 2011, Kauder et al. 2013).

Followed by: MST1 binds MST1R

Literature references

Kirchhofer, D., Lipari, MT., Fan, B., Peek, M., Billeci, K., Moran, P. (2005). Hepsin activates pro-hepatocyte growth factor and is inhibited by hepatocyte growth factor activator inhibitor-1B (HAI-1B) and HAI-2. *FEBS Lett., 579*, 1945-50. ↗

Herzberg, O., Araj, RH., Pal, LR., Moult, J., Galkin, A., Chao, K. et al. (2011). Protein characterization of a candidate mechanism SNP for Crohn's disease: the macrophage stimulating protein R689C substitution. *PLoS ONE, 6*, e27269. ↗

Kurachi, K., Tsuji, A., Torres-Rosado, A., Chou, SH., O'Shea, KS. (1993). Hepsin, a putative cell-surface serine protease, is required for mammalian cell growth. *Proc. Natl. Acad. Sci. U.S.A., 90*, 7181-5. ↗

Egen, JG., Kauder, SE., Wright, LY., Mai, E., Young, J., Sa, SM. et al. (2013). Functional consequences of the macrophage stimulating protein 689C inflammatory bowel disease risk allele. *PLoS ONE, 8*, e83958. ↗

Le Beau, MM., Kurachi, K., Lemons, RS., Torres-Rosado, A., Tsuji, A., Chou, SH. et al. (1991). Hepsin, a cell membrane-associated protease. Characterization, tissue distribution, and gene localization. *J. Biol. Chem., 266*, 16948-53. ↗

Editions

2015-09-28	Authored, Edited	Jassal, B.
2016-01-11	Reviewed	D'Eustachio, P.

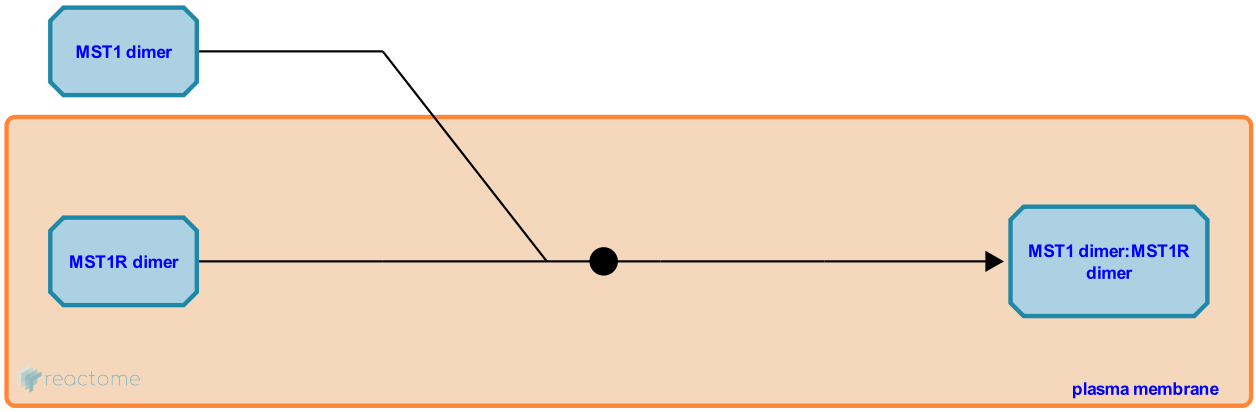
MST1 binds MST1R ↗

Location: Signaling by MST1

Stable identifier: R-HSA-6800315

Type: binding

Compartments: plasma membrane, extracellular region



The receptor tyrosine kinase macrophage stimulating 1 receptor (MST1R, aka recepteur d'origine nantais, RON) is the cell surface receptor for macrophage stimulating protein 1 (MST1, aka MSP) (Wang et al. 1997). Like their ligands, MST1R (and MET) is a cleaved disulfide-linked heterodimer, the mature receptor consisting of alpha and beta chains. The MST1/MST1R pathway is involved in several important biological processes, including macrophage activity, wound healing, and epithelial cell behaviour (Kretschmann et al. 2010). MST1 binding to MST1R promotes receptor dimerisation followed by receptor autophosphorylation.

Preceded by: HPN heterodimer cleaves pro-MST1 to form MST1 dimer

Followed by: MST1 dimer:MST1R dimer binds MST1R dimer

Literature references

Takehara, T., Hagiya, M., Leonard, EJ., Yoshikawa, W., Godowski, PJ., Julian, FM. et al. (1997). Macrophage stimulating protein (MSP) binds to its receptor via the MSP beta chain. *J. Biol. Chem., 272,* 16999-7004. ↗

Kretschmann, KL., Buys, SS., Eyob, H., Welm, AL. (2010). The macrophage stimulating protein/Ron pathway as a potential therapeutic target to impede multiple mechanisms involved in breast cancer progression. *Curr Drug Targets, 11,* 1157-68. ↗

Editions

2015-09-29	Authored, Edited	Jassal, B.
2016-01-11	Reviewed	D'Eustachio, P.

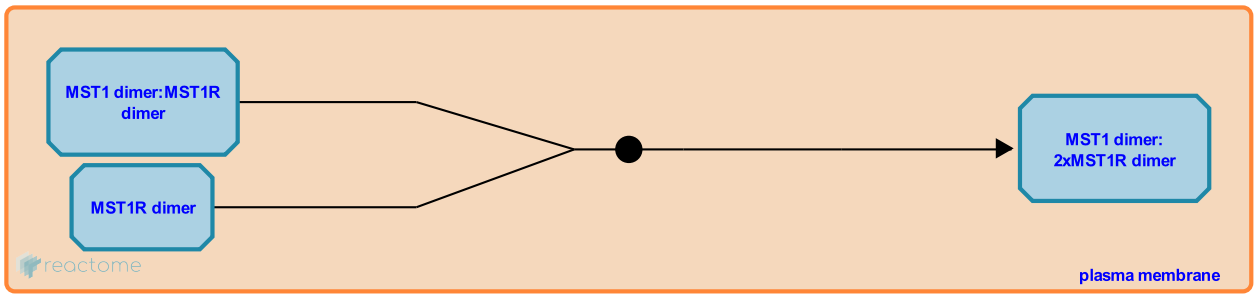
MST1 dimer:MST1R dimer binds MST1R dimer ↗

Location: Signaling by MST1

Stable identifier: R-HSA-8852522

Type: binding

Compartments: plasma membrane, extracellular region



The receptor tyrosine kinase macrophage stimulating 1 receptor (MST1R, aka recepteur d'origine nantais, RON) is the cell surface receptor for macrophage stimulating protein 1 (MST1, aka MSP). Once ligand binding takes place, MST1R can undergo homodimerisation (Miller & Leonard 1998, Chao et al. 2014).

Preceded by: MST1 binds MST1R

Followed by: MST1R autophosphorylates

Literature references

Gorlatova, NV., Herzberg, O., Chao, KL., Eisenstein, E. (2014). Structural basis for the binding specificity of human Recepteur d'Origine Nantais (RON) receptor tyrosine kinase to macrophage-stimulating protein. *J. Biol. Chem., 289*, 29948-60. ↗

Miller, M., Leonard, EJ. (1998). Mode of receptor binding and activation by plasminogen-related growth factors. *FEBS Lett., 429*, 1-3. ↗

Editions

2016-01-11	Reviewed	D'Eustachio, P.
2016-01-19	Authored, Edited	Jassal, B.

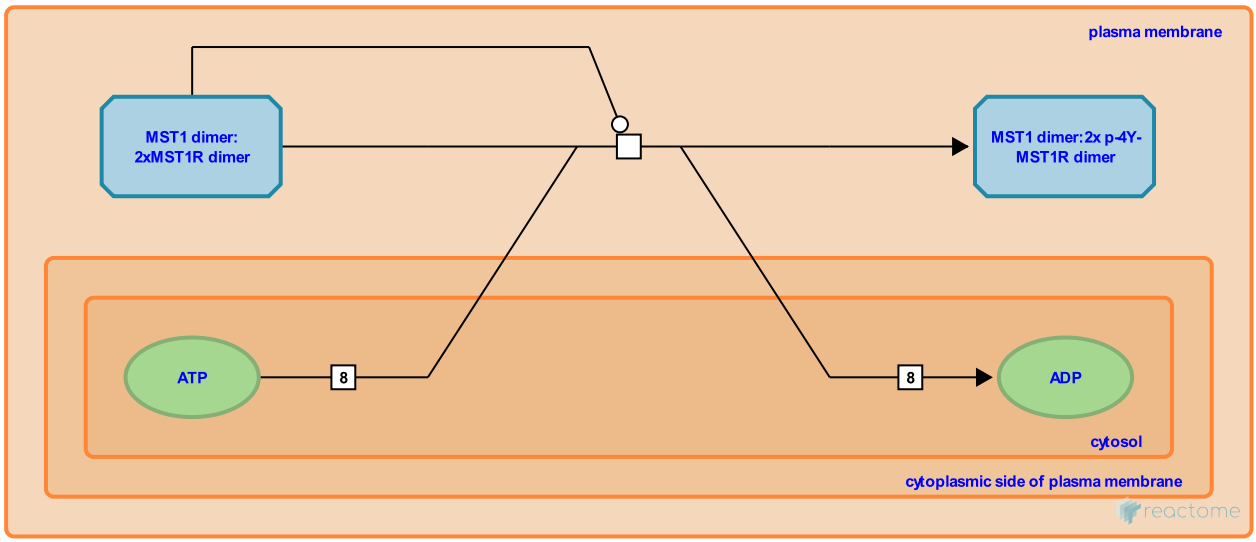
MST1R autophosphorylates ↗

Location: Signaling by MST1

Stable identifier: R-HSA-8852552

Type: transition

Compartments: plasma membrane, extracellular region



In response to ligand binding and receptor dimerisation, macrophage-stimulating protein receptor (MST1R aka RON) autophosphorylates on Tyr-1238 and Tyr-1239 in the kinase domain. This leads to further phosphorylation of Tyr-1353 and Tyr-1360 in the C-terminal multifunctional docking site (Yokoyama et al. 2005, Wang et al. 2010).

Preceded by: MST1 dimer:MST1R dimer binds MST1R dimer

Literature references

Hayman, MJ., Ischenko, I., Miller, WT., Yokoyama, N. (2005). The C terminus of RON tyrosine kinase plays an autoinhibitory role. *J. Biol. Chem., 280*, 8893-900. ↗

Wang, J., Schreiner, P., Augustin, M., Steinbacher, S., Epstein, D., Mulvihill, MJ. et al. (2010). The crystal structure of a constitutively active mutant RON kinase suggests an intramolecular autophosphorylation hypothesis. *Biochemistry, 49*, 7972-4. ↗

Editions

2016-01-11	Reviewed	D'Eustachio, P.
2016-01-19	Authored, Edited	Jassal, B.

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