

Met

Key References

Hepatocyte growth factor/scatter factor, Met and cancer references. <http://www.vai.org/vari/metandcancer/>

Birchmeier, C., et al., Met, metastasis, motility and more., *Nat. Rev. Mol. Cell. Biol.*, **4**, 915-925 (2003).

Gherardi, E., et al., Functional map and domain structure of MET, the product of the *c-met* protooncogene and receptor for hepatocyte growth factor/scatter factor., *Proc. Natl. Acad. Sci. USA*, **100**, 12039-12044 (2003).

Huh, C.G., et al., Hepatocyte growth factor/*c-met* signaling pathway is required for efficient liver regeneration and repair., *Proc. Natl. Acad. Sci. USA*, **101**, 4477-4482 (2004).

Ma, P.C., et al., *c-Met*: structure, functions and potential for therapeutic inhibition., *Cancer Metastasis Rev.*, **22**, 309-325 (2003).

Michieli, P., et al., Targeting the tumor and its micro-environment by a dual-function decoy Met receptor., *Cancer Cell*, **6**, 61-73 (2004).

Peschard, P., et al., Mutation of the *c-Cbl* TKB domain binding site on the Met receptor tyrosine kinase converts it into a transforming protein., *Mol. Cell*, **8**, 995-1004 (2001).

Rosario, M., et al., How to make tubes: signaling by the Met receptor tyrosine kinase., *Trends Cell. Biol.*, **13**, 328-335 (2003).

Schiering, N., et al., Crystal structure of the tyrosine kinase domain of the hepatocyte growth factor receptor *c-Met* and its complex with the microbial alkaloid K-252a., *Proc. Natl. Acad. Sci. USA*, **100**, 12654-12659 (2003).

Shen, Y., et al., InlB-dependent internalization of *Listeria* is mediated by the Met receptor tyrosine kinase., *Cell*, **103**, 501-510 (2000).

Wang, M.H., et al., Oncogenic and invasive potentials of human macrophage-stimulating protein receptor, the RON receptor tyrosine kinase., *Carcinogenesis*, **24**, 1291-1300 (2003).

Wang, M.H., et al., Macrophage-stimulating protein and RON receptor tyrosine kinase: potential regulators of macrophage inflammatory activities., *Scand. J. Immunol.*, **56**, 545-553 (2002).

Overview

The Met family of receptor tyrosine kinases (RTKs) contains two members in mammals, referred to as Met and Ron. Met is the receptor for hepatocyte growth factor/scatter factor (HGF/SF), while Ron is the receptor for macrophage stimulating protein (MSP).

In the adult, Met is predominantly expressed in epithelial and endothelial cells. Met regulates diverse cellular processes including cell scattering, proliferation and survival. It is involved in organ regeneration following kidney and liver damage. The Met and Ron receptors are essential for embryonic development as *Met^{-/-}* and *Ron^{-/-}* embryos die at E14.5-16.5 and E3.5, respectively. HGF/Met signaling is required for the development of the placenta, the liver and nervous system as well as the migration of myogenic precursor cells.

The Ron receptor is expressed in lineages of hematopoietic origin, in some epithelial cells, in cells of neuro-ectodermal origin and in osteoclasts. Ron is essential for embryonic implantation and is involved in a wide spectrum of physiological processes including the development of hematopoietic-derived cells, the inflammatory response of macrophages and bone resorption by osteoclasts.

Chronic activation of the Met or Ron receptors is associated with several human and murine tumors. Notably, the Met receptor was first identified in a cell line treated with a carcinogenic agent as a constitutively activated cytoplasmic oncoprotein, Tpr-Met, generated following chromosomal translocation. Met receptor amplification and/or overexpression have been reported in human tumors, including multiple carcinomas, some sarcomas and hematopoietic malignancies. Point mutations in the

kinase domain of Met have been identified in hereditary and sporadic papillary renal carcinoma while mutations in the juxta-membrane domain have been identified in lung and gastric carcinomas. Ron is overexpressed in human breast and colorectal carcinoma. Three constitutively activated splicing variants of Ron have been identified in human gastric and colon cancer cell lines and in primary colorectal adenocarcinomas. Transgenic mice overexpressing Ron in lung epithelia developed multiple lung adenomas and adenocarcinomas.

Met and Ron are synthesized as a single polypeptide chain that is glycosylated. Upon translocation to the cell surface, Met is cleaved extracellularly by a furin protease to generate a disulphide-linked heterodimer composed of an extracellular α chain (307 amino acids) and a transmembrane β chain (1083 amino acids) that contains the intracellular kinase domain. The extracellular domain contains a Sema domain that is conserved in all semaphorins and plexins, a cysteine-rich PSI domain (found in plexins, semaphorins, and integrins), and four immunoglobulin-like repeats (also found in plexins). The Sema domain of Met, which is formed by the α chain and the first 212 residues of the β chain, is sufficient for HGF/SF binding.

Ligand binding to the Met and Ron receptors induces their homodimerization, activation of the kinase and trans-phosphorylation on tyrosine residues of the cytoplasmic domain. Phosphorylation of two conserved tyrosine residues located within the activation loop (Tyr¹²³⁴/Tyr¹²³⁵ in human Met, Tyr¹²³⁸/Tyr¹²³⁹ in human Ron) is required for activation of the intrinsic kinase activity of the receptor. A conserved twin tyrosine docking site (Tyr¹³⁴⁹/Tyr¹³⁵⁶ in human Met,

Tyr¹³⁵³/Tyr¹³⁶⁰ in human Ron), located at the carboxy-terminus of the receptor, mediates substrate recruitment. The phosphorylated docking site directly recruits multiple signaling proteins containing either a Src-homology-2 (SH2) or a phosphotyrosine binding (PTB) domain. These include Grb2, Shc, SHP-1, the p85 subunit of PI3K, Stat3, and Src (Tyr1356 in human Met, Tyr360 in human Ron), as well as Gab1 (Grb2-associated binder-1), a scaffolding adaptor protein that is highly tyrosine phosphorylated upon Met and Ron activation. Gab1 is a major transducer of Met and Ron signaling. Gab1 is recruited directly to Tyr1349 in human Met and indirectly via Grb2. Gab1 recruits multiple signaling proteins including SHP-2, PLC- γ , CrkII, CrkL and the p85 subunit of PI3K. These events induce the activation of downstream effectors such as the Ras-MAPK pathway, Akt, Src, Jnk, Rho, Rac1, Cdc42 and PAK, and are necessary for Met biological activity.

Activation of Met or Ron induces their ubiquitination, internalization and lysosomal degradation. Cbl ubiquitin-protein ligases are recruited directly to a juxtamembrane tyrosine in Met and Ron (Tyr1003 in human Met, Tyr1017 in human Ron) and via Grb2. Downregulation of Met and Ron is essential for their normal biological activity and impairment of their downregulation leads to their oncogenic activation.

Met

FAMILY MEMBERS	Met	Ron/Sea
OTHER NAMES	Hepatocyte growth factor (HGF)/Scatter factor (SF) receptor	Stem cell-derived tyrosine kinase, STK
MOLECULAR WEIGHT/ STRUCTURAL DATA	1390 aa 170 kDa (unglycosylated) 190 kDa (glycosylated - uncleaved) α chain: 50 kDa; β chain: 145 kDa	1400 aa 170 kDa (unglycosylated) 185 kDa (glycosylated - uncleaved) α chain: 35 kDa; β chain: 150 kDa
ISOFORMS	Not known	Not known
SPECIES	Vertebrates	Vertebrates
DOMAIN ORGANIZATION	Extracellular Sema, cysteine-rich PSI, four immunoglobulin-like IPT, single-pass transmembrane, cytoplasmic (tyrosine kinase)	Extracellular (Sema, cysteine-rich PSI, four immunoglobulin-like IPT), single-pass transmembrane, cytoplasmic tyrosine kinase
PHOSPHORYLATION SITES	Tyr ¹⁰⁰³ , Tyr ¹²³⁴ -Tyr ¹²³⁵ , Tyr ¹³⁴⁹ -Tyr ¹³⁵⁶ -Tyr ¹³⁶⁵	Tyr ¹⁰¹⁷ , Tyr ¹²³⁸ -Tyr ¹²³⁹ , Tyr ¹³⁵³ -Tyr ¹³⁶⁰
TISSUE DISTRIBUTION	Epithelial tissues, brain, blood vessels	Peritoneal macrophages, osteoclasts and megakaryocytes and skin gastrointestinal tracts, brain
SUBCELLULAR LOCALIZATION	Plasma membrane, endosomal-lysosomal pathway	Plasma membrane, endosomal lysosomal pathway
BINDING PARTNERS/ ASSOCIATED PROTEINS	Grb2, Shc, SHP-1, STAT3, Src, Gab1, p85 subunit of PI3K, RanBP9	β-Catenin, cbl, Grb2, PLCγ, Src, p85 subunit of PI3K, Shc
UPSTREAM ACTIVATORS	Hepatocyte growth factor (HGF)/Scatter factor (SF); Internalin B (InLB) of <i>Listeria monocytogenes</i> B1 ligand, Sema 4D	Macrophage-stimulating protein (MSP), Plexin,
DOWNSTREAM ACTIVATION	Akt, Src, Jnk, Rho, Rac1, Cdc42, PAK, Ras-MAPK	Disheveled (DVL), GSK-3β, PI3K, PKCζ, Src, JNK, MAPK, FAK, JNK
ACTIVATORS	Semaphorin 4D (SEMA4D) receptor, plexin B1 (PLXB1), CD44	Plexin B1 ligand, Sema 4D
SELECTIVE INHIBITORS	PHA-665752, SU11274	Not known
NON-SELECTIVE INHIBITORS	K252a (K6139), SU5416 (S8442), Genestein (G6649), Geldanamycin (G3381)	Not known
SELECTIVE ACTIVATORS	Agonistic monoclonal antibody DO-24	Not known
PHYSIOLOGICAL FUNCTION	Cell proliferation, morphogenesis, motility	Regulator of macrophage function and inflammation
DISEASE RELEVANCE	Multiple carcinomas, musculoskeletal sarcomas, soft tissue sarcomas, hematopoietic malignancies, listeria infection, malaria	Breast, gastric and colon carcinoma

FOOTNOTES