

## MST1R (Macrophage stimulating 1 receptor)

### Identity

Other names

**C-MET-related tyrosine kinase (RON)**

**RON protein tyrosine kinase (RON);  
Macrophage stimulating protein receptor (MSP-receptor)**

Hugo

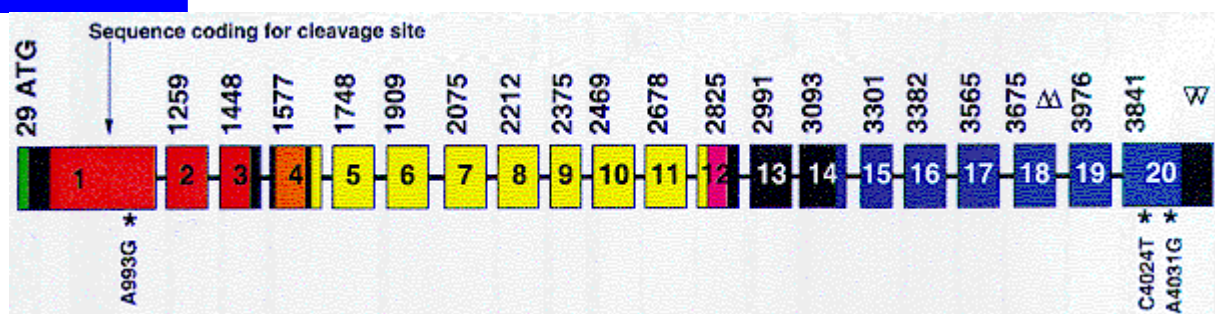
**MST1R**

Location

3p21.31

between LIMD1 and CCXCR1; between D3S1568 and D3S3822

### DNA/RNA



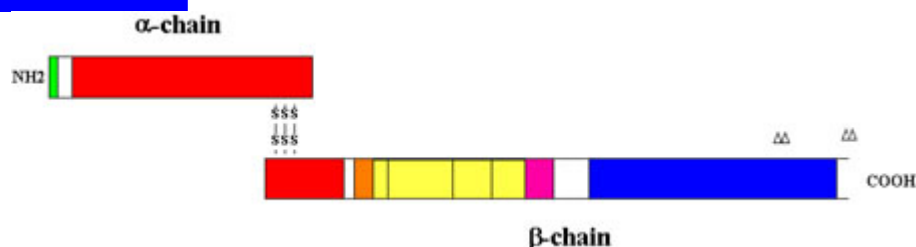
Description

Twenty coding exons. All exons are small in size, ranging from 93 bp to 253 bp, with the exception of exon 1 (>1 kb). Exon 1, 2 and 3 code for the SEMA domain of the RON protein (red). Exons 4 codes for a PSI domain (orange), a modular structure about 50 amino acid long containing eight conserved Cys residues, putatively involved in protein-protein interactions. The sequence between exon 4 and 12 codes for four repeated modular structures called IPT (yellow); these domains are found in cell surface receptors such as [MET](#) and RON as well as in intracellular transcription factors where they are involved in DNA binding. Part of exon 12 codes for the transmembrane domain, (pink). Exons 14 to 20 codes for the kinase domain (blue). Four-digit numbers refer to splice sites location, based on RON cDNA sequence

Transcription

Two major transcripts are detected, respectively 4.5 kb and 2 kb. ORF: 4204 bp

### Protein



Description

The RON protein is a glycosylated heterodimeric protein composed of one  $\alpha$ - (35 kD) and one  $\beta$ -chain (150 kD) linked by an unknown number of disulfide bonds. The two chains derive from a single-chain precursor of about 185 kD that undergoes proteolytic cleavage at the basic amino acid site KRRRR. The  $\alpha$ -chain is extracellular. The  $\beta$ -chain has an

extracellular part, a one-pass transmembrane helix and an intracellular part containing the tyrosine kinase domain. The first 24 amino acids made the putative signal peptide (green). The SEMA domain (consisting of most of a- and part of b- chain) contains the ligand (MSP) binding pocket (unpublished data). Tyrosine residues 1238 and 1239 (upward arrowheads in the figure) are essential for up-regulation of RON catalytic activity. Tyrosine residues 1353 and 1360 (downward arrowheads, in the figure) make a docking site that mediates high affinity interactions with multiple SH2-containing signal transducers

|              |   |
|--------------|---|
| Expression   | RON is expressed in human keratinocytes (it was initially cloned from a keratinocytes cDNA library). By Northern blot was found expressed in the following normal human tissues: skin, lung, bone marrow, small intestine, heart, pancreas, thyroid, prostate, testis (unpublished data), colonic mucosa and in a variety of cell types: granulocytes and monocytes, hematopoietic cells such as erythroid and myeloid progenitor cells, macrophages, osteoclasts, bone marrow megakaryocytes, epithelial and neuroendocrine cells  |
| Localisation | Transmembrane protein.  |
| Function     | The ligand for RON is MSP. Originally, MSP was described as a serum factor enhancing the chemotactic response of murine peritoneal macrophage to the C5a fraction of complement, but RON/MSP complex has a much broader spectrum of activity. Ligand-stimulated RON activates the pathways regulating cell adhesion and motility, growth and survival. STK (the mouse ortholog) is essential for peri-implantation development during gestation, as STK-deficient mice (STK <sup>-/-</sup> ) are viable only through the blastocyst stage. Hemizygous mice (STK <sup>+/-</sup> ) grow to adulthood; however, they are highly susceptible to endotoxic shock and appear to be compromised in their ability to down-regulate nitric oxide production. These results suggest STK has a limiting role not only in the inflammatory response but also in early mouse development |
| Homology     | RON belongs to the MET receptor tyrosine kinase (RTK) family. On the basis of the presence of multiple PSI domains and a SEMA domain, it has been proposed that plexins, MET RTK family and VESPR (virus-encoded semaphorin receptor) are classified as semaphorins. RON orthologs have been identified in mouse (STK), chicken (c-sea) and Xenopus   |

## Mutations

|          |  |
|----------|--|
| Germinal | Several Single Nucleotide Polymorphisms (SNPs) were found in healthy CEPH individuals: A993G :Gln322Arg (index of heterozygosity: 0.28); C4024T (same-sense variant, index of heterozygosity: 0.03); A4031G: Arg1344Gly (index of heterozygosity: 0.46)  |
| Somatic  | T915C: Leu296Pro was found in the tumor DNA of one single patient affected with adenocarcinoma of the <a href="#">lung</a> . The mutated protein is not constitutively activated. The mutation has no causative role in the disease. Experimental introduction in the RON kinase domain of amino acid substitutions D1232V and M1254T - initially found in the oncogenes <a href="#">KIT</a> , <a href="#">RET</a> and <a href="#">MET</a> , involved respectively in <a href="#">mastocytosis</a> , <a href="#">Multiple Endocrine Neoplasia type 2B</a> and <a href="#">renal papillary carcinoma</a> - results in activation of oncogenic capacity and triggers a strong metastatic activity of RON. Expression of these RON mutants causes cellular accumulation |

of b-catenin via inhibition of its association with the axin/GSK complex and subsequent protection from proteasomal degradation (Danilkovitch-Miagkova, personal communication).

## Implicated in

**Entity** RON was found over-expressed in infiltrating [breast carcinomas](#). A constitutively activated splicing variant of RON (lacking exon 11) was found in the gastric carcinoma cell line KATO-III. This variant induces activation of cell dissociation, motility and invasion of extracellular matrices. The same variant was found in malignant colonic mucosa. Another splicing variant, lacking exons 5 and 6, was found in the human colon carcinoma cell line HT-29. Truncated STK - the mouse RON ortholog - confers susceptibility to Friend virus-induced erythroleukemia in mice, and c-sea, the avian ortholog, causes erythroblastosis in chickens.

## External links

|                             |  |
|-----------------------------|--|
|                             | <b>Nomenclature</b>  |
| <a href="#">Hugo</a>        | <a href="#">MST1R</a>  |
| <a href="#">GDB</a>         | <a href="#">MST1R</a>  |
| <a href="#">Entrez Gene</a> | <a href="#">MST1R 4486</a> macrophage stimulating 1 receptor (c-met-related tyrosine kinase)           |
|                             | <b>Cards</b>   |
| <a href="#">Atlas</a>       | <a href="#">RONID287</a>   |
| <a href="#">GeneCards</a>   | <a href="#">MST1R</a>  |
| <a href="#">Ensembl</a>     | <a href="#">MST1R</a>  |
| <a href="#">CancerGene</a>  | <a href="#">MST1R</a>  |
| <a href="#">Genatlas</a>    | <a href="#">MST1R</a>  |
| <a href="#">GeneLynx</a>    | <a href="#">MST1R</a>  |
| <a href="#">eGenome</a>     | <a href="#">MST1R</a>  |
| <a href="#">euGene</a>      | <a href="#">4486</a>   |
|                             | <b>Genomic and cartography</b>   |
| <a href="#">GoldenPath</a>  | <a href="#">MST1R - 3p21.31</a> <a href="#">chr3:49899442-49916074 - 3p21.31</a> (hg17-May_2004)       |
| <a href="#">Ensembl</a>     | <a href="#">MST1R - 3p21.31 [CytoView]</a>   |
| <a href="#">NCBI</a>        | <a href="#">Genes Cyto</a> <a href="#">Gene Seq</a> [Map View - NCBI]                                  |
| <a href="#">OMIM</a>        | <a href="#">Disease map [OMIM]</a>   |
| <a href="#">HomoloGene</a>  | <a href="#">MST1R</a>  |
|                             | <b>Gene and transcription</b>  |
| <a href="#">Genbank</a>     | <a href="#">X70040</a> [SRS] <a href="#">X70040</a> [ENTREZ]   |
| <a href="#">RefSeq</a>      | <a href="#">NM_002447</a> [SRS] <a href="#">NM_002447</a> [ENTREZ]                                     |
| <a href="#">RefSeq</a>      | <a href="#">NT_086638</a> [SRS] <a href="#">NT_086638</a> [ENTREZ]                                     |
| <a href="#">AceView</a>     | <a href="#">MST1R</a> AceView - NCBI   |
| <a href="#">TRASER</a>      | <a href="#">MST1R</a> Traser - Stanford  |
| <a href="#">Unigene</a>     | <a href="#">Hs.517973</a> [SRS] <a href="#">Hs.517973</a> [NCBI] <a href="#">HS517973</a> [spliceNest] |
|                             | <b>Protein : pattern, domain, 3D structure</b>   |
| <a href="#">SwissProt</a>   | <a href="#">Q04912</a> [SRS] <a href="#">Q04912</a> [EXPASY] <a href="#">Q04912</a> [INTERPRO]         |
| <a href="#">Prosite</a>     | <a href="#">PS00107</a> PROTEIN KINASE ATP [SRS] <a href="#">PS00107</a>                               |
|                             | <a href="#">PROTEIN KINASE ATP</a> [Expasy]  |
| <a href="#">Prosite</a>     | <a href="#">PS50011</a> PROTEIN KINASE DOM [SRS] <a href="#">PS50011</a>                               |
|                             | <a href="#">PROTEIN KINASE DOM</a> [Expasy]  |

|                             |  |
|-----------------------------|--|
| <a href="#">Prosite</a>     | <a href="#">PS00109 PROTEIN KINASE TYR</a> [SRS] <a href="#">PS00109 PROTEIN KINASE TYR</a> [Expasy]   |
| <a href="#">Prosite</a>     | <a href="#">PS51004 SEMA</a> [SRS] <a href="#">PS51004 SEMA</a> [Expasy]   |
| <a href="#">Interpro</a>    | <a href="#">IPR002909 IPT/TIG_recept</a> [SRS] <a href="#">IPR002909 IPT/TIG_recept</a> [EBI]  |
| <a href="#">Interpro</a>    | <a href="#">IPR011009 Kinase_like</a> [SRS] <a href="#">IPR011009 Kinase_like</a> [EBI]  |
| <a href="#">Interpro</a>    | <a href="#">IPR002165 Plexin_repeat</a> [SRS] <a href="#">IPR002165 Plexin_repeat</a> [EBI]  |
| <a href="#">Interpro</a>    | <a href="#">IPR000719 Prot_kinase</a> [SRS] <a href="#">IPR000719 Prot_kinase</a> [EBI]  |
| <a href="#">Interpro</a>    | <a href="#">IPR001627 Sema</a> [SRS] <a href="#">IPR001627 Sema</a> [EBI]  |
| <a href="#">Interpro</a>    | <a href="#">IPR001245 Tyr_pkinase</a> [SRS] <a href="#">IPR001245 Tyr_pkinase</a> [EBI]  |
| <a href="#">Interpro</a>    | <a href="#">IPR008266 Tyr_pkinase_AS</a> [SRS] <a href="#">IPR008266 Tyr_pkinase_AS</a> [EBI]  |
| <a href="#">CluSTr</a>      | <a href="#">Q04912</a>   |
| <a href="#">Pfam</a>        | <a href="#">PF00069 Pkinase</a> [SRS] <a href="#">PF00069 Pkinase</a> [Sanger] <a href="#">pfam00069</a> [NCBI-CDD]                            |
| <a href="#">Pfam</a>        | <a href="#">PF01437 PSI</a> [SRS] <a href="#">PF01437 PSI</a> [Sanger] <a href="#">pfam01437</a> [NCBI-CDD]                                    |
| <a href="#">Pfam</a>        | <a href="#">PF01403 Sema</a> [SRS] <a href="#">PF01403 Sema</a> [Sanger] <a href="#">pfam01403</a> [NCBI-CDD]                                  |
| <a href="#">Pfam</a>        | <a href="#">PF01833 TIG</a> [SRS] <a href="#">PF01833 TIG</a> [Sanger] <a href="#">pfam01833</a> [NCBI-CDD]                                    |
| <a href="#">Prodom</a>      | <a href="#">PD000001 Prot_kinase</a> [INRA-Toulouse]   |
| <a href="#">Prodom</a>      | <a href="#">Q04912 RON_HUMAN</a> [Domain structure] <a href="#">Q04912 RON_HUMAN</a> [sequences sharing at least 1 domain]                     |
| <a href="#">Blocks</a>      | <a href="#">Q04912</a>   |
|                             | <b>Polymorphism : SNP, mutations, diseases</b>   |
| <a href="#">OMIM</a>        | <a href="#">600168</a> [map]   |
| <a href="#">GENECLINICS</a> | <a href="#">600168</a>   |
| <a href="#">SNP</a>         | <a href="#">MST1R</a> [dbSNP-NCBI]   |
| <a href="#">SNP</a>         | <a href="#">NM_002447</a> [SNP-NCI]  |
| <a href="#">SNP</a>         | <a href="#">MST1R</a> [GeneSNPs - Utah] <a href="#">MST1R</a> [SNP - CSHL] <a href="#">MST1R</a> [HGBASE - SRS]                                |
|                             | <b>General knowledge</b>   |
| <a href="#">Family</a>      | <a href="#">MST1R</a> [UCSC Family Browser]  |
| <a href="#">Browser</a>     |  |
| <a href="#">SOURCE</a>      | <a href="#">NM_002447</a>  |
| <a href="#">SMD</a>         | <a href="#">Hs.517973</a>  |
| <a href="#">SAGE</a>        | <a href="#">Hs.517973</a>  |
| <a href="#">Enzyme</a>      | <a href="#">2.7.1.112</a> [Enzyme-SRS] <a href="#">2.7.1.112</a> [Brenda-SRS] <a href="#">2.7.1.112</a> [KEGG] <a href="#">2.7.1.112</a> [WIT] |
| <a href="#">Amigo</a>       | <a href="#">function ATP binding</a>   |
| <a href="#">Amigo</a>       | <a href="#">process cell motility</a>  |
| <a href="#">Amigo</a>       | <a href="#">process defense response</a>   |
| <a href="#">Amigo</a>       | <a href="#">process fertilization (sensu Metazoa)</a>  |
| <a href="#">Amigo</a>       | <a href="#">component integral to plasma membrane</a>  |
| <a href="#">Amigo</a>       | <a href="#">function macrophage colony stimulating factor receptor activity</a>  |
| <a href="#">Amigo</a>       | <a href="#">process positive regulation of cell proliferation</a>  |
| <a href="#">Amigo</a>       | <a href="#">process protein amino acid phosphorylation</a>   |
| <a href="#">Amigo</a>       | <a href="#">function protein-tyrosine kinase activity</a>  |
| <a href="#">Amigo</a>       | <a href="#">function receptor activity</a>   |
| <a href="#">Amigo</a>       | <a href="#">process signal transduction</a>  |
| <a href="#">Amigo</a>       | <a href="#">function transferase activity</a>  |
| <a href="#">BIOCARTA</a>    | <a href="#">Msp/Ron Receptor Signaling Pathway</a>   |
| <a href="#">PubGene</a>     | <a href="#">MST1R</a>  |
|                             | <b>Other databases</b>   |
|                             | <b>Probes</b>  |
| <a href="#">Probe</a>       | <a href="#">MST1R Related clones (RZPD - Berlin)</a>   |

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