Atlas of Genetics and Cytogenetics in Oncology and Haematology

OPEN ACCESS JOURNAL AT INIST-CNRS

Gene Section
Review

MST1R (Macrophage stimulating 1 receptor)

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Published in Atlas Database: January 2001

Online updated version: http://AtlasGeneticsOncology.org/Genes/RONID287.html
DOI: 10.4267/2042/37697

Identity

Other names: C-MET-related tyrosine kinase (RON); RON protein tyrosine kinase (RON);; Macrophage stimulating protein receptor (MSP-receptor**)**

HGNC (Hugo): MST1R

Location: 3p21.31

Local order: 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.

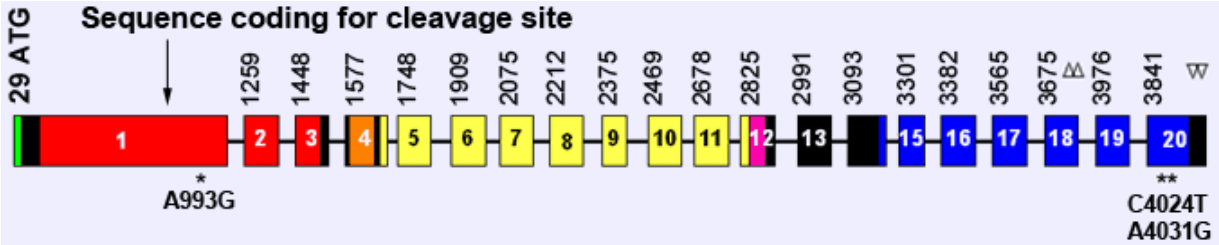
Transcription

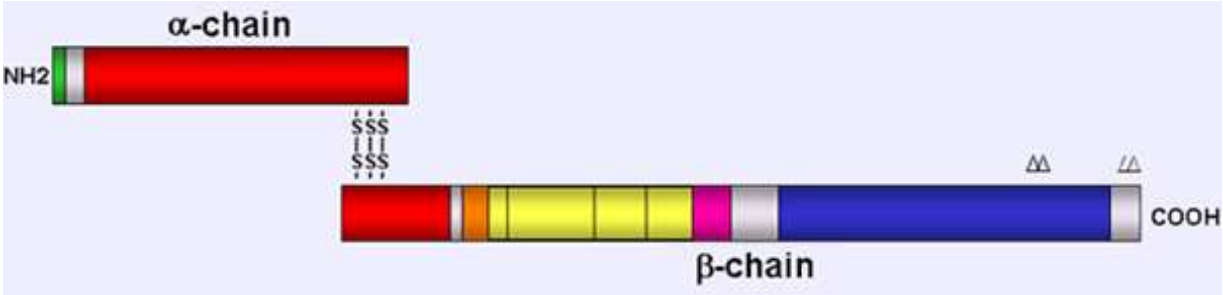
Two major transcripts are detected, respectively 4.5 kb and 2 kb. ORF: 4204 bp.

Protein

Description

The RON protein is a glycosilated heterodimeric protein composed of one a- (35 kD) and one b-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 a-chain is extracellular. The b-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 residues1353 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 intestin, 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-/-) are viable only through the blastocyst stage. Hemizygous mice (STK+/-) 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 lung. 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 KIT, RET and MET, involved respectively in mastocytosis, Multiple Endocrine Neoplasia type 2B and renal papillary carcinoma - 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

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.

References

Leonard EJ, Skeel A. A serum protein that stimulates macrophage movement, chemotaxis and spreading. Exp Cell Res. 1976 Oct 15;102(2):434-8

Smith DR, Vogt PK, Hayman MJ. The v-sea oncogene of avian erythroblastosis retrovirus S13: another member of the protein-tyrosine kinase gene family. Proc Natl Acad Sci U S A. 1989 Jul;86(14):5291-5

Dausset J, Cann H, Cohen D, Lathrop M, Lalouel JM, White R. Centre d'etude du polymorphisme humain (CEPH): collaborative genetic mapping of the human genome. Genomics. 1990 Mar;6(3):575-7

Ronsin C, Muscatelli F, Mattei MG, Breathnach R. A novel putative receptor protein tyrosine kinase of the met family. Oncogene. 1993 May;8(5):1195-202

Gaudino G, Follenzi A, Naldini L, Collesi C, Santoro M, Gallo KA, Godowski PJ, Comoglio PM. RON is a heterodimeric tyrosine kinase receptor activated by the HGF homologue MSP. EMBO J. 1994 Aug 1;13(15):3524-32

Hofstra RM, Landsvater RM, Ceccherini I, Stulp RP, Stelwagen T, Luo Y, Pasini B, Höppener JW, van Amstel HK, Romeo G. A mutation in the RET proto-oncogene associated with multiple endocrine neoplasia type 2B and sporadic medullary thyroid carcinoma. Nature. 1994 Jan 27;367(6461):375-6

Iwama A, Okano K, Sudo T, Matsuda Y, Suda T. Molecular cloning of a novel receptor tyrosine kinase gene, STK, derived from enriched hematopoietic stem cells. Blood. 1994 Jun 1;83(11):3160-9

Skeel A, Leonard EJ. Action and target cell specificity of human macrophage-stimulating protein (MSP). J Immunol. 1994 May 1;152(9):4618-23

Wang MH, Ronsin C, Gesnel MC, Coupey L, Skeel A, Leonard EJ, Breathnach R. Identification of the ron gene product as the receptor for the human macrophage stimulating protein. Science. 1994 Oct 7;266(5182):117-9

Gaudino G, Avantaggiato V, Follenzi A, Acampora D, Simeone A, Comoglio PM. The proto-oncogene RON is involved in development of epithelial, bone and neuro-endocrine tissues. Oncogene. 1995 Dec 21;11(12):2627-37

Iwama A, Wang MH, Yamaguchi N, Ohno N, Okano K, Sudo T, Takeya M, Gervais F, Morissette C, Leonard EJ, Suda T. Terminal differentiation of murine resident peritoneal macrophages is characterized by expression of the STK protein tyrosine kinase, a receptor for macrophage-stimulating protein. Blood. 1995 Nov 1;86(9):3394-403

Banu N, Price DJ, London R, Deng B, Mark M, Godowski PJ, Avraham H. Modulation of megakaryocytopoiesis by human macrophage-stimulating protein, the ligand for the RON receptor. J Immunol. 1996 Apr 15;156(8):2933-40

Collesi C, Santoro MM, Gaudino G, Comoglio PM. A splicing variant of the RON transcript induces constitutive tyrosine kinase activity and an invasive phenotype. Mol Cell Biol. 1996 Oct;16(10):5518-26

Kurihara N, Iwama A, Tatsumi J, Ikeda K, Suda T. Macrophage-stimulating protein activates STK receptor tyrosine kinase on osteoclasts and facilitates bone resorption by osteoclast-like cells. Blood. 1996 May 1;87(9):3704-10

Medico E, Mongiovi AM, Huff J, Jelinek MA, Follenzi A, Gaudino G, Parsons JT, Comoglio PM. The tyrosine kinase receptors Ron and Sea control "scattering" and morphogenesis of liver progenitor cells in vitro. Mol Biol Cell. 1996 Apr;7(4):495-504

Nakamura T, Aoki S, Takahashi T, Matsumoto K, Kiyohara T, Nakamura T. Cloning and expression of Xenopus HGF-like protein (HLP) and Ron/HLP receptor implicate their involvement in early neural development. Biochem Biophys Res Commun. 1996 Jul 16;224(2):564-73

Tsujimura T. Role of c-kit receptor tyrosine kinase in the development, survival and neoplastic transformation of mast cells. Pathol Int. 1996 Dec;46(12):933-8

Wang MH, Dlugosz AA, Sun Y, Suda T, Skeel A, Leonard EJ. Macrophage-stimulating protein induces proliferation and migration of murine keratinocytes. Exp Cell Res. 1996 Jul 10;226(1):39-46

Wang MH, Montero-Julian FA, Dauny I, Leonard EJ. Requirement of phosphatidylinositol-3 kinase for epithelial cell migration activated by human macrophage stimulating protein. Oncogene. 1996 Nov 21;13(10):2167-75

Schmidt L, Duh FM, Chen F, Kishida T, Glenn G, Choyke P, Scherer SW, Zhuang Z, Lubensky I, Dean M, Allikmets R, Chidambaram A, Bergerheim UR, Feltis JT, Casadevall C, Zamarron A, Bernues M, Richard S, Lips CJ, Walther MM, Tsui LC, Geil L, Orcutt ML, Stackhouse T, Lipan J, Slife L, Brauch H, Decker J, Niehans G, Hughson MD, Moch H, Storkel S, Lerman MI, Linehan WM, Zbar B. Germline and somatic mutations in the tyrosine kinase domain of the MET proto-oncogene in papillary renal carcinomas. Nat Genet. 1997 May;16(1):68-73

Maggiora P, Marchio S, Stella MC, Giai M, Belfiore A, De Bortoli M, Di Renzo MF, Costantino A, Sismondi P, Comoglio PM. Overexpression of the RON gene in human breast carcinoma. Oncogene. 1998 Jun 4;16(22):2927-33

Santoro MM, Penengo L, Minetto M, Orecchia S, Cilli M, Gaudino G. Point mutations in the tyrosine kinase domain release the oncogenic and metastatic potential of the Ron receptor. Oncogene. 1998 Aug 13;17(6):741-9

Waltz SE, Toms CL, McDowell SA, Clay LA, Muraoka RS, Air EL, Sun WY, Thomas MB, Degen SJ. Characterization of the mouse Ron/Stk receptor tyrosine kinase gene. Oncogene. 1998 Jan 8;16(1):27-42

Willett CG, Wang MH, Emanuel RL, Graham SA, Smith DI, Shridhar V, Sugarbaker DJ, Sunday ME. Macrophage-stimulating protein and its receptor in non-small-cell lung tumors: induction of receptor tyrosine phosphorylation and cell migration. Am J Respir Cell Mol Biol. 1998 Apr;18(4):489-96

Bork P, Doerks T, Springer TA, Snel B. Domains in plexins: links to integrins and transcription factors. Trends Biochem Sci. 1999 Jul;24(7):261-3

Danilkovitch A, Skeel A, Leonard EJ. Macrophage stimulating protein-induced epithelial cell adhesion is mediated by a PI3-K-dependent, but FAK-independent mechanism. Exp Cell Res. 1999 May 1;248(2):575-82

Muraoka RS, Sun WY, Colbert MC, Waltz SE, Witte DP, Degen JL, Friezner Degen SJ. The Ron/STK receptor tyrosine kinase is essential for peri-implantation development in the mouse. J Clin Invest. 1999 May;103(9):1277-85

Okino T, Egami H, Ohmachi H, Takai E, Tamori Y, Nakagawa K, Nakano S, Akagi J, Sakamoto O, Suda T, Ogawa M. Presence of RON receptor tyrosine kinase and its splicing variant in malignant and non-malignant human colonic mucosa. Int J Oncol. 1999 Oct;15(4):709-14

Persons DA, Paulson RF, Loyd MR, Herley MT, Bodner SM, Bernstein A, Correll PH, Ney PA. Fv2 encodes a truncated form of the Stk receptor tyrosine kinase. Nat Genet. 1999 Oct;23(2):159-65

Wahl RC, Hsu RY, Huff JL, Jelinek MA, Chen K, Courchesne P, Patterson SD, Parsons JT, Welcher AA. Chicken macrophage stimulating protein is a ligand of the receptor protein-tyrosine kinase Sea. J Biol Chem. 1999 Sep 10;274(37):26361-8

Angeloni D, Danilkovitch-Miagkova A, Ivanov SV, Breathnach R, Johnson BE, Leonard EJ, Lerman MI. Gene structure of the human receptor tyrosine kinase RON and mutation analysis in lung cancer samples. Genes Chromosomes Cancer. 2000 Oct;29(2):147-56

Chen YQ, Zhou YQ, Angeloni D, Kurtz AL, Qiang XZ, Wang MH. Overexpression and activation of the RON receptor tyrosine kinase in a panel of human colorectal carcinoma cell lines. Exp Cell Res. 2000 Nov 25;261(1):229-38

Danilkovitch A, Donley S, Skeel A, Leonard EJ. Two independent signaling pathways mediate the antiapoptotic action of macrophage-stimulating protein on epithelial cells. Mol Cell Biol. 2000 Mar;20(6):2218-27

This article should be referenced as such:

Angeloni D, Lerman MI. MST1R (Macrophage stimulating 1 receptor). Atlas Genet Cytogenet Oncol Haematol. 2001; 5(1):23-26.