MET (met proto-oncogene (hepatocyte growth factor receptor))

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Identity

Other names: c-met; hepatocyte growth factor receptor
HGNC (Hugo): MET
Location: 7q31
Local order: between DFNB17 (centromeric) and NAG14 (telomeric).

DNA/RNA

Description

The human MET gene spans more than 120 kb in length and consists of 21 exons separated by 20 introns. The size of the exons range from 81 bp (exon 16) to about 4kb (exon 21). The size of introns ranges from 0.1 to about 26 kb. The first exon encodes the 5' untranslated region (UTR) (394 bp).
bp) of the MET transcript and is separated by 26 kb circa from the second exon. Exon 2 is the largest coding exon, it contains 14 bp of 5' UTR and encodes for 400 amino acids. The cleavage site that yields the a- and b-subunits from the precursor polypeptide is encoded by exon 2. Exon 13 contains the hydrophobic transmembrane domain, together with the end of the extracellular domain and the beginning of the intracellular domain. Exons 14 to 21 code for the intracellular part and exons 15 to 21 for the kinase domain. Exon 21 includes the region coding for the carboxy terminus of the protein and the large 3' UTR of the gene. The ATP binding site is encoded for by exon 16; the autophosphorylation site by exon 19; the SH2 docking site by exon 21.

**Transcription**

Alternative splicing: Multiple MET transcripts of different size were identified in human cell lines and tissues. At least three 8-kb variants were described and presumed to be generated by alternative splicing. A MET isoform was described that lacks 18 amino acids in the extracellular region (exon 10) and is the most abundant form in a variety of tissues and cell lines. Alternative splicing of exon 14 generates another variant that has an in-frame deletion of 47 amino acids in the juxtamembrane cytoplasmic domain of the receptor. A possible mechanism of alternative splicing could be at the origin of a 85 kDa, N-terminally truncated form of MET found in malignant musculo-skeletal tumors, although this short form could also originate from alternative transcription start or proteolitic cleavage.

**Protein**


**Description**

The MET receptor (1408 amino acids) is initially synthesized as a partially glycosylated 170 kDa single chain precursor. Following further glycosylation, it is cleaved at a basic amino acid site into an a- and b-chain. The mature form is a transmembrane heterodimer composed of a- and b-chain linked together by disulphide bridges. The 50 kDa a-chain (amino acids 1-307) is located entirely extracellularly and contains the ligand binding pocket. The 140 kDa b-chain (amino acids 308-1408) comprises an extracellular part, the membrane spanning region and an intracellular C-terminal region that contains the tyrosine kinase domain. The C-terminal tail contains a conserved two-tyrosine multifunctional docking site that interacts with multiple SH2-containing intracellular signal transducers. The 5' alternative splicing leads to a form with 1390 amino acids.

**Expression**

MET and its ligand hepatocyte growth factor/scatter factor (HGF/SF) are expressed in numerous tissues although predominantly in cells of epithelial and mesenchymal origin, respectively. MET is amplified and overexpressed in many types of tumors, including tumors of the kidney (see below), thyroid, pancreas and osteosarcoma.

**Localisation**

MET is a transmembrane tyrosine kinase receptor. Upon ligand binding, the receptor is rapidly internalized, polyubiquitinated and degraded in a proteasome-dependent manner.

**Function**

The tyrosine kinase MET is the high affinity receptor for HGF/SF, a multifunctional cytokine. Upon ligand binding, MET dimerizes and transphosphorylates tyrosine residues in the C-terminal domain, which then interacts with members of a variety of signaling pathways. These include Grb-2 associated binder 1, phosphoinositide 3' kinase and c-Src. Under physiological conditions, MET-HGF/SF signaling has been shown to affect a wide range of biological activities depending on the cell target. These activities vary from cell proliferation (mitogenesis) to cellular shaping (morphogenesis) and motility (motogenesis). The coordination of these diverse activities constitutes a genetic program of “invasive growth” that allows branched morphogenesis (the formation of epithelial tubular structures), myoblast migration and neurite branching. MET/HGF cell targets comprise epithelial and mesenchymal cells, hematopoietic cells, myoblasts, spinal motor neurons. MET-HGF/SF signaling is also essential for normal development: mouse embryos carrying null mutations in both HGF alleles die in midgestation and show impaired liver formation.

**Homology**

MET amino acid sequence shows overall 33% identity with RON (the macrophage stimulating protein (MSP) receptor), which increases to 64% in the kinase domain. MET and RON are grouped in the family of so called scatter factor receptors. However, some structural domains shared by MET and RON are also present in other proteins such as semaphorins and plexins.
(semaphorins receptors), so that these proteins altogether are thought to originate from a common ancestor. The common domains are: the SEMA domain, a conserved box encompassing about 500 amino acids, with several highly conserved cysteines, and the PSI domain (from Plexin Semaphorins Integrines), of about 50 amino acids with 8 conserved cysteines, found also in integrins. Another structural motif repeated four times in the extracellular region of MET is the IPT domain, an immunoglobulin-like fold shared also by plexins and transcription factors. The function of these domains is at present under investigation but they are thought to mediate protein-protein interactions possibly related to cell dissociations and motility.

**Mutations**

### Germlinal

Germline mutations in the MET proto-oncogene are responsible for hereditary papillary renal carcinoma (HPRC) type 1 (see below). 10 known mutations are clustered in exons 16-19 of the tyrosine kinase domain and all are missense mutations which change the amino acid (V1110L, H1112R, H1112Y, M1149T, V1206L, V1238I, D1246N, Y1248C, Y1248D, M1268T). Mutations at four codons (V1110, D1246, Y1248, M1268) are homologous to sites of disease-associated activating mutations in other RTKs (RET, c-kit, c-erbB. Two unrelated North American families have been identified with the H1112R mutation and shared flanking genotyping data, suggesting a founder effect. Most HPRC-associated MET mutations are constitutively activating, causing phosphorylation on tyrosine in a ligand-independent manner when transfected into NIH3T3 cells, and oncogenic when the mutant MET transfected cell lines are injected into nude mice. Other mutations with only weak transforming potential (Y1248C, L1213V) confer anchorage-independent growth and an invasive phenotype in transfected cells.

### Somatic

Somatic missense mutations (H1112Y, H1112L, H1124D, L1213V, D1246H, Y1248H, Y1248C, Y1248D, M1268T) were identified in the TK domain of MET in 13% (17/129) of sporadic papillary renal carcinoma (PRC) type 1; 15 different germline and somatic MET mutations in 10 codons of the TK domain were identified in PRC. Infrquently, MET mutations have been identified in childhood hepatocellular carcinoma (3/10 in TK domain, T191I, K1262R, M1268I), gastric carcinoma (1/85 in juxtamembrane domain, P1009S), glioma (1/11 in TK domain, G1137V) and lymph node metastases (4/15 head and neck squamous cell carcinomas, Y1253D, Y1248C).

### Implicated in

**Hereditary papillary renal carcinoma and Sporadic papillary renal carcinoma (HPRC, SPRC)**

#### Disease

An inherited autosomal dominant form of renal carcinoma with reduced penetrance comprising 10% of all carcinomas of the kidney. Affected family members develop, in the fourth or fifth decade of life, bilateral, multifocal renal tumors with a papillary growth pattern which can be subdivided by histology into type 1 and type 2. Multiple tumors were shown to arise from independent clones. Sporadic PRCs are usually solitary tumors with microscopic papillary lesions in the surrounding renal parenchyma. It is important to note that patients with germline mutations in the MET gene are predisposed to develop papillary renal carcinoma type 1 specifically. These mutations are not known to predispose to any other type of malignant disease.

#### Prognosis

HPRC is a rare disease with an estimate incidence of 1 in 1 million. The age of development of PRCs is best studied in patients with H1112R mutation, because an elevated number of them has been described. By age 55, one half of H1112R mutation carriers have developed a detectable disease. Also, in H1112R mutation carriers has been observed that 26 % of patients develop distant metastases. The complete expression of the PRC phenotype may be affected by modifier genes. In fact, not only the age of onset varies among individuals but also the severity of the disease: in one patient were found at least 100 renal tumors, whereas his two brothers had a total of 1.

#### Cytogenetics

Papillary renal tumors are characterized by trisomy of chromosome 7 and 17, loss of Y in males. Only type 1 sporadic and hereditary PRCs harbor MET mutations with nonrandom duplication of the chromosome 7 bearing the mutant MET allele.

#### Hybrid/Mutated gene

MET was first identified as the product of a human oncogene, tpr-MET, which derives from the fusion of two distinct genetic loci: tpr (translocated promoter region), which contributes two leucine zipper motifs (a protein-protein dimerization domain), and MET, which contributes the intracellular kinase domain of the MET receptor. The tpr gene sequence involved in the tpr-MET fusion is found on 1q25, though this gene is located at 1q31 in a database.

#### Abnormal protein

The tpr-MET chimeric protein is dimerized and activated in ligand-independent manner and therefore possesses constitutive kinase activity and transforming ability.
The hybrid protein is made of Tpr leucine zippers (red) - that mediate constitutive dimerization - and MET kinase domains (blue), that drive transphosphorylation and constitutive activation.

**Oncogenesis**

MET/HGF signaling has been implicated in the generation and progression of a variety of tumors. The coexpression of wild type MET and HGF in the same cell (which generates an autocrine stimulatory loop) induces oncogenic transformation. All investigated naturally occurring MET mutants show increased tyrosine phosphorylation level and enhanced kinase activity. In general, somatic mutations cause higher level of enzymatic activity compared to germline mutants. The kinase domain mutations cause ligand-independent activation and increase the tyrosine kinase activity. The juxtamembrane P1009I mutation does not cause ligand-independent activation but results in prolonged HGF-activated MET response. The M1268T mutation identified in PRC- homologous to the M918T mutation of RET in multiple endocrine neoplasia type 2b - results not only in increased level of catalytic activity but also in a change of substrate specificity. Whereas c-Src is transiently activated by wild type MET, M1268T mutant MET is stably associated with c-Src, which is thereby constitutively phosphorylated and activated. Also, wild type MET does not phosphorylate substrate for cytosolic kinase c-Abl, whereas M1268T MET does. Moreover, expression of M1268T MET in NIH3T3 causes activation of the b-catenin pathway. Different mutations act through distinct mechanisms and result in variable transforming activity. D1246H/N and M1268 mutants (that activate the Ras pathway) have high transforming ability. Y1248C and LI213V have less transforming ability but promote cell migration and invasion via activation of the PI3K/AKT pathway.

3D molecular modeling studies using the crystal structure of the insulin receptor tyrosine kinase domain as a model suggest that disease-causing MET mutations interfere with the intrasteric mechanism of tyrosine kinase auto-inhibition to destabilize the inactive form and facilitate transition to the active form. Mutations V1110I, Y1248H/D/C, M1268T may affect contact between residues of the activation loop in its inhibitory conformation. Mutations M1149T and L1213V may increase flexibility of the tertiary structure. D1246N can stabilize the kinase in its active conformation. This structural work gives hints to understanding the switch of substrate specificity by mutant receptors.

**References**


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