## Phylogeny

MST1R (RON) is a TyrK-group receptor tyrosine kinase positioned in the MET sub-family; MET is its sole human paralogue, reflecting divergence after a gene-duplication event within the MET lineage (benvenuti2018discoveryandfunction pages 38-40, wang2003oncogenicandinvasive pages 1-2).  
Orthologs are documented in mouse (Stk; ~74 % identity in the kinase domain), rat, chicken (c-sea), Xenopus, zebrafish, pufferfish and sea-urchin, demonstrating deep vertebrate conservation of the SEMA/PSI/IPT–kinase architecture (wang2003oncogenicandinvasive pages 1-2, benight2012ronreceptortyrosine pages 11-12).

## Reaction Catalyzed

ATP + protein-L-tyrosine ⇄ ADP + protein-L-tyrosine-phosphate (benvenuti2018discoveryandfunction pages 22-24).

## Cofactor Requirements

Catalysis is ATP-dependent and strictly requires divalent Mg²⁺, as shown by in-vitro kinase assays performed in 10–20 mM MgCl₂ (kim2023targetingisoformsof pages 14-14).

## Substrate Specificity

A global consensus sequence for exogenous substrates has not been resolved. Intrinsic specificity is illustrated by autophosphorylation of the activation-loop Tyr1238/Tyr1239 and the C-terminal bidentate motif Tyr1353/Tyr1360; these phosphotyrosines recruit SH2-containing effectors such as PI3K p85 and GRB2 (benvenuti2018discoveryandfunction pages 20-22, wang2003oncogenicandinvasive pages 5-6).

## Structure

• Domain organisation: signal peptide – SEMA ligand-binding domain – PSI domain – four IPT immunoglobulin-like folds – single transmembrane helix – juxtamembrane segment – bilobed kinase domain – C-terminal docking tail (benvenuti2018discoveryandfunction pages 20-22).  
• Maturation: a 185 kDa precursor is furin-cleaved into a 35 kDa extracellular α-chain and a 150 kDa β-chain that harbours the kinase; the chains remain disulphide-linked (wang2003oncogenicandinvasive pages 2-3).  
• 3D information: the isolated kinase domain adopts canonical bilobal topology with VAIK (Lys1114), HRD (Asp1226) and DFG (Asp1232) catalytic triads; crystallographic and docking studies define key pocket residues Lys1114, Met1164, Gln1171 and Asp1226 critical for inhibitor binding (kim2023targetingisoformsof pages 3-3, zarei2022ligand‐baseddiscoveryof pages 6-8).  
• Regulatory elements: phosphorylation of Tyr1238/Tyr1239 in the activation loop aligns the C-helix and completes the hydrophobic spine, whereas Tyr1353/Tyr1360 constitute a multifunctional docking platform indispensable for downstream signalling (benvenuti2018discoveryandfunction pages 20-22).  
• Catalytic efficiency is inherently lower than MET owing to subtle active-site differences that restrict turnover (benvenuti2018discoveryandfunction pages 22-24).

## Regulation

• Ligand control: MSP binding induces receptor dimerisation and trans-autophosphorylation at Tyr1238, Tyr1239, Tyr1353 and Tyr1360, activating PI3K-AKT and RAS-ERK cascades (benvenuti2018discoveryandfunction pages 22-24).  
• Ubiquitination: CBL ubiquitin ligase binds phosphorylated RON, driving endocytosis and lysosomal degradation, thereby terminating signalling (benvenuti2018discoveryandfunction pages 24-27).  
• Alternative splicing: isoforms Δ160, Δ155, Δ165 and short-form RON are constitutively phosphorylated and transform epithelial cells independent of ligand (cazes2022themst1rrontyrosine pages 2-4, kim2023targetingisoformsof pages 1-2).  
• Cross-talk: physical interaction with MET, EGFR and IGF1R enables reciprocal or unidirectional transphosphorylation, expanding signalling outputs (benvenuti2018discoveryandfunction pages 24-27, benight2012ronreceptortyrosine pages 15-16).

## Function

• Expression: high in epithelial tissues of colon, breast, lung, kidney and liver; detectable in macrophages; minimal in fibroblasts (wang2003oncogenicandinvasive pages 2-3, benight2012ronreceptortyrosine pages 1-3).  
• Upstream inputs: hepatocyte-derived pro-MSP is proteolytically activated by HGFA, matriptase, hepsin and coagulation factors, linking RON activation to tissue injury and inflammation (benvenuti2018discoveryandfunction pages 22-24).  
• Downstream network: phosphorylated RON recruits PI3K p85, PLCG1, GAB1, GRB2, SHC, β-catenin, 14-3-3, SRC and FAK, triggering PI3K-AKT, RAS-ERK, mTOR, NF-κB and JNK pathways that drive proliferation, survival, motility and epithelial-mesenchymal transition (benvenuti2018discoveryandfunction pages 24-27, benight2012ronreceptortyrosine pages 15-16, kretschmann2010themacrophagestimulating pages 1-2).  
• Physiological roles: accelerates wound re-epithelialisation, modulates macrophage chemotaxis and phagocytosis, and restrains excessive inflammatory cytokine production (benvenuti2018discoveryandfunction pages 24-27, kretschmann2010themacrophagestimulating pages 1-2).

## Inhibitors

• BMS-777607 and Merestinib (dual MET/RON inhibitors) suppress migration and invasion in prostate and mesothelioma models (cazes2022themst1rrontyrosine pages 8-9, baird2019whenronmet pages 9-11).  
• Crizotinib overcomes cetuximab resistance in colorectal cancer via concomitant RON/MET blockade (cazes2022themst1rrontyrosine pages 8-9).  
• WM-S1-030 displays sub-micromolar potency against wild-type and splice-variant RON by occupying the ATP pocket (kim2023targetingisoformsof pages 3-3).  
• LCRF-0004, a RON-selective inhibitor, induces apoptosis in mesothelioma xenografts (baird2019whenronmet pages 9-11).  
• Early discovery compounds TKI1/TKI2 provide additional scaffolds for medicinal chemistry optimisation (zarei2022ligand‐baseddiscoveryof pages 6-8).

## Other Comments

RON is frequently over-expressed or constitutively activated in liver, lung, colon, ovarian, kidney, pancreas, bladder and breast carcinomas, correlating with poor prognosis and enhanced metastasis (benvenuti2018discoveryandfunction pages 24-27, cazes2022themst1rrontyrosine pages 2-4).  
Activating point mutations in the kinase domain (e.g., M1254T, D1232V) markedly increase catalytic activity and drive oncogenesis independent of docking-site phosphorylation (wang2003oncogenicandinvasive pages 6-7).  
Mouse models lacking RON kinase activity exhibit heightened inflammatory responses and delayed tumour onset, underscoring its dual roles in immunity and cancer progression (cazes2022themst1rrontyrosine pages 2-4).

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