## Phylogeny

• Receptor tyrosine kinase of the Met/Ron subfamily; catalytic domain homologous to insulin-like growth factor-I receptor and Tyro3/Axl/Mer family members (cecchi2011thehepatocytegrowth pages 3-4)  
• Closest paralogs are Ron, Mer, Axl, Tyro3 and RYK based on sequence comparison (underiner2010discoveryofsmall pages 1-2)  
• Orthologs conserved throughout vertebrates (human, mouse, rat, zebrafish, Xenopus); no orthologs in Drosophila or C. elegans, indicating vertebrate-specific emergence (schiering2003crystalstructureof pages 1-2)  
• Mouse knock-in models carrying human MET oncogenic mutations recapitulate tumour phenotypes, confirming functional conservation in mammals (cecchi2011thehepatocytegrowth pages 3-4)

## Reaction Catalyzed

• ATP + [protein]-L-tyrosine → ADP + [protein]-L-tyrosine-phosphate (wang2006structuralcharacterizationof pages 1-1)

## Cofactor Requirements

• Requires divalent cations for catalysis; Mg²⁺ is optimal and Mn²⁺ can substitute (gradler2023biophysicalandstructural pages 14-14)

## Substrate Specificity

• Positional scanning peptide arrays define a MET-preferred motif with acidic residues at −2 and hydrophobic residues at +1/+3 flanking the target Tyr (yaronbarir2024theintrinsicsubstrate pages 2-2)  
• MET motif activity is enriched in afatinib-treated HER2⁺ lung adenocarcinoma cells, validating cellular usage (yaronbarir2024theintrinsicsubstrate pages 5-6)

## Structure

• Domain architecture: SEMA β-propeller → PSI → four IPT repeats → single TM helix → juxtamembrane (JM) → tyrosine kinase (TK) → C-terminal docking tail (cecchi2011thehepatocytegrowth pages 3-4)  
• Autoinhibited TK (2.15 Å, PDB 1R0P) shows activation loop blocking the active site and a unique α-helix absent in FGFR/IRK (schiering2003crystalstructureof pages 2-4)  
• K-252a bound inactive structure (PDB 1R1W) displays activation-loop displacement and G-loop rearrangement (schiering2003crystalstructureof pages 5-6)  
• Activated, doubly phosphorylated TK (1.6 Å) exhibits helix-C rotation, ejection of residues 1225-1244 and open ATP cleft (rickert2011structuralbasisfor pages 3-4)  
• MK-2461 complexes (PDB 3Q6U/3Q6W) stabilise the regulatory spine with partial Lys1110–Glu1127 salt bridge (rickert2011structuralbasisfor pages 1-2)  
• JM Tyr1003 interfaces with the kinase lobe; phosphorylation of Tyr1234/Tyr1235 disrupts this contact and aligns the DFG motif for catalysis (wang2006structuralcharacterizationof pages 4-5)

## Regulation

• Ligand-induced dimerisation triggers trans-autophosphorylation on Tyr1234/Tyr1235, activating the kinase (rickert2011structuralbasisfor pages 1-2)  
• Phosphorylation of Tyr1349/Tyr1356 in the C-tail creates SH2 docking sites for Grb2, Gab1, PI3K, PLCγ, Shc, Src, Shp2, Ship1 and STAT3 (cecchi2011thehepatocytegrowth pages 3-4)  
• Phospho-Tyr1003 recruits c-Cbl, leading to ubiquitination and lysosomal degradation (cecchi2011thehepatocytegrowth pages 3-4)  
• SHP-2 phosphatase binds phosphorylated Gab1, contributing to negative feedback dephosphorylation (baldanzi2014physiologicalsignalingand pages 6-8)  
• Activating TK-domain mutations (e.g., D1246N, M1268T, Y1248C) or JM deletions abrogate autoinhibition or ubiquitination, yielding constitutive signalling (unknownauthors2010traffickingandsignalling pages 77-82)  
• Endocytic trafficking balances receptor recycling and degradation, modulating signal duration (unknownauthors2010traffickingandsignalling pages 77-82)

## Function

• HGF-activated MET drives epithelial proliferation, scattering, morphogenesis and survival (cecchi2011thehepatocytegrowth pages 3-4)  
• Grb2-SOS complex activates RAS-ERK pathway, mediating morphogenetic responses (baldanzi2014physiologicalsignalingand pages 6-8)  
• Gab1-PI3K recruitment activates AKT, promoting cell survival (baldanzi2014physiologicalsignalingand pages 6-8)  
• PLCγ engagement elevates intracellular Ca²⁺ and PKC activity, supporting proliferation (baldanzi2014physiologicalsignalingand pages 6-8)  
• Src family kinases and FAK phosphorylation reorganise the cytoskeleton, enhancing motility (baldanzi2014physiologicalsignalingand pages 6-8)  
• STAT3 phosphorylation drives transcriptional programmes required for tubulogenesis (baldanzi2014physiologicalsignalingand pages 6-8)

## Inhibitors

• K-252a: type I ATP-competitive inhibitor, low-nanomolar potency, co-crystal structure available (schiering2003crystalstructureof pages 1-2)  
• MK-2461 (“compound 1”): selective for activated MET, IC₅₀ ≈ 11 nM in peptide assay (rickert2011structuralbasisfor pages 3-4)  
• SU-11274, PHA-665752, PF-2341066 (crizotinib) and PF-4217903 inhibit MET in pre-clinical models (unknownauthors2010traffickingandsignalling pages 77-82)  
• JNJ-38877605, PF-02341066, ARQ197 (tivantinib) and multi-target agents XL880/XL184 (cabozantinib) are clinical-stage MET inhibitors (underiner2010discoveryofsmall pages 1-2)  
• BMS-777607 and MGCD265 inhibit MET catalytic activity in cellular assays (cecchi2011thehepatocytegrowth pages 12-12)  
• Activation-loop phosphorylation enhances binding affinity of the approved inhibitor tepotinib, as shown by structural studies (gradler2023biophysicalandstructural pages 14-14)

## Other Comments

• Recurrent activating substitutions Y1235D, Y1230H/C, D1228N/H and M1250T/I destabilise autoinhibition and increase kinase activity (wang2006structuralcharacterizationof pages 4-5)  
• Exon 14 skipping or Y1003F mutation abrogates c-Cbl binding, preventing ubiquitination and prolonging receptor signalling (cecchi2011thehepatocytegrowth pages 3-4)  
• MET amplification or activating mutations drive papillary renal cell carcinoma, lung and head-and-neck cancers and confer resistance to EGFR-targeted therapies (cecchi2011thehepatocytegrowth pages 3-4, underiner2010discoveryofsmall pages 1-2)

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