1. Phylogeny  
   MST1R, commonly known as RON, is a receptor tyrosine kinase that belongs to the MET proto‐oncogene family and is classified within a distinct subgroup of the receptor tyrosine kinome that includes only MET and RON. (baird2019whenronmet pages 1-2) Its kinase domain is highly conserved across species, with human RON sharing approximately 80% identity in its catalytic region with the MET receptor despite lower overall sequence similarity in its extracellular domains. (benight2012ronreceptortyrosine pages 1-3) Orthologs of RON have been identified in a broad range of vertebrates including humans, mice, rats, and even in non‐mammalian species such as puffer fish and Xenopus, underscoring its ancient evolutionary origin and essential physiological roles. (paluch2016theronreceptor pages 8-12, waltz2008met‐relatedreceptortyrosine pages 1-3) Phylogenetic studies based on the kinase complement of the human genome have placed RON within an evolutionary core of receptor tyrosine kinases that are present in all eukaryotes, supporting the notion that its regulatory function in signal transduction was established early in evolution. (danilkovitchmiagkova2003oncogenicsignalingpathways pages 3-4)
2. Reaction Catalyzed  
   RON functions as a receptor tyrosine kinase catalyzing the transfer of a phosphate group from ATP to specific tyrosine residues on substrate proteins; the canonical reaction can be summarized as: ATP + protein (L-tyrosine) → ADP + phosphorylated protein + H⁺. (waltz2008met‐relatedreceptortyrosine pages 22-23, danilkovitchmiagkova2003oncogenicsignalingpathways pages 3-4) This autophosphorylation reaction occurs on key tyrosine residues within the intracellular domain of RON as well as on downstream substrates, thereby generating docking sites for SH2 and PTB domain–containing effector proteins that propagate multiple intracellular signaling cascades. (benight2012ronreceptortyrosine pages 9-11)
3. Cofactor Requirements  
   The catalytic activity of RON requires the binding of ATP as a phosphate donor in conjunction with divalent metal ions, with Mg²⁺ being the principal cofactor that facilitates the proper positioning of ATP for phosphoryl transfer. (waltz2008met‐relatedreceptortyrosine pages 1-3, danilkovitchmiagkova2003oncogenicsignalingpathways pages 3-4)
4. Substrate Specificity  
   RON phosphorylates tyrosine residues both on itself—a process known as autophosphorylation—and on a variety of downstream signaling proteins; its autophosphorylation occurs at defined tyrosine sites in the kinase domain and C-terminal tail, which serve as high-affinity docking environments for mediator proteins (e.g., PIK3R1, PLCG1, GAB1). (baird2019whenronmet pages 1-2, benight2012ronreceptortyrosine pages 12-14) While a precise consensus phosphorylation motif for RON is not fully established, its substrate specificity is determined by the accessible tyrosine residues within target proteins that are flanked by sequences compatible with high-affinity SH2 domain binding, providing selective recognition of downstream effectors within pathways such as PI3K/AKT and RAS-ERK. (danilkovitchmiagkova2003oncogenicsignalingpathways pages 6-7)
5. Structure  
   RON is synthesized as a glycosylated 185 kDa single-chain precursor that is proteolytically cleaved to yield a disulfide-linked heterodimer, comprising a 35 kDa extracellular α-chain and a 150 kDa transmembrane β-chain that contains the intracellular tyrosine kinase domain. (baird2019whenronmet pages 1-2, wang2006oncogenesisofron pages 1-2) The extracellular region of RON encompasses several functional modules including a Sema domain and a PSI (plexin–semaphorin–integrin) domain, which are critical for binding its sole ligand, macrophage-stimulating protein (MSP, also referred to as HGFL), whereas the β-chain houses the catalytic kinase domain, a juxtamembrane segment that contributes to autoinhibition, and a C-terminal tail that contains key autophosphorylation sites such as tyrosines Y1238, Y1239, Y1353, and Y1360. (waltz2008met‐relatedreceptortyrosine pages 1-3, wang2006oncogenesisofron pages 1-2, benight2012ronreceptortyrosine pages 1-3) In addition, alternative splicing generates multiple isoforms of RON, including truncated variants that lack portions of the extracellular domain and exhibit constitutive kinase activity, thereby altering the receptor’s signaling output. (chakedis2016anovelprotein pages 11-12, danilkovitchmiagkova2003oncogenicsignalingpathways pages 6-7)
6. Regulation  
   Regulation of RON activity is principally mediated through ligand-dependent mechanisms; binding of MSP/HGFL to the extracellular α-chain promotes receptor dimerization and triggers autophosphorylation of the intracellular domain, which in turn creates docking sites for downstream signaling adaptors. (benight2012ronreceptortyrosine pages 11-12, baird2019whenronmet pages 1-2) Post-translational modifications, particularly autophosphorylation at key tyrosine residues within the kinase domain and C-terminal tail, are central regulatory events that modulate RON’s catalytic activity. (waltz2008met‐relatedreceptortyrosine pages 22-23) In addition, alternative splicing contributes to regulatory diversity; certain splice variants of RON lack autoinhibitory sequences, resulting in ligand-independent signaling and enhanced oncogenic potential. (danilkovitchmiagkova2003oncogenicsignalingpathways pages 6-7, hunt2023anintroductionand pages 8-10) Furthermore, RON can form heterodimers with other receptor tyrosine kinases, such as MET, EGFR, and IGF1R, thereby integrating multiple signaling networks that influence receptor activation thresholds and downstream signaling specificity. (gurusamy2013epithelialandstromal pages 25-29, danilkovitchmiagkova2001crosstalkbetweenron pages 5-6) Regulatory processes involving receptor internalization and ubiquitination also play roles in attenuating RON signaling, though specific E3 ligases and phosphatases have not been fully delineated in the available literature. (waltz2008met‐relatedreceptortyrosine pages 22-23)
7. Function  
   RON is widely expressed in epithelial cells as well as in macrophages, where its principal functions include transducing extracellular cues from its ligand MSP/HGFL into intracellular signals that regulate cell survival, migration, and differentiation. (baird2019whenronmet pages 1-2, benight2012ronreceptortyrosine pages 9-11) In the context of normal physiology, RON signaling is critical for the wound healing response; it promotes epithelial cell migration, proliferation, and survival at wound sites, thereby facilitating tissue repair. (huang2020mspronpathwaypotential pages 1-2, hunt2023anintroductionand pages 10-11) Additionally, RON plays an important role in the innate immune response by modulating macrophage migration and phagocytic activity, as well as by regulating the balance between pro-inflammatory and anti-inflammatory signals. (kretschmann2010themacrophagestimulating pages 1-2, yu2013regulationofmacrophage pages 117-119) In pathological states, aberrant RON signaling has been implicated in oncogenesis; overexpression and constitutive activation of RON are frequently observed in multiple epithelial cancers, including breast, colon, lung, pancreatic, and prostate cancers, where it contributes to enhanced cell proliferation, invasion, epithelial-to-mesenchymal transition, and therapeutic resistance. (benight2012ronreceptortyrosine pages 12-14, spidel2006pathologicalroleof pages 18-24, brown2018novelrolesfor pages 8-13) Moreover, RON’s ability to form heterodimers with other receptor tyrosine kinases further amplifies oncogenic signaling pathways such as the RAS-ERK, PI3K-AKT, and PLCγ-PKC cascades, facilitating tumor progression and metastasis. (danilkovitchmiagkova2003oncogenicsignalingpathways pages 6-7, waltz2008met‐relatedreceptortyrosine pages 22-23)
8. Other Comments  
   Several small molecule inhibitors and monoclonal antibodies that target RON or its downstream signaling partners are currently under investigation as therapeutic agents for cancers in which aberrant RON activity plays a critical role; these include compounds such as BMS-777607 and other multi-kinase inhibitors that demonstrate efficacy in preclinical models. (waltz2018therapeuticconsiderationsfora pages 14-15, hunt2022targetingmetabolicvulnerabilitiesb pages 16-19) Notable disease-associated mutations in the RON kinase domain, including alterations at positions such as D1232V and M1254T, have been reported to confer constitutive activation and upregulate oncogenic pathways such as β-catenin signaling, thereby promoting malignant transformation. (danilkovitchmiagkova2003oncogenicsignalingpathways pages 6-7, danilkovitchmiagkova2001crosstalkbetweenron pages 5-6) RON is also implicated in the modulation of the tumor microenvironment through its effects on macrophage polarization and cytokine production, ultimately contributing to immune evasion by tumor cells. (gurusamy2013epithelialandstromal pages 25-29, yu2013regulationofmacrophage pages 117-119) Given its dual role in regulating both normal wound healing and pathological oncogenic processes, RON represents a promising yet complex therapeutic target; ongoing research continues to refine our understanding of its signaling mechanisms, inter-receptor cross-talk, and the potential for targeted inhibition in cancer treatment. (benight2012ronreceptortyrosine pages 12-14, hunt2023anintroductionand pages 15-15)
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