## Phylogeny

• ROR2 belongs to the ROR sub-family within the NTRK superfamily of receptor tyrosine kinases, a lineage that diverged early from the MuSK, Nrk, Ddr and Trk families (green2008rorreceptortyrosine pages 12-17).  
• Orthologs are documented in Caenorhabditis elegans (cam-1), Drosophila melanogaster (Ror), Xenopus laevis (Xror2) and Mus musculus (Ror2), with homologous sequences already present in basal metazoans such as sea anemones (minami2010ror‐familyreceptortyrosine pages 1-2, green2008rorreceptortyrosine pages 12-17).  
• ROR2 is partially redundant with the closely related vertebrate paralog ROR1 (yoda2003expressionandfunction pages 8-10).  
• Kinase-domain sequence clustering places ROR2 closest to MuSK and Discoidin Domain Receptors within the RTK group (debebe2015ror2asa pages 4-6).

## Reaction Catalyzed

ATP + [protein]-L-tyrosine → ADP + [protein]-O-phospho-L-tyrosine (minami2010ror‐familyreceptortyrosine pages 2-3).

## Cofactor Requirements

Divalent-cation requirement has not been reported in the available literature (minami2010ror‐familyreceptortyrosine pages 2-3).

## Substrate Specificity

• Verified substrate: scaffold protein 14-3-3β (YWHAB) is phosphorylated on tyrosine after WNT5A-dependent receptor activation (minami2010ror‐familyreceptortyrosine pages 2-3, green2008rorreceptortyrosine pages 6-8).  
• Autophosphorylation occurs at Y645 and Y755 within the intracellular domain (debebe2015ror2asa pages 12-14).  
• A consensus phosphorylation motif for exogenous substrates has not been delineated (debebe2015ror2asa pages 1-3).

## Structure

• Modular organisation: Ig-like domain – Frizzled-type cysteine-rich domain (CRD; 10 conserved cysteines) – Kringle domain – single-pass transmembrane helix – intracellular tyrosine-kinase-like domain – proline-rich segment flanked by serine/threonine-rich regions (green2008rorreceptortyrosine pages 1-3, debebe2015ror2asa pages 3-4).  
• Crystal structure of the isolated kinase domain (PDB 5DN3) adopts an autoinhibited conformation in which the activation loop blocks the ATP pocket, a tyrosine side chain occupies the adenine site, and the canonical DFG motif contains an Asp→Gly substitution that ablates normal Mg²⁺ coordination (debebe2015ror2asa pages 4-6).  
• The HRD catalytic triad is followed by a non-canonical YXXDYY autophosphorylation segment; the hydrophobic spine is incomplete and the αC-helix is displaced, consistent with pseudokinase architecture (debebe2015ror2asa pages 4-6).  
• Overall fold is most similar to insulin receptor kinase despite the inactivating deviations noted above (debebe2015ror2asa pages 4-6).

## Regulation

• WNT5A binding induces receptor homodimerisation and increases tyrosine phosphorylation of ROR2 (liu2008wnt5ainduceshomodimerization pages 6-6).  
• Artificial dimerisation or over-expression produces a comparable phosphorylation response (minami2010ror‐familyreceptortyrosine pages 2-3).  
• Casein kinase Iε and GSK3α/β phosphorylate serine/threonine residues in the cytoplasmic tail, modulating cell migration (green2008rorreceptortyrosine pages 4-6).  
• Src family kinases are activated downstream of WNT5A/ROR2 and further phosphorylate the receptor, promoting internalisation (green2008rorreceptortyrosine pages 6-8).  
• Autophosphorylation at Y645 and Y755 provides additional intracellular signalling sites (debebe2015ror2asa pages 12-14).  
• The activation loop-mediated occlusion of the ATP pocket functions as an intrinsic autoinhibitory mechanism (debebe2015ror2asa pages 4-6).  
• Reports disagree on intrinsic catalytic competence: low but measurable kinase activity has been detected, whereas structural analyses classify the domain as a pseudokinase (minami2010ror‐familyreceptortyrosine pages 2-3, debebe2015ror2asa pages 4-6).

## Function

• Developmental expression is high in forebrain, midbrain, presomitic mesoderm, neural-crest derivatives, craniofacial mesenchyme, limb buds, heart, lung, kidney, gut and nervous system; adult expression is largely restricted to uterus and osteoblasts (minami2010ror-familyreceptortyrosine pages 2-3, debebe2015ror2asa pages 1-3).  
• Acts as a receptor or co-receptor for WNT5A (and context-dependently WNT3A), channeling non-canonical WNT/JNK signalling that controls planar cell polarity and convergent extension, and modulating canonical β-catenin signalling positively or negatively depending on cellular context (green2008rorreceptortyrosine pages 4-6, green2008rorreceptortyrosine pages 6-8).  
• Interacting partners include Frizzled receptors FZD2/5, collagen triple helix repeat containing protein-1 (Cthrc1), filamin-A, casein kinase Iε, GSK3β, Src and 14-3-3β (green2008rorreceptortyrosine pages 6-8, debebe2015ror2asa pages 3-4).  
• Biological roles encompass chondrocyte differentiation, growth-plate organisation, skeletal morphogenesis, neurite outgrowth, cytoskeletal remodelling and osteogenesis (green2008rorreceptortyrosine pages 4-6, yoda2003expressionandfunction pages 8-10).  
• In cancer, ROR2 is up-regulated in renal cell carcinoma, osteosarcoma, melanoma, breast cancer and head-and-neck squamous carcinoma, where it enhances migration, invasion and epithelial-mesenchymal transition; in renal carcinoma its transcription is driven by HIF-1α/HIF-2α (debebe2015ror2asa pages 6-8, debebe2015ror2asa pages 1-3).

## Inhibitors

• No selective small-molecule inhibitors have been reported; therapeutic efforts focus on monoclonal or bispecific antibodies, antibody-drug conjugates and CAR-engineered immune cells directed against the extracellular domain (debebe2015ror2asa pages 8-10).  
• Experimental bivalent antibodies or ROR2-Fc fusion proteins can induce receptor dimerisation and phosphorylation but have not been optimised for inhibition (green2008rorreceptortyrosine pages 6-8).

## Other Comments

• Loss-of-function variants in ROR2 cause autosomal recessive Robinow syndrome and autosomal dominant brachydactyly type B, both characterised by skeletal and craniofacial malformations (green2008rorreceptortyrosine pages 3-4, yoda2003expressionandfunction pages 10-12).  
• Pathogenic kinase-domain truncations such as p.Trp749\* and frameshift p.Gly666fs abolish receptor function (debebe2015ror2asa pages 1-3).  
• Combined deletion of Ror1 and Ror2 in mice produces more severe skeletal and cardiac defects than single knockouts, underscoring functional redundancy (yoda2003expressionandfunction pages 8-10).

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