## Phylogeny

ROR2 is a member of the ROR sub-family within the NTRK superfamily of receptor tyrosine kinases, a branch that diverged early from MuSK, Nrk, Ddr and Trk lineages (Green et al., 2008). Orthologs occur in Caenorhabditis elegans (cam-1), Drosophila melanogaster (Ror), Xenopus laevis (Xror2) and Mus musculus (Ror2), with related sequences already present in basal metazoans such as sea anemones (Minami et al., 2010; Green et al., 2008). In vertebrates, ROR2 is partially redundant with the closely related paralog ROR1 (Yoda et al., 2003). Kinase-domain clustering places ROR2 nearest to MuSK and Discoidin Domain Receptors (Debebe & Rathmell, 2015).

## Reaction Catalyzed

ATP + [protein]-L-tyrosine ⇌ ADP + [protein]-O-phospho-L-tyrosine (Minami et al., 2010).

## Cofactor Requirements

A specific divalent-cation requirement has not been reported (Minami et al., 2010).

## Substrate Specificity

• Verified substrate: scaffold protein 14-3-3β (YWHAB) becomes tyrosine-phosphorylated following WNT5A-dependent receptor activation (Minami et al., 2010; Green et al., 2008).  
• Autophosphorylation sites: Y645 and Y755 within the intracellular domain (Debebe & Rathmell, 2015).  
• No consensus phosphorylation motif for exogenous substrates has been defined (Debebe & Rathmell, 2015).

## Structure

ROR2 is a single-pass membrane protein organised as Ig-like domain – Frizzled-type cysteine-rich domain – Kringle domain – transmembrane helix – intracellular tyrosine-kinase-like domain – proline-rich segment bordered by Ser/Thr-rich regions (Green et al., 2008; Debebe & Rathmell, 2015).  
The isolated kinase domain structure (PDB 5DN3) adopts an autoinhibited fold: the activation loop occludes the ATP pocket, a Tyr side chain occupies the adenine site, and an Asp→Gly substitution in the DFG motif disrupts Mg²⁺ binding (Debebe & Rathmell, 2015). The HRD catalytic triad is followed by a non-canonical YXXDYY segment; the hydrophobic spine is incomplete and the αC-helix is displaced, features consistent with pseudokinase architecture. Despite these deviations, the overall fold resembles that of the insulin receptor kinase (Debebe & Rathmell, 2015).

## Regulation

• WNT5A binding promotes receptor homodimerisation and elevates tyrosine phosphorylation (Liu et al., 2008).  
• Forced dimerisation or over-expression elicits a similar phosphorylation response (Minami et al., 2010).  
• Casein kinase Iε and GSK3α/β phosphorylate Ser/Thr sites in the cytoplasmic tail, influencing cell migration (Green et al., 2008).  
• Src family kinases are activated downstream of WNT5A/ROR2 and further phosphorylate the receptor, facilitating internalisation (Green et al., 2008).  
• Autophosphorylation at Y645 and Y755 generates additional signalling sites (Debebe & Rathmell, 2015).  
• Occlusion of the ATP pocket by the activation loop provides intrinsic autoinhibition; reports disagree on whether the domain retains low catalytic activity or functions as a pseudokinase (Minami et al., 2010; Debebe & Rathmell, 2015).

## Function

Developmental expression is high in forebrain, midbrain, presomitic mesoderm, neural-crest derivatives, craniofacial mesenchyme, limb buds, heart, lung, kidney, gut and nervous system, while adult expression is largely confined to uterus and osteoblasts (Minami et al., 2010; Debebe & Rathmell, 2015).  
ROR2 acts as a receptor/co-receptor for WNT5A (and context-dependently WNT3A), mediating non-canonical WNT/JNK signalling that governs planar cell polarity and convergent extension, and modulating canonical β-catenin signalling in a context-dependent manner (Green et al., 2008). Interacting partners include FZD2/5, Cthrc1, filamin-A, CKIε, GSK3β, Src and 14-3-3β (Green et al., 2008; Debebe & Rathmell, 2015). Biological roles encompass chondrocyte differentiation, growth-plate organisation, skeletal morphogenesis, neurite outgrowth, cytoskeletal remodelling and osteogenesis (Green et al., 2008; Yoda et al., 2003). 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, transcription is driven by HIF-1α/HIF-2α (Debebe & Rathmell, 2015).

## Inhibitors

No selective small-molecule inhibitors have been described. Current therapeutic strategies centre on monoclonal or bispecific antibodies, antibody-drug conjugates and CAR-engineered immune cells targeting the extracellular domain. Experimental bivalent antibodies or ROR2-Fc fusion proteins can induce receptor dimerisation and phosphorylation but have not been optimised for inhibition (Debebe & Rathmell, 2015; Green et al., 2008).

## 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 (Green et al., 2008; Yoda et al., 2003). Pathogenic kinase-domain truncations such as p.Trp749\* and p.Gly666fs abolish receptor function (Debebe & Rathmell, 2015). Combined deletion of Ror1 and Ror2 in mice yields more severe skeletal and cardiac defects than single knockouts, underscoring functional redundancy (Yoda et al., 2003).

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