## Phylogeny

Discoidin domain receptor 2 (DDR2) belongs to the receptor tyrosine kinase group, DDR sub-family, and clusters phylogenetically near the ErbB/HER branch (Richters et al., 2014). Verified orthologues occur in Homo sapiens, Mus musculus, Rattus norvegicus, Danio rerio, Drosophila melanogaster and Caenorhabditis elegans (Vogel et al., 2006). A Ddr2-null mouse displays dwarfism and shortened long bones, indicating a conserved role in skeletal development (Valiathan et al., 2012). The kinase domains of DDR1 and DDR2 share 68 % sequence identity, consistent with a recent duplication within the DDR lineage (Canning et al., 2014).

## Reaction Catalyzed

ATP + [protein]-L-tyrosine ⇌ ADP + [protein]-L-tyrosine-phosphate (Sammon et al., 2020; Fu et al., 2013).

## Cofactor Requirements

Catalysis requires Mg²⁺; biochemical assays employ ~10 mM MgCl₂. Mn²⁺ dependence has not been reported (Day et al., 2008; Richters et al., 2014).

## Substrate Specificity

In peptide profiling, DDR2 favours acidic residues (Asp/Glu) at –2/–3 and a hydrophobic residue (Ile/Leu/Val) at +1 relative to the acceptor tyrosine (Yaron-Barir et al., 2024).

## Structure

N-terminal discoidin (DS) domain → DS-like domain → flexible extracellular juxtamembrane segment → single-pass transmembrane helix with leucine zipper → intracellular juxtamembrane region → C-terminal kinase domain (Fu et al., 2013; Elkamhawy et al., 2021).  
• DS domain crystal structure bound to a collagen triple helix (PDB 2WUH) reveals an amphiphilic trench; Trp52, Asp69, Arg105 and Glu113 bind the GVMGFO motif (Carafoli et al., 2009).  
• Kinase domain exhibits the canonical bilobal fold with conserved Lys621 (VAIK), Glu672 (αC), HRD Asp784, gatekeeper Thr654 and the DFG motif (Fu et al., 2013).  
• DDR1 structures show a DFG-Asp-out/αC-Glu-in inactive state with a β-hairpin P-loop; 68 % identity suggests DDR2 adopts the same conformation (Canning et al., 2014).  
• An Asp–Arg salt bridge stabilises the DFG-out conformation and is predicted to be retained in DDR2 (Hanson et al., 2019).  
• Autoinhibition involves an intracellular juxtamembrane hairpin occupying the active-site cleft; phosphorylation releases this hairpin (Sammon et al., 2020).

## Regulation

• Constitutive phosphorylation: Tyr471, Tyr481 (Iwai et al., 2013).  
• Collagen- or Src-inducible sites: Tyr684, Tyr736, Tyr740, Tyr741, Tyr813 (Iwai et al., 2013; Yang et al., 2005; Iwai et al., 2016).  
• Src directly phosphorylates Tyr740, initiating intramolecular autophosphorylation and Shc recruitment (Yang et al., 2005).  
• N-glycosylation at Asn211 and Asn260 promotes folding and surface expression (Fu et al., 2013).  
• Cbl-b-mediated ubiquitination drives receptor turnover (Iwai et al., 2016).  
• ADAM metalloproteinases shed the ectodomain, dampening signalling (Fu et al., 2013).  
• Insulin enhances receptor phosphorylation independently of collagen (Fu et al., 2013).

## Function

Expression is highest in fibroblasts, myofibroblasts, smooth-muscle cells and chondrocytes; additional expression occurs in heart, skeletal muscle, lung, brain, kidney and other connective tissues (Elkamhawy et al., 2021; Vogel, 1999). DDR2 is activated by fibrillar collagens I, II, III and X via DS-domain recognition of the GVMGFO motif (Valiathan et al., 2012; Fu et al., 2013). Upstream activator: Src family kinases. Early adaptor proteins: SHC1, NCK1, SHP-2 (Iwai et al., 2016). Downstream cascades: MAPK/ERK, p38, JNK and PI3K pathways, leading to RUNX2 activation and induction of MMP1, MMP2 and MMP13 (Iwai et al., 2016; Chen et al., 2021). Biological roles include osteoblast differentiation, chondrocyte maturation, fibroblast proliferation/migration, wound healing and promotion of tumour invasion through extracellular-matrix remodelling (Valiathan et al., 2012; Elkamhawy et al., 2021).

## Inhibitors

Dasatinib (type I, IC₅₀ ≈ 1.4 nM); Ponatinib (multi-target type II, 9 nM); Nilotinib (type II, 55 nM); Imatinib (type II, 675 nM); GZD824 (imatinib analogue, 220 nM); Pyrazolo-urea 1a (selective type III, ~3 nM); Quinazolinyl-urea 1 (18.6 nM) (Day et al., 2008; Canning et al., 2014; Matada et al., 2021; Terai et al., 2015). Thr654Met reduces dasatinib potency, whereas S768R increases sensitivity (Richters et al., 2014; Elkamhawy et al., 2021).

## Other Comments

Germline missense variants E113K and R752C impair collagen binding or trafficking, causing spondylo-meta-epiphyseal dysplasia with short limbs (Ali et al., 2010). Somatic lung squamous-cell-carcinoma mutations L63V, G505S and I638F alter signalling output (Iwai et al., 2013). The S768R lung-cancer mutation confers pronounced dasatinib responsiveness (Elkamhawy et al., 2021).

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