Phylogeny  
DDR1 is a tyrosine-protein kinase belonging to the Discoidin Domain Receptor (DDR) family within the TK group of the human kinome (Kothiwale et al., 2015). The catalytic domain shares 68 % sequence identity with DDR2 and superposes on ABL1 with a 3.6 Å Cα RMSD, illustrating conservation of the bilobal kinase fold (Canning et al., 2014). Orthologues are found throughout vertebrates; mouse Ddr1 is experimentally characterised and additional DDR1 genes are reported in other vertebrate lineages (Mariadoss & Wang, 2023).

Reaction Catalyzed  
ATP + protein-L-tyrosine ⇌ ADP + protein-L-tyrosine-phosphate (Kothiwale et al., 2015).

Cofactor Requirements  
Catalytic activity requires a divalent cation; Mg²⁺ is routinely used in vitro (Hanson et al., 2019).

Substrate Specificity  
• Autophosphorylates Tyr513 in the juxtamembrane region and a YxYxY motif (Tyr792, Tyr796, Tyr797) within the activation loop (Kothiwale et al., 2015; Juskaite et al., 2017).  
• Peptide-docking studies identified Axltide (KKSRGDYMTMQIG) as an efficient substrate, revealing preference for basic residues at positions −3/−2 relative to the target Tyr and a Met at +2 (Hanson et al., 2019).  
• Phosphotyrosine proteomics shows multiple intracellular pTyr sites that recruit SH2/PTB adaptors such as SHC1, NCK2, RasGAP, SHIP1/2 and the PI3K p85 subunit (Lemeer et al., 2012).

Structure  
Domain layout: N-terminal Discoidin (DS) domain – DS-like domain – single-pass transmembrane helix – long cytoplasmic juxtamembrane segment – kinase domain (Carafoli & Hohenester, 2013; Juskaite et al., 2017).  
Extracellular region  
• DS domain: eight-stranded β-barrel that recognises the GVMGFO motif in triple-helical collagen (Carafoli & Hohenester, 2013).  
• DS-like domain: jelly-roll fold bearing two N-glycans and a Ca²⁺ site, contributing to ectodomain rigidity (Carafoli et al., 2012).  
Kinase domain (e.g., PDB 3ZOS, 4BKJ)  
• Canonical bilobal fold with intact αC helix (Glu672), HRD motif (His764–Arg765–Asp766) and a β-hairpin P-loop (Canning et al., 2014; Kothiwale et al., 2015).  
• DFG motif adopts an inactive Asp-out conformation stabilised by an Asp671–Arg752 ion pair that also creates an allosteric pocket (Hanson et al., 2019).  
• Lys655–Glu672 salt bridge anchors ATP; hydrophobic spine residues (Met676, Leu687, His764, Phe785) align on activation (Kothiwale et al., 2015).  
• The P-loop β-hairpin (residues 618–624) differs from the cage-like loop of ABL1 and influences inhibitor binding (Canning et al., 2014).

Regulation  
Post-translational control  
• Collagen engagement triggers autophosphorylation at Tyr513 and Tyr792/796/797, creating docking sites for SH2/PTB adaptors and fully activating the kinase (Juskaite et al., 2017; Lemeer et al., 2012).  
Conformational/allosteric control  
• DDR1 exists as a constitutive dimer; ligand binding induces higher-order clustering that enables trans-phosphorylation between neighbouring dimers (Juskaite et al., 2017).  
• Disrupting the Asp671–Arg752 clasp shifts the kinase to the DFG-in state, increasing catalytic turnover about ten-fold (Hanson et al., 2019).

Function  
Expression – Highly expressed in epithelial tissues including lung, brain, kidney, spleen and placenta (Mariadoss & Wang, 2023).  
Ligand binding – Activated by triple-helical collagens I-III, V and IV, displaying slow but sustained signalling kinetics (Carafoli & Hohenester, 2013; Juskaite et al., 2017).  
Downstream signalling – Active DDR1 recruits SRC family kinases and propagates ERK/MAPK, PI3K, JAK/STAT, RAP1 and Notch pathways, up-regulating MMP2, MMP7 and MMP9 to remodel extracellular matrix and promote cell migration (Gadiya & Chakraborty, 2018; Kothiwale et al., 2015).  
Mechanical coupling – Phosphorylated Tyr792 associates with non-muscle myosin IIA, enhancing force transmission at collagen contacts (Coelho & McCulloch, 2018).

Inhibitors  
Type II (bind DFG-out/allosteric pocket): imatinib, nilotinib, ponatinib; co-crystal structures 4BKJ (imatinib) and 3ZOS (ponatinib) (Canning et al., 2014).  
Type I (bind ATP site with kinase DFG-out): dasatinib, VX-680; structural data PDB 6BSD (dasatinib) and 6BRJ (VX-680) (Hanson et al., 2019).  
Selective chemical probe: DDR1-IN-1 exploits Thr701 gatekeeper and the hydrophobic allosteric pocket (Kothiwale et al., 2015).

Other Comments  
DDR1 over-expression or hyperactivation is linked to breast and lung carcinomas, tissue fibrosis, atherosclerosis and osteoarthritis; genetic or pharmacological inhibition ameliorates disease phenotypes in pre-clinical models (Mariadoss & Wang, 2023; Gadiya & Chakraborty, 2018). Missense mutations within the kinase core impair catalytic activity and receptor trafficking (Carafoli & Hohenester, 2013).

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