## Phylogeny

– Member of the receptor tyrosine kinase (RTK) group, discoidin domain receptor (DDR) sub-family, placed phylogenetically close to the ErbB/HER branch (richters2014identificationoftype pages 1-2).  
– Verified orthologs in Homo sapiens, Mus musculus, Rattus norvegicus, Danio rerio, Drosophila melanogaster and Caenorhabditis elegans (vogel2006sensingextracellularmatrix pages 6-7).  
– Mouse Ddr2 knockout causes dwarfism and shortened long bones, demonstrating conserved skeletal function (valiathan2012discoidindomainreceptor pages 13-15).  
– Sequence identity within the kinase domains of DDR1 and DDR2 is 68 %, underscoring a recent duplication within the DDR lineage (canning2014structuralmechanismsdetermining pages 5-6).

## Reaction Catalyzed

– ATP + [protein]-L-tyrosine ⇌ ADP + [protein]-L-tyrosine-phosphate (sammon2020twostepreleaseof pages 6-7, fu2013discoidindomainreceptors pages 1-2).

## Cofactor Requirements

– Catalytic activity requires Mg²⁺; biochemical kinase assays are performed in buffers containing 10 mM MgCl₂ (day2008inhibitionofcollageninduced pages 3-5).  
– Mn²⁺ dependence has not been reported; standard assays omit Mn²⁺ (richters2014identificationoftype pages 8-9).

## Substrate Specificity

– Intrinsic tyrosine‐kinase motif preference: acidic residues (Asp/Glu) at −2/−3 and a hydrophobic residue (Ile/Leu/Val) at +1 relative to the target tyrosine (yaronbarir2024theintrinsicsubstrate pages 16-16).

## Structure

– Domain organisation: 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 (fu2013discoidindomainreceptors pages 2-3, elkamhawy2021thejourneyof pages 1-3).  
– DS domain crystal structure bound to a collagen triple helix (PDB 2WUH) shows an amphiphilic trench; key binding residues Trp52, Asp69, Arg105 and Glu113 contact the GVMGFO motif (carafoli2009crystallographicinsightinto pages 6-7).  
– Kinase domain has the canonical bilobal fold; conserved motifs include Lys621 (VAIK), Glu672 (αC), HRD Asp784, gatekeeper Thr654 and the DFG motif (fu2013discoidindomainreceptors pages 3-4).  
– DDR1 crystal structures reveal a DFG-Asp-out/αC-Glu-in inactive state with a β-hairpin P-loop; 68 % identity supports conservation of these features in DDR2 (canning2014structuralmechanismsdetermining pages 5-6).  
– A distinctive Asp–Arg salt bridge stabilises the DFG-out conformation, predicted to be conserved in DDR2 (hanson2019whatmakesa pages 6-8).  
– Autoinhibited conformation involves an intracellular juxtamembrane hairpin occupying the active-site cleft; phosphorylation disengages the hairpin (sammon2020twostepreleaseof pages 1-2).

## Regulation

– Constitutive phosphorylation sites: Tyr471 and Tyr481 in the juxtamembrane region (iwai2013phosphoproteomicsofcollagen pages 4-6).  
– Collagen-induced or Src-dependent inducible sites: Tyr684, Tyr736, Tyr740, Tyr741 and Tyr813 within the kinase domain/activation loop (iwai2013phosphoproteomicsofcollagen pages 4-6, yang2005tyrosine740phosphorylation pages 5-6, iwai2016discoidindomainreceptor pages 9-12).  
– Src directly phosphorylates Tyr740, triggering intramolecular autophosphorylation and Shc recruitment (yang2005tyrosine740phosphorylation pages 5-6).  
– N-glycosylation at Asn211 and Asn260 supports proper folding and surface expression (fu2013discoidindomainreceptors pages 3-4).  
– Cbl-b ubiquitinates activated receptor, promoting turnover (iwai2016discoidindomainreceptor pages 9-12).  
– ADAM-family metalloproteinases mediate ectodomain shedding, attenuating signalling (fu2013discoidindomainreceptors pages 3-4).  
– Insulin enhances phosphorylation independently of collagen (fu2013discoidindomainreceptors pages 9-9).

## Function

– Predominant expression in fibroblasts, myofibroblasts, smooth-muscle cells and chondrocytes (elkamhawy2021thejourneyof pages 1-3).  
– Additional expression detected in heart, skeletal muscle, lung, brain, kidney and connective tissues (vogel1999discoidindomainreceptors pages 1-2).  
– Activated by fibrillar collagens I, II, III and X through DS-domain recognition of the GVMGFO motif (valiathan2012discoidindomainreceptor pages 2-4, fu2013discoidindomainreceptors pages 7-7).  
– Upstream kinase: Src family; early adaptor partners: SHC1, NCK1 and SHP-2 (iwai2016discoidindomainreceptor pages 9-12).  
– Downstream pathways: MAPK/ERK, p38, JNK and PI3K cascades leading to RUNX2 activation and induction of MMP1, MMP2 and MMP13 (iwai2016discoidindomainreceptor pages 9-12, chen2021recentadvancesin pages 4-6).  
– Biological roles include osteoblast differentiation, chondrocyte maturation, fibroblast proliferation/migration, cutaneous wound healing and facilitation of tumour invasion via extracellular-matrix remodeling (valiathan2012discoidindomainreceptor pages 13-15, elkamhawy2021thejourneyof pages 3-4).

## Inhibitors

– Dasatinib, type I, IC₅₀ = 1.4 nM (day2008inhibitionofcollageninduced pages 3-5).  
– Nilotinib, type II, IC₅₀ = 55 nM (day2008inhibitionofcollageninduced pages 5-6).  
– Imatinib, type II, IC₅₀ = 675 nM (day2008inhibitionofcollageninduced pages 3-5).  
– Ponatinib, multi-target type II, IC₅₀ = 9 nM (canning2014structuralmechanismsdetermining pages 9-11).  
– GZD824, imatinib analogue, IC₅₀ = 220 nM (matada2021ddr1andddr2 pages 7-9).  
– Pyrazolo-urea compound 1a, selective type III, IC₅₀ ≈ 3 nM (matada2021ddr1andddr2 pages 7-9).  
– Quinazolinyl-urea compound 1, IC₅₀ = 18.6 nM (terai2015characterizationofddr2 pages 1-7).  
– Gatekeeper Thr654Met mutation diminishes dasatinib efficacy, whereas S768R mutation enhances sensitivity (richters2014identificationoftype pages 2-3, elkamhawy2021thejourneyof pages 4-5).

## Other Comments

– Germline missense mutations E113K and R752C impair collagen binding or trafficking, causing spondylo-meta-epiphyseal dysplasia with short limbs (SMED-SL) (ali2010traffickingdefectsand pages 9-9).  
– Somatic lung-squamous-cell-carcinoma mutations L63V, G505S and I638F alter signalling output (iwai2013phosphoproteomicsofcollagen pages 11-12).  
– S768R mutation in lung SCC confers marked dasatinib sensitivity, identifying a clinically actionable subset (elkamhawy2021thejourneyof pages 4-5).

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