1. Phylogeny  
   Epithelial discoidin domain‐containing receptor 1 (DDR1) belongs to the discoidin domain receptor subfamily of receptor tyrosine kinases (RTKs), a group distinguished by their extracellular discoidin (DS) domains that specifically bind fibrillar collagens rather than soluble growth factors (canning2014structuralmechanismsdetermining pages 1-3). DDR1 and its paralog DDR2 share a conserved DS domain and similar overall domain architecture; they are considered to have arisen through a gene duplication event early in metazoan evolution, and orthologs of DDR1 have been identified across a wide range of vertebrates (leitinger2003molecularanalysisof pages 1-1, kothiwale2015discoidindomainreceptor pages 1-2). Within the human kinome, DDR1 is phylogenetically assigned to the RTK family that mediates cell–matrix interactions, reflecting an ancient mechanism for integrating extracellular collagen cues with intracellular signal transduction (iwai2014discoidindomainreceptors pages 1-3). This receptor thus occupies a unique evolutionary niche distinct from classical growth factor receptors, and its conservation underscores a critical role in tissue homeostasis and remodeling (canning2014structuralmechanismsdetermining pages 1-3).
2. Reaction Catalyzed  
   DDR1 functions as a tyrosine kinase that catalyzes the phosphorylation of tyrosine residues on substrate proteins. The chemical reaction it mediates can be summarized as follows: ATP + [protein]–L‐tyrosine → ADP + [protein]–L‐phosphotyrosine + H⁺ (kim2013discoveryofa pages 3-4, leitinger2003molecularanalysisof pages 1-1). This reaction reflects the classical kinase mechanism in which DDR1 transfers the γ‐phosphate group of ATP to specific tyrosine residues in target proteins, thereby modulating downstream signaling events.
3. Cofactor Requirements  
   The catalytic activity of DDR1 is dependent on the presence of ATP as the phosphate donor, and as with most kinases, its enzymatic activity is enhanced by the binding of divalent metal ions such as Mg²⁺ (denny2021inhibitorsofdiscoidin pages 15-16, kim2013discoveryofa pages 6-6). These cofactors are required to correctly position and stabilize the ATP molecule within the catalytic cleft of the kinase domain, thereby facilitating efficient phosphoryl transfer during signal transduction.
4. Substrate Specificity  
   DDR1 exhibits substrate specificity that primarily involves the phosphorylation of tyrosine residues on target proteins. In addition to autophosphorylating its own intracellular domain, DDR1 phosphorylates signaling molecules such as the protein tyrosine phosphatase, PTPN11 (canning2014structuralmechanismsdetermining pages 1-3, Information section). Although a strict consensus substrate motif for DDR1 has not been as clearly defined as for some other tyrosine kinases, its activity is directed toward substrates involved in cell adhesion, extracellular matrix remodeling, and migratory responses (dagamajalu2023anetworkmap pages 3-5, kim2013discoveryofa pages 3-4).
5. Structure  
   DDR1 is composed of several distinct domains that collectively mediate its function as a collagen-activated receptor tyrosine kinase. The extracellular portion includes an N-terminal discoidin domain, which is responsible for high-affinity collagen binding, followed by a DS-like domain that further supports ligand interaction (canning2014structuralmechanismsdetermining pages 1-3, leitinger2003molecularanalysisof pages 8-8). This extracellular region is connected via a juxtamembrane segment to a single transmembrane helix, which in turn is followed by a cytosolic tail containing a juxtamembrane domain and a catalytic tyrosine kinase domain (iwai2014discoidindomainreceptors pages 1-3, kim2013discoveryofa pages 3-4).  
   The kinase domain itself adopts a canonical bilobal structure in which the N-terminal lobe comprises a five-stranded β-sheet and a conserved αC helix, while the C-terminal lobe is predominantly α-helical (canning2014structuralmechanismsdetermining pages 3-5, kim2013discoveryofa pages 6-6). Notably, DDR1’s kinase domain features unique elements such as a prolonged loop insertion between the β2 and β3 strands and an activation loop capable of adopting an inactive DFG-out conformation upon inhibitor binding (canning2014structuralmechanismsdetermining pages 3-5, denny2021inhibitorsofdiscoidin pages 7-10). Moreover, DDR1 is known to form constitutive dimers on the cell surface, a property that distinguishes it from many other RTKs, and this dimerization is mediated in part by disulfide bonds and/or a transmembrane leucine zipper motif (canning2014structuralmechanismsdetermining pages 1-3, kothiwale2015discoidindomainreceptor pages 1-2).
6. Regulation  
   DDR1 activity is tightly regulated through multiple mechanisms that govern its activation and downstream signaling. Collagen binding to the extracellular discoidin domain induces receptor clustering and dimerization, which in turn triggers slow and sustained autophosphorylation of intracellular tyrosine residues (canning2014structuralmechanismsdetermining pages 3-5, dorison2017theroleof pages 1-2). In addition, DDR1 autophosphorylation is dependent on receptor aggregation into dense clusters on the cell surface—a phenomenon established by advanced imaging analyses (corcoran2019ddr1autophosphorylationis pages 15-15). Phosphorylation events occur primarily within the activation loop and juxtamembrane regions, serving as docking sites for intracellular adaptor proteins that mediate further signal propagation (kim2013discoveryofa pages 3-4, denny2021inhibitorsofdiscoidin pages 12-14).  
   Post-translational modifications such as glycosylation, which may occur in the extracellular domain, also contribute to the proper folding and function of DDR1 (iwai2014discoidindomainreceptors pages 10-11). Furthermore, extracellular processes such as ligand-induced shedding of the DDR1 ectodomain modulate receptor availability and signaling intensity (dorison2017theroleof pages 8-9). Inhibitory regulation can be achieved pharmacologically; for example, type II kinase inhibitors (e.g., imatinib, ponatinib) selectively stabilize DDR1 in an inactive conformation by binding to its ATP site and adjacent hydrophobic pockets (denny2021inhibitorsofdiscoidin pages 14-15).
7. Function  
   DDR1 serves as a critical mediator of cell–matrix interactions by functioning as a receptor for various types of fibrillar and nonfibrillar collagens. Upon collagen engagement, DDR1 undergoes autophosphorylation and initiates a cascade of intracellular signaling events that regulate cell attachment, migration, proliferation, differentiation, and survival (canning2014structuralmechanismsdetermining pages 1-3, Information section). In epithelial tissues, DDR1 plays an essential role in remodeling the extracellular matrix by upregulating the expression of matrix metalloproteinases (MMP2, MMP7, and MMP9), thereby facilitating cell migration and wound healing (Information section, denny2021inhibitorsofdiscoidin pages 15-16).  
   DDR1 signaling also involves the activation of SRC family kinases and subsequent stimulation of MAP kinase pathways, which contribute to cell survival and proliferation (dorison2017theroleof pages 1-2, dagamajalu2023anetworkmap pages 1-3). In the context of development, DDR1 is required for normal blastocyst implantation, mammary gland differentiation and lactation, as well as the formation of proper ear architecture that is critical for hearing (Information section, dorison2017theroleof pages 1-2). Additionally, DDR1 promotes smooth muscle cell migration, a function that contributes to arterial wound healing (Information section). In tumors, dysregulated DDR1 expression and activity are associated with increased invasion and metastasis, partly through its ability to phosphorylate the phosphatase PTPN11 and modulate extracellular matrix remodeling (canning2014structuralmechanismsdetermining pages 1-3, dagamajalu2023anetworkmap pages 3-5).
8. Other Comments  
   DDR1 is known by multiple alternative names including CD167 antigen-like family member A, CAK, NEP, NTRK4, PTK3A, RTK6, and TRKE, reflecting its discovery in various contexts such as mammary carcinoma and cell adhesion kinase activities (Information section). Several selective and multi-targeted small-molecule inhibitors have been developed against DDR1; these include compounds such as DDR1-IN-1 and DDR1-IN-2, as well as clinically used tyrosine kinase inhibitors like imatinib, nilotinib, dasatinib, and ponatinib—all of which exploit the unique structural features of DDR1’s ATP-binding pocket to stabilize its inactive conformation (denny2021inhibitorsofdiscoidin pages 12-14, kim2013discoveryofa pages 6-6). DDR1 overexpression or mutation has been implicated in a variety of pathological conditions, including several solid tumors (e.g., non-small cell lung carcinoma, breast cancer, pancreatic ductal adenocarcinoma), fibrotic diseases, and inflammatory conditions (dorison2017theroleof pages 1-2, huo2015highexpressionof pages 7-7, dagamajalu2023anetworkmap pages 1-3). Its role in modulating extracellular matrix remodeling also makes DDR1 a promising target for inhibiting tumor invasion and metastasis, as well as for alleviating fibrosis in organs such as the kidney and lung (dong2022discoveryofa pages 11-11, denny2021inhibitorsofdiscoidin pages 15-16).
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