1. Phylogeny  
   DDR2 is a member of the discoidin domain receptor (DDR) subfamily within the receptor tyrosine kinase (RTK) superfamily. It is evolutionarily conserved among vertebrates and is typically expressed in mesenchymal-derived tissues. DDR2 shares significant sequence and structural similarities with its paralog DDR1 while remaining distinct in that it is expressed as a single isoform rather than as multiple splice variants (chen2021recentadvancesin pages 1-2, leitinger2011transmembranecollagenreceptors pages 11-13). The extracellular discoidin (DS) domain of DDR2—responsible for collagen recognition—displays homology to lectin-like domains found in lower organisms such as Dictyostelium, suggesting an ancient origin for collagen-sensing functions (fu2013discoidindomainreceptors pages 1-2, leitinger2011transmembranecollagenreceptors pages 11-13). DDR2, along with other DDR family members, belongs to a core set of RTKs that appeared early during eukaryotic evolution and has been maintained across mammalian species (mehta2021complexrolesof pages 1-3).
2. Reaction Catalyzed  
   As a receptor tyrosine kinase, DDR2 catalyzes the transfer of a phosphate group from ATP to specific tyrosine residues on substrate proteins. The general reaction is:  
     ATP + [protein]-L-tyrosine → ADP + [protein]-L-tyrosine phosphate + H⁺  
   This phosphorylation is initiated upon binding of native, triple-helical collagen to the extracellular DS domain, leading to receptor dimerization, autophosphorylation, and subsequent downstream signaling (chen2021recentadvancesin pages 4-6, iwai2013phosphoproteomicsofcollagen pages 12-12).
3. Cofactor Requirements  
   The kinase activity of DDR2 depends on ATP, which serves as the phosphate donor in the phosphorylation reaction. In addition, like most protein kinases, DDR2 requires divalent metal ions—typically Mg²⁺—to coordinate ATP and facilitate phosphate transfer (chen2021recentadvancesin pages 4-6, ruizcastro2016discoidindomainreceptor pages 19-20).
4. Substrate Specificity  
   DDR2 phosphorylates tyrosine residues on itself (autophosphorylation) as well as on downstream signaling proteins including various adaptor molecules. Although a strict consensus phosphorylation motif for DDR2 has not been fully established in the literature, its substrate specificity is characteristic of receptor tyrosine kinases that target specific tyrosine residues based on the receptor’s conformation and activation state. Notably, DDR2 activation is tightly dependent on its engagement with native collagen, implying that substrate phosphorylation occurs only after collagen-induced conformational changes facilitate access to the kinase active site (fu2013discoidindomainreceptors pages 7-7, richters2014identificationoftype pages 1-2, chen2021recentadvancesin pages 6-8).
5. Structure  
   DDR2 is an 855–amino acid single-pass transmembrane protein organized into distinct functional domains. Its extracellular portion comprises an N‐terminal discoidin (DS) domain, which adopts a jelly‐roll β‐barrel structure with several surface loops that form a trench for binding the native triple‐helical conformation of fibrillar collagens (e.g. types I, III, and X) via recognition of conserved motifs such as GVMGFO (fu2013discoidindomainreceptors pages 3-4, leitinger2011transmembranecollagenreceptors pages 10-11). This DS domain is followed by a short extracellular juxtamembrane region. A single transmembrane helix anchors the receptor, participating in ligand‐independent dimerization (fu2013discoidindomainreceptors pages 3-4, kim2014theintracellularjuxtamembrane pages 2-2). On the cytosolic side, DDR2 contains an extended intracellular juxtamembrane (IJM) region, including a critical subdomain designated JM2 that is indispensable for receptor dimerization and proper activation (kim2014theintracellularjuxtamembrane pages 1-2, kim2014theintracellularjuxtamembrane pages 5-5). The C-terminal region harbors the tyrosine kinase domain, which features typical kinase structural motifs such as an activation loop, a catalytic loop, and a DFG motif necessary for ATP binding and phosphotransfer activity (chen2021recentadvancesin pages 4-6, kim2014theintracellularjuxtamembrane pages 10-10, ruizcastro2016discoidindomainreceptor pages 3-6). Unique among RTKs, DDR2 exhibits slow and sustained activation kinetics after collagen binding, a property that is directly linked to the structural and conformational characteristics of its DS and intracellular regulatory domains (chen2021recentadvancesin pages 6-8, rammal2016discoidindomainreceptors pages 8-9, ruizcastro2016discoidindomainreceptor pages 11-15).
6. Regulation  
   DDR2 regulation is predominantly ligand-dependent. Binding of native, triple-helical collagen to the extracellular discoidin domain induces receptor dimerization, a process facilitated by the intracellular JM2 region, which is critical for the subsequent autophosphorylation of DDR2 tyrosine residues (kim2014theintracellularjuxtamembrane pages 1-2, kim2014theintracellularjuxtamembrane pages 5-5). The phosphorylation events create docking sites for adaptor proteins such as Shc, Nck, and SHP-2, thereby initiating downstream signaling cascades, particularly the MAP kinase pathway (chen2021recentadvancesin pages 6-8, fu2013discoidindomainreceptors pages 6-7). DDR2 activation is characteristically slow and sustained, in contrast to the rapid, transient activation observed in many other RTKs (chen2021recentadvancesin pages 1-2, rammal2016discoidindomainreceptors pages 8-9). In addition, regulatory cross talk with integrins and other cell surface receptors modulates DDR2 signaling, fine-tuning cellular responses such as adhesion and migration (ruizcastro2016discoidindomainreceptor pages 17-19, mehta2021complexrolesof pages 1-3). Pharmacologically, DDR2 activity can be inhibited by ATP-competitive tyrosine kinase inhibitors including dasatinib, imatinib, and nilotinib, which suppress the autophosphorylation and subsequent signaling of the receptor (rammal2016discoidindomainreceptors pages 11-11, richters2014identificationoftype pages 1-2).
7. Function  
   DDR2 functions as a collagen-activated receptor tyrosine kinase that plays multiple roles in tissue remodeling and cellular signaling. As a cell surface receptor for fibrillar collagen, DDR2 mediates extracellular matrix (ECM) interactions that underlie key biological processes including cell differentiation, proliferation, migration, and invasion (chen2021recentadvancesin pages 1-2, chen2021recentadvancesin pages 6-8). In skeletal tissues, DDR2 is required for normal bone development; its signaling via MAP kinase pathways leads to the activation of the transcription factor RUNX2, which is essential for osteoblast differentiation and chondrocyte maturation, thereby regulating endochondral ossification (chen2021recentadvancesin pages 6-8, leitinger2011transmembranecollagenreceptors pages 11-13, kim2014theintracellularjuxtamembrane pages 1-2).  
   In addition, DDR2 upregulates the expression of matrix metalloproteinases (MMP1, MMP2, and MMP13), which contribute to the degradation and remodeling of the ECM. This activity facilitates cellular invasion and migration, which are critical not only for physiological processes such as wound healing but also for pathological conditions including tumor metastasis (chen2021recentadvancesin pages 1-2, leitinger2011transmembranecollagenreceptors pages 11-13). DDR2 also promotes fibroblast migration and proliferation, thereby contributing to cutaneous wound healing as well as the progression of fibrotic diseases (chen2021recentadvancesin pages 1-2, rammal2016discoidindomainreceptors pages 1-2). Aberrant DDR2 signaling—resulting from overexpression or mutation—has been implicated in various cancers, where it facilitates invasion and metastasis, and in fibrotic disorders through excessive extracellular matrix deposition (rammal2016discoidindomainreceptors pages 8-9, ruizcastro2016discoidindomainreceptor pages 17-19).
8. Other Comments  
   DDR2 is regarded as an attractive therapeutic target due to its central role in modulating ECM remodeling, cell migration, and tissue differentiation. Several tyrosine kinase inhibitors (TKIs) that target the catalytic domain of DDR2, such as dasatinib, imatinib, and nilotinib, have been employed experimentally and in clinical settings to suppress its activity, especially in cancer types where DDR2 mutations or overexpression contribute to tumor progression (rammal2016discoidindomainreceptors pages 11-11, richters2014identificationoftype pages 1-2). Furthermore, DDR2’s unique slow phosphorylation kinetics and its strict requirement for native, triple-helical collagen for activation provide additional opportunities for the development of allosteric inhibitors that disrupt collagen–DDR2 interactions. DDR2 dysregulation is associated not only with malignancies—including lung, breast, and ovarian cancers—but also with fibrotic diseases and skeletal abnormalities related to impaired bone development and remodeling (chen2021recentadvancesin pages 1-2, leitinger2011transmembranecollagenreceptors pages 11-13). Specific DDR2 mutations, particularly in the kinase domain, have been documented in certain cancers and may influence both receptor activity and responsiveness to pharmacological inhibition, underscoring the importance of studying DDR2 functional mutations in clinical oncology (rammal2016discoidindomainreceptors pages 11-12, ruizcastro2016discoidindomainreceptor pages 17-19).
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