Phylogeny  
ROCK1 is a serine/threonine protein kinase of the AGC (PKA/PKG/PKC) family and one of two closely related Rho-associated kinases (ROCK1 and ROCK2). The two isoforms share ~60–65 % overall amino-acid identity and ~92 % identity within the catalytic domain (Feng et al., 2016; Surma et al., 2011; Guan et al., 2013; Liao et al., 2007). Orthologues occur throughout mammalian species, including human and mouse (Zanin-Zhorov et al., 2016; Surma et al., 2011).

Reaction Catalyzed  
ATP + L-seryl/threonyl-[protein] ⇌ ADP + O-phospho-L-seryl/threonyl-[protein] (Feng et al., 2016; Julian & Olson, 2014).

Cofactor Requirements  
Mg²⁺ is required together with ATP for catalysis (Feng et al., 2016; Julian & Olson, 2014).

Substrate Specificity  
ROCK1 phosphorylates serine or threonine residues within basic, basophilic motifs. Preferred consensus sequences are R/K-X-S/T or R/K-X-X-S/T, often with arginine at the −3 and −2 positions (Julian & Olson, 2014; Surma et al., 2011; Liao et al., 2007). Kinome-wide peptide library screening confirmed recognition of such basophilic motifs and highlighted strong negative selectivity based on electrostatic filtering (Johnson et al., 2023). Rnd3 is a known ROCK1-selective substrate not phosphorylated by ROCK2 (Hartmann et al., 2015).

Structure  
Human ROCK1 is a ~160 kDa, 1354-residue protein encoded on chromosome 18q11.1 (Feng et al., 2016; Julian & Olson, 2014). It contains:  
• N-terminal catalytic kinase domain  
• Central coiled-coil region harbouring the Rho-binding domain (RBD) and mediating homodimerisation (Julian & Olson, 2014; Shah & Savjani, 2016)  
• C-terminal split pleckstrin-homology (PH) domain interrupted by a cysteine-rich domain (CRD) that acts as an autoinhibitory segment (Hartmann et al., 2015).  
Phosphorylation of the activation loop is not essential for activity, distinguishing ROCK1 from many other AGC kinases (Hartmann et al., 2015; Julian & Olson, 2014).

Regulation  
• Autoinhibition: the C-terminal region folds over the kinase domain to block activity (Hartmann et al., 2015; Liao et al., 2007).  
• Activation by GTP-bound RhoA/B/C binding to the RBD, which releases autoinhibition (Feng et al., 2016; Hartmann et al., 2015; Zhou et al., 2011).  
• Proteolytic activation: caspase-3 cleavage at DETD¹¹¹³ ↓ G during apoptosis and granzyme B cleavage remove the inhibitory tail, yielding constitutively active kinase fragments (Hartmann et al., 2015; Julian & Olson, 2014; Zhou et al., 2011).  
• Autophosphorylation on Ser1333 correlates with activation (Hartmann et al., 2015).  
• Negative regulators: Rnd3 (RhoE), Gem and Rad1 bind the N-terminus and suppress activity; PDK1 can antagonise the Rnd3 effect (Julian & Olson, 2014; Hartmann et al., 2015; Liao et al., 2007).  
• Lipid activation: arachidonic acid can stimulate kinase activity (Surma et al., 2011; Zhou et al., 2011).

Function  
ROCK1 is a central effector of RhoA signalling, orchestrating actin-myosin cytoskeletal dynamics to regulate contraction, adhesion, migration, proliferation and cell shape (Feng et al., 2016; Julian & Olson, 2014).  
Expression: Ubiquitous, enriched in heart, lung, liver, kidney, pancreas and skeletal muscle; relatively low in brain (Feng et al., 2016; Hartmann et al., 2015).  
Sub-cellular localisation: cytoplasm, plasma membrane and centrosomes (Hartmann et al., 2015; Julian & Olson, 2014).  
Major substrates: MYPT1, LIMK1/2, adducin, neurofilament proteins, CRMP2 and ERM family members (Feng et al., 2016). Phosphorylation of MYPT1 inhibits myosin phosphatase, raising myosin light-chain phosphorylation and contractility (Feng et al., 2016; Yu et al., 2020).  
Signalling pathways: contributes to MRTF/SRF and TGF-β transcriptional programmes, notably in fibrotic responses (Hartmann et al., 2015; Yu et al., 2020).  
Genetic studies: ROCK1-deficient mice display eyelid and ventral body-wall closure defects, underscoring isoform-specific developmental roles (Feng et al., 2016; Julian & Olson, 2014).

Inhibitors  
Clinically used ATP-competitive inhibitors include Fasudil (cerebral vasospasm) and Ripasudil (glaucoma). Widely used research probes are Y-27632, H-1152 and Netarsudil/AR-13324 (IC₅₀ ≈ 1 nM for both isoforms). Additional inhibitors: RKI-1447, SR3677, GSK269962A and Belumosudil (Feng et al., 2016; Surma et al., 2011; Guan et al., 2013; Zheng et al., 2025).

Other Comments  
ROCK1 dysregulation links to cardiovascular disorders (hypertension, atherosclerosis, heart failure, fibrosis), asthma, cancer, erectile dysfunction, glaucoma, insulin resistance and neurodegeneration (Feng et al., 2016; Hartmann et al., 2015; Zhou et al., 2011). Enhanced caspase-3-mediated cleavage in failing hearts contributes to apoptosis-associated membrane blebbing (Hartmann et al., 2015). Tissue-specific manipulation reveals therapeutic potential: ROCK1 haplo-insufficiency reduces cardiac fibrosis, whereas adipose-specific deletion improves metabolic homeostasis (Julian & Olson, 2014).

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