## Phylogeny

Bone morphogenetic protein receptor type-1A (BMPR1A, ALK3) is a serine/threonine kinase receptor of the Tyrosine Kinase-Like group within the transforming growth factor-β receptor (TGFβR) family of the human kinome (Manning et al., 2002; Gipson et al., 2020; Sanchez-Duffhues et al., 2020). As a type I BMP receptor, it forms part of the activin receptor-like kinase (ALK) subfamily together with ALK1, ALK2 and ALK6 (Gomez-Puerto et al., 2019; Lin et al., 2016). Orthologs occur in mouse, fly, worm, chordates and other metazoans, underscoring its conserved developmental role (Manning et al., 2002; Gipson et al., 2020).

## Reaction Catalyzed

ATP + [protein]-L-serine ⇌ ADP + [protein]-L-serine-phosphate  
ATP + [protein]-L-threonine ⇌ ADP + [protein]-L-threonine-phosphate (Gomez-Puerto et al., 2019)

## Cofactor Requirements

Mg²⁺ is required for catalytic activity (Gipson et al., 2020; Gomez-Puerto et al., 2019; Sanchez-Duffhues et al., 2020).

## Substrate Specificity

High-throughput peptide-array profiling assigns BMPR1A/ALK3 to motif cluster 3 of serine/threonine kinases, characterised by preference for acidic (Asp/Glu) or pre-phosphorylated residues flanking the Ser/Thr phospho-acceptor (Johnson et al., 2023). A precise consensus motif was not explicitly defined (Johnson et al., 2023).

## Structure

BMPR1A is a single-pass transmembrane receptor comprising:  
• N-terminal extracellular cysteine-rich ligand-binding domain  
• Single transmembrane helix  
• C-terminal intracellular kinase domain with a canonical bilobal fold (Gipson et al., 2020; Sanchez-Duffhues et al., 2020)

Key regulatory elements include a ~30-residue juxtamembrane glycine/serine-rich (GS) domain, the L45 loop (SMAD specificity), the αC helix, activation loop and the NANDOR box (Gipson et al., 2020; Sanchez-Duffhues et al., 2020). A crystal structure of the kinase domain is available (PDB 3MDY; Gipson et al., 2020).

## Regulation

• Ligand binding (e.g., BMP2, BMP4) promotes assembly of a heterotetrameric complex with a type II receptor whose constitutive activity phosphorylates GS-domain Ser/Thr residues, activating BMPR1A (Ehata & Miyazono, 2022; Sanchez-Duffhues et al., 2020).  
• In the absence of ligand, FKBP12 binds a Leu-Pro motif in the GS domain, shielding the phosphorylation sites; phosphorylation triggers FKBP12 dissociation (Gomez-Puerto et al., 2019; Gipson et al., 2020).  
• Negative regulation involves SMURF1/2-mediated ubiquitination and inhibitory SMAD6/7, which recruit SMURFs or block R-SMAD phosphorylation (Ehata & Miyazono, 2022; Lin et al., 2016; Ruan et al., 2023).

## Function

Widely expressed, including in articular cartilage and subchondral bone (Ruan et al., 2023). Activated by BMP2/4/6/7/9/10; ligand availability is modulated by extracellular antagonists such as noggin, chordin and gremlin-1 (Ehata & Miyazono, 2022). Activated BMPR1A phosphorylates SMAD1/5/8, which partner with SMAD4 to regulate transcription of targets such as ID1 (Gomez-Puerto et al., 2019; Ehata & Miyazono, 2022). BMPR1A also triggers non-SMAD pathways (p38, JNK MAPKs; Rho and Rac GTPases) (Gomez-Puerto et al., 2019). Signalling controls embryonic development, tissue homeostasis, osteogenesis, chondrogenesis, and impacts cell proliferation, differentiation, motility and angiogenesis (Ehata & Miyazono, 2022; Lin et al., 2016).

## Inhibitors

ATP-competitive small-molecule inhibitors include:  
• Dorsomorphin, IC₅₀ ≈ 222 nM  
• LDN-193189, IC₅₀ ≈ 14.3 nM  
• LDN-212854, K02288, Saracatinib  
• LJ000328 (ALK3-biased), IC₅₀ ≈ 5.1 nM  
Experimental ALK3-Fc fusion proteins are also used to modulate signalling (Ehata & Miyazono, 2022; Sanchez-Duffhues et al., 2020; Gomez-Puerto et al., 2019).

## Other Comments

Loss-of-function germline BMPR1A mutations cause Juvenile Polyposis Syndrome (JPS) (~23 % of patients). Variants include nonsense, point mutations and large deletions; R443C is most frequent. Dominant-negative R443H associates with JPS and atrioventricular septal defects, while mutations such as R478H, D429V, P481S and R406L are linked to atrial septal defects (Gomez-Puerto et al., 2019; Sanchez-Duffhues et al., 2020).

## References

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