## Phylogeny

Bone morphogenetic protein receptor type-1A (BMPR1A), also known as ALK3, is a serine/threonine kinase receptor classified within the Tyrosine Kinase-Like (TKL) group and the transforming growth factor-beta receptor (TGFbR) family of the human kinome (manning2002theproteinkinase pages 3-3, gipson2020structuralperspectiveof pages 12-14, sanchezduffhues2020bonemorphogeneticprotein pages 1-2). As a type I BMP receptor, it belongs to the activin receptor-like kinase (ALK) family, which also includes ALK1, ALK2, and ALK6 (gomez‐puerto2019bonemorphogeneticprotein pages 1-6, lin2016thebiologicalfunction pages 1-2). The TGFbR family and its components are evolutionarily conserved, with orthologs of BMPR1A identified in model organisms such as mouse, fly, and worm, as well as across chordates and other metazoans, indicating a conserved role in development and tissue homeostasis (manning2002theproteinkinase pages 2-3, gipson2020structuralperspectiveof pages 12-14).

## Reaction Catalyzed

The enzyme catalyzes the transfer of a phosphate group from ATP to a protein substrate (gomez‐puerto2019bonemorphogeneticprotein pages 1-6). The reaction is: ATP + [a protein]-L-serine = ADP + [a protein]-L-serine phosphate. ATP + [a protein]-L-threonine = ADP + [a protein]-L-threonine phosphate.

## Cofactor Requirements

Catalytic activity requires the divalent cation Mg²⁺ as a cofactor to facilitate phosphoryl transfer (gipson2020structuralperspectiveof pages 12-14, gomez‐puerto2019bonemorphogeneticprotein pages 1-6, sanchezduffhues2020bonemorphogeneticprotein pages 3-4).

## Substrate Specificity

Based on a high-throughput peptide array screen, BMPR1A/ALK3 is classified into motif cluster 3 of serine/threonine kinases (johnson2023anatlasof pages 2-3). This cluster, which also includes kinases from the YANK, GRK, and CK families, is characterized by a general preference for acidic residues, such as aspartic acid (Asp) or glutamic acid (Glu), or phosphorylated residues surrounding the serine/threonine phosphoacceptor site (johnson2023anatlasof pages 2-3). While detailed position-specific scoring matrices for BMPR1A were generated in the analysis, the specific consensus phosphorylation motif is not explicitly provided in the context (johnson2023anatlasof pages 2-3, johnson2023anatlasof pages 5-6).

## Structure

BMPR1A is a transmembrane receptor composed of an N-terminal extracellular cysteine-rich domain for ligand binding, a single transmembrane helix, and a C-terminal intracellular serine/threonine kinase domain (sanchezduffhues2020bonemorphogeneticprotein pages 2-3). The kinase domain adopts a canonical protein kinase fold with a five-stranded β-sheet N-lobe and an α-helical C-lobe connected by a hinge region (gipson2020structuralperspectiveof pages 11-12). A key regulatory feature is the juxtamembrane glycine-serine-rich (GS) domain, a ~30 amino acid segment located between the plasma membrane and the N-lobe that is essential for receptor activation (gipson2020structuralperspectiveof pages 11-12, sanchezduffhues2020bonemorphogeneticprotein pages 2-3). Other critical regions within the kinase domain include the L45 loop, which confers SMAD specificity, the αC helix, the activation loop, and a region termed the NANDOR BOX, which is necessary for receptor activation (gipson2020structuralperspectiveof pages 12-14, sanchezduffhues2020bonemorphogeneticprotein pages 2-3). Structural studies of the ALK3 kinase domain are available (PDB: 3MDY) (gipson2020structuralperspectiveof pages 27-31).

## Regulation

BMPR1A activation requires ligand-induced formation of a heterotetrameric complex with a type II receptor (e.g., BMPR-II, ActR-II, ActR-IIB) (ehata2022bonemorphogeneticprotein pages 1-2). The constitutively active type II receptor kinase then phosphorylates BMPR1A at specific serine and threonine residues within its GS domain, which activates BMPR1A’s kinase function (ehata2022bonemorphogeneticprotein pages 1-2, sanchezduffhues2020bonemorphogeneticprotein pages 2-3). This phosphorylation induces a conformational change involving the repositioning of the GS domain and the αC helix, which shifts the kinase into an open, active state (gipson2020structuralperspectiveof pages 11-12).

In the absence of ligand, the immunophilin FKBP12 binds to a leucine-proline motif within the GS domain, shielding phosphorylation sites and preventing ligand-independent activation (gomez‐puerto2019bonemorphogeneticprotein pages 1-6, sanchezduffhues2020bonemorphogeneticprotein pages 2-3). Upon receptor phosphorylation, FKBP12 dissociates (gipson2020structuralperspectiveof pages 11-12, gomez‐puerto2019bonemorphogeneticprotein pages 1-6).

Signaling is negatively regulated by the E3 ubiquitin ligases SMURF1 and SMURF2, which target BMPR1A and SMADs for ubiquitination and proteasomal degradation (ehata2022bonemorphogeneticprotein pages 1-2, lin2016thebiologicalfunction pages 5-6). Inhibitory SMADs (I-SMADs), such as SMAD6 and SMAD7, also attenuate the pathway by recruiting SMURFs or by interfering with R-SMAD phosphorylation (ruan2023multiplerolesof pages 1-2, sanchezduffhues2020bonemorphogeneticprotein pages 3-4).

## Function

BMPR1A is widely expressed in tissues including articular cartilage and subchondral bone (ruan2023multiplerolesof pages 1-2). Upstream ligands that activate BMPR1A include BMP2, BMP4, BMP6, BMP7, BMP9, and BMP10 (gomez‐puerto2019bonemorphogeneticprotein pages 1-6). Ligand availability is modulated by extracellular antagonists like noggin, chordin, and gremlin1 (ehata2022bonemorphogeneticprotein pages 1-2). Upon activation, BMPR1A phosphorylates the receptor-regulated SMADs (R-SMADs) 1, 5, and 8 (gomez‐puerto2019bonemorphogeneticprotein pages 1-6, lin2016thebiologicalfunction pages 1-2). Phosphorylated R-SMADs form a complex with the common mediator SMAD4, translocate to the nucleus, and regulate the transcription of target genes such as ID1 (ehata2022bonemorphogeneticprotein pages 1-2). BMPR1A can also activate non-SMAD pathways, including MAP kinases (p38, JNK) and small GTPases (Rho, Rac) (gomez‐puerto2019bonemorphogeneticprotein pages 27-30). This signaling is critical for embryonic development, tissue homeostasis, osteogenesis, and chondrogenesis, and it influences cell proliferation, differentiation, motility, and angiogenesis (ehata2022bonemorphogeneticprotein pages 1-2, lin2016thebiologicalfunction pages 1-2).

## Inhibitors

Experimental small molecule ATP-competitive inhibitors of BMPR1A/ALK3 have been developed. Dorsomorphin is a prototype inhibitor with an IC50 of 222 nM against ALK3 in vitro (ehata2022bonemorphogeneticprotein pages 7-9, sanchezduffhues2020bonemorphogeneticprotein pages 6-7). Its derivative, LDN-193189, shows improved potency with an IC50 of 14.3 nM for ALK3 (sanchezduffhues2020bonemorphogeneticprotein pages 6-7). Other inhibitors include LDN-212854, K02288, and Saracatinib (ehata2022bonemorphogeneticprotein pages 7-9, sanchezduffhues2020bonemorphogeneticprotein pages 6-7, sanchezduffhues2020bonemorphogeneticprotein pages 8-9). LJ000328 is described as an ALK3-biased inhibitor with an IC50 of 5.1 nM (sanchezduffhues2020bonemorphogeneticprotein pages 8-9). In addition to small molecules, ALK3-Fc fusion proteins are used as experimental therapeutics to modulate signaling (gomez‐puerto2019bonemorphogeneticprotein pages 27-30).

## Other Comments

Germline mutations in BMPR1A are a cause of Juvenile Polyposis Syndrome (JPS), an autosomal dominant disorder characterized by gastrointestinal polyps and an increased risk of cancer (gomez‐puerto2019bonemorphogeneticprotein pages 12-16, sanchezduffhues2020bonemorphogeneticprotein pages 5-6). JPS-associated mutations are typically loss-of-function and include nonsense mutations that result in truncated receptors, point mutations, and large gene deletions, which are found in approximately 23% of JPS patients (gomez‐puerto2019bonemorphogeneticprotein pages 12-16). The missense mutation R443C is the most frequent variant identified in JPS, while a dominant negative R443H mutation is associated with JPS and congenital heart defects, such as atrioventricular septal defects (AVSD) (sanchezduffhues2020bonemorphogeneticprotein pages 4-5). Other mutations that impair receptor signaling, including R478H, D429V, P481S, and R406L, are associated with atrial septal defects (ASD) (sanchezduffhues2020bonemorphogeneticprotein pages 4-5).

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