1. Phylogeny  
   ACVRL1, also known as ALK1, is a type I serine/threonine kinase receptor that belongs to the TGF‑β receptor family and, more specifically, to the activin receptor‐like kinases (ALKs). This receptor is conserved among vertebrates and is present in all mammalian species, where orthologs exhibit high amino acid sequence conservation in its extracellular ligand‐binding region and intracellular kinase domain. ALK1 shares a common evolutionary origin with other type I TGF‑β receptors such as ALK2 (ACVR1) and ALK5, and its structural motifs—especially the glycine‑serine (GS) motif and the catalytic kinase domain—can be traced back to an ancestral kinase present in early eukaryotes. Its close phylogenetic relationship with other members of the activin receptor‐like kinase subfamily underpins its conserved function in vascular biology, a feature that has been maintained through evolution (garridomartin2010characterizationofthe pages 1-2, scotti2011bioinformaticanalysisof pages 1-2, ivaldo2021studyofvecadherin pages 17-23).
2. Reaction Catalyzed  
   The catalytic reaction mediated by ALK1 is a phosphorylation event in which the receptor transfers a phosphate group from ATP to serine/threonine residues on its substrate proteins. In biochemical terms, the reaction can be summarized as:  
     ATP + [protein]–(L‑serine or L‑threonine) → ADP + [protein]–(L‑serine/threonine)-phosphate + H⁺.  
   This reaction is a mechanistic hallmark of receptor serine/threonine kinases, and in the case of ALK1, the primary substrates are receptor‑regulated SMAD proteins (R‑Smads), particularly those in the SMAD1/5/8 subgroup, which are phosphorylated upon ligand binding and receptor activation (kim2012bmp9inducesephrinb2 pages 10-11, garridomartin2010characterizationofthe pages 1-2).
3. Cofactor Requirements  
   The kinase activity of ALK1 is dependent on divalent metal ion cofactors. In particular, Mg²⁺ ions are required to coordinate ATP binding in the active site, facilitating the transfer of the phosphate group to the substrate. This cofactor requirement is a typical characteristic of serine/threonine kinases and is essential for the catalytic efficiency of ALK1 (garridomartin2010characterizationofthe pages 1-2).
4. Substrate Specificity  
   ALK1 exhibits substrate specificity primarily toward receptor‑regulated SMAD proteins, especially SMAD1, SMAD5, and SMAD8, which become phosphorylated at their C‑terminal SSXS motifs following receptor activation. The enzyme recognizes conserved sequence motifs on its substrates, and the phosphorylation of these SMAD proteins is a critical step in propagating the BMP9/BMP10 signal downstream to effect changes in gene transcription. In this signaling pathway, the ALK1‐mediated phosphorylation of SMAD1/5/8 contrasts with the activity of other TGF‑β receptors, such as ALK5, which preferentially activate SMAD2/3. The specificity of ALK1 for its substrates has been elucidated by studies that emphasize its role in endothelial cells where it governs vascular homeostasis (kim2012bmp9inducesephrinb2 pages 10-11, scotti2011bioinformaticanalysisof pages 1-2).
5. Structure  
   ALK1 is a single-pass transmembrane receptor characterized by a modular architecture. It comprises an extracellular ligand-binding domain, a single transmembrane helix, and a cytoplasmic kinase domain. The extracellular portion is responsible for binding BMP family ligands – chiefly BMP9 and BMP10 – and is predicted to form a disulfide-rich, domain‐organized structure with features that resemble a three-finger toxin fold, although detailed crystallographic data have relied on homology modeling approaches (scotti2011bioinformaticanalysisof pages 1-2, garridomartin2010characterizationofthe pages 2-4).  
   The intracellular region contains a GS domain followed by the serine/threonine kinase domain. The GS domain, rich in glycine and serine residues, serves as a regulatory module; it becomes phosphorylated by type II receptors following ligand binding to relieve autoinhibition. The kinase domain itself adopts the canonical bilobal structure found in other serine/threonine kinases, with an N-terminal lobe mainly composed of β-sheets and a larger C-terminal lobe rich in α-helices. Critical catalytic motifs within the kinase domain include the ATP-binding pocket, the activation loop (T-loop), and conserved motifs such as the AxK, DLG, and HRD sequences that are essential for substrate binding and catalytic activity. In addition, features such as the L45 loop play a role in the specificity and interaction with downstream SMAD proteins. These structural features collectively ensure that ALK1 effectively transduces extracellular signals into intracellular phosphorylation events (jimmidi2024discoveryofhighly pages 1-2, iwasa2023computationalandexperimental pages 17-18, kroon2015activinreceptorlikekinase pages 4-5).
6. Regulation  
   The activity of ALK1 is tightly regulated at multiple levels. At the membrane, ALK1 requires binding to its ligands BMP9 or BMP10 in order to form a heterotetrameric receptor complex with two type II receptors. The type II receptors phosphorylate the GS domain of ALK1, which then undergoes autophosphorylation and conformational changes that facilitate the recruitment and phosphorylation of downstream SMAD proteins. Post-translational modifications, particularly phosphorylation, are central to this activation process. Moreover, the transcription of the ACVRL1 gene is subject to regulation by specific transcription factors such as Sp1, which binds to the GC-rich promoter region; the presence of multiple Sp1 consensus sites and the methylation status of nearby CpG islands have been shown to modulate gene expression in endothelial cells (garridomartin2010characterizationofthe pages 15-17, garridomartin2010characterizationofthe pages 21-22).  
   In addition to ligand-induced activation, the regulatory landscape of ALK1 is influenced by coreceptors such as endoglin, which modulate the efficiency of ligand binding and subsequent signal transduction. The balance between ALK1 and ALK5 signaling pathways (the latter primarily activating SMAD2/3) further refines the cellular response during angiogenesis and vascular remodeling. Experimental studies have demonstrated that modulation of ALK1 expression and activity can alter endothelial cell behavior, with compounds that inhibit ALK1 (such as ALK1-Fc fusion proteins or specific monoclonal antibodies) shown to reduce BMP9-induced signaling and endothelial sprouting (kim2012bmp9inducesephrinb2 pages 10-11, iwasa2023computationalandexperimental pages 17-18).
7. Function  
   ALK1 plays a central role in vascular biology and is predominantly expressed in endothelial cells. Its primary function is to mediate the signaling of TGF‑β family ligands, particularly BMP9 and BMP10, which are critical for normal blood vessel development and homeostasis. Upon ligand binding and activation, ALK1 phosphorylates receptor-regulated SMAD proteins (SMAD1/5/8), which then form complexes with SMAD4 and translocate to the nucleus to regulate gene expression. This cascade controls key aspects of endothelial cell behavior, including proliferation, migration, and differentiation, thereby ensuring the proper formation and stabilization of blood vessels.  
   Functionally, ALK1 signaling establishes a balance within the TGF‑β pathway by counteracting the effects of ALK5 signaling; ALK1-mediated activation generally promotes angiogenic quiescence and vascular stabilization, whereas ALK5 signaling tends to inhibit endothelial proliferation and migration. Mutations in the ACVRL1 gene are directly linked to hereditary hemorrhagic telangiectasia type 2 (HHT2), a vascular disorder characterized by arteriovenous malformations and telangiectases, underscoring the vital role of ALK1 in maintaining vascular integrity (garridomartin2010characterizationofthe pages 1-2, kim2012bmp9inducesephrinb2 pages 1-2, ivaldo2021studyofvecadherin pages 17-23).  
   In addition, ALK1 signaling interfaces with other pathways; for instance, in the context of chondrogenic differentiation of mesenchymal stem cells, both ALK1 and ALK5 are required for TGF‑β-induced cartilage matrix formation, illustrating the receptor’s broader involvement in mesenchymal cell function (kroon2015activinreceptorlikekinase pages 17-18). Furthermore, studies in diabetic endothelial cells have revealed that modulation of ALK1, along with other TGF‑β receptors, contributes to the regulation of endothelial proliferation, network formation, and resistance to apoptosis, indicating its role in vascular remodeling under pathophysiological conditions (mestareehi2023quantitativeproteomicsreveals pages 6-8).
8. Other Comments  
   Multiple experimental approaches have underlined the clinical relevance of ALK1. Notably, mutations in ACVRL1 are causative for hereditary hemorrhagic telangiectasia type 2 (HHT2), a genetic vascular disorder marked by the development of telangiectases and arteriovenous malformations. Inhibitory strategies, including the use of ALK1-Fc fusion proteins and anti-ALK1 monoclonal antibodies, have been demonstrated to attenuate BMP9-induced ALK1 signaling and suppress endothelial cell sprouting, illustrating potential therapeutic avenues for diseases associated with dysregulated vascular remodeling (wooderchakdonahue2013bmp9mutationscause pages 8-8, sanvitale2014investigationofkinase pages 193-194).  
   Additionally, high-throughput approaches such as DNA-encoded chemistry have led to the discovery of highly potent kinase inhibitors that are selective for ALK1 (and related receptors such as ALK2), providing novel tools for dissecting receptor function and for potential clinical application in conditions involving aberrant BMP signaling (jimmidi2024discoveryofhighly pages 1-2, jimmidi2024discoveryofhighly pages 8-9).  
   Beyond its established role in vascular development, ALK1 is also implicated in regulating endothelial responses under stress conditions, such as in diabetic endothelial dysfunction where modulation of ALK1 expression by compounds like the combined trans-resveratrol and hesperetin formulation (tRES+HESP) has been shown to restore aspects of normal angiogenic function (mestareehi2023quantitativeproteomicsreveals pages 6-8).  
   Furthermore, computational and experimental analyses of ACVRL1 missense variants have provided insights into the functional impact of disease-associated mutations, thereby improving our understanding of genotype–phenotype correlations in HHT2 (iwasa2023computationalandexperimental pages 15-17, scotti2011bioinformaticanalysisof pages 13-13).  
   No additional distinct cofactors beyond Mg²⁺ are reported, and its regulation primarily occurs via ligand engagement, receptor complex formation, and transcriptional control by factors such as Sp1, as evidenced by extensive promoter analysis studies (garridomartin2010characterizationofthe pages 15-17, garridomartin2010characterizationofthe pages 6-10).  
   Disease associations beyond HHT2 include potential roles in pulmonary arterial hypertension and vascular anomalies when ALK1 signaling is perturbed, and interactions with co-receptors like endoglin further underscore its importance in endothelial biology (lafyatis2014transforminggrowthfactor pages 5-6, thalgott2019generalintroductionand pages 1-6).

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