1. Phylogeny  
   Activin receptor type‑1C (ACVR1C), also known as ALK7, is a member of the TGF‑β superfamily of type I serine/threonine kinases that is conserved across vertebrate species. It clusters within a subgroup of activin receptors that includes ALK4 (ACVR1B) and TGFBR1; these receptors preferentially transduce signals via phosphorylation of SMAD2 and SMAD3. Phylogenetic analyses based on sequence homology reveal that ALK7 shares considerable evolutionary conservation with other activin receptor‐like kinases, and its grouping with ALK4 and ALK5 reflects its specialization for activin and nodal ligands (hinck2011structuresoftgf&#946; pages 2-4, fortin2014regulationofpituitary pages 61-65, hilden2002expressionandregulation pages 17-20).
2. Reaction Catalyzed  
   ACVR1C/ALK7 functions as a serine/threonine protein kinase and catalyzes the transfer of a phosphate group from ATP to specific serine or threonine residues on substrate proteins. In this catalytic reaction, ATP is used to donate a phosphate to the hydroxyl group present in the target residue of the substrate (typically SMAD2 and SMAD3), yielding ADP, a phosphorylated substrate, and a proton. This reaction can be represented as:  
     ATP + [protein]‑(L‑serine/threonine) → ADP + [protein]‑(L‑serine/threonine‑phosphate) + H⁺  
   This reaction mechanism is fundamental for propagating downstream signaling events in the TGF‑β pathway (valderrama2007mechanismsofaction pages 35-40, hilden2002expressionandregulation pages 12-15).
3. Cofactor Requirements  
   The catalytic activity of ACVR1C/ALK7 requires the presence of divalent metal ions that facilitate ATP binding and phosphoryl transfer. In particular, Mg²⁺ is essential as a cofactor for its serine/threonine kinase activity, supporting the proper coordination of ATP in the enzyme’s active site (stepurko2023molecularinsightsinto pages 26-31).
4. Substrate Specificity  
   ACVR1C/ALK7 displays substrate specificity for receptor‑regulated SMAD proteins, predominantly phosphorylating SMAD2 and SMAD3. Upon receptor activation, the kinase domain selectively targets specific serine residues located in the C-terminal SSXS motif of these SMAD proteins. Although the full consensus substrate motif has not been delineated in complete detail within the available literature, the prevailing evidence indicates that ALK7 functions in a manner similar to ALK4 and TGFBR1 by promoting SMAD2/3 activation (fortin2014regulationofpituitary pages 61-65, spender2019preclinicalevaluationof pages 5-7).
5. Structure  
   ACVR1C/ALK7 is organized as a modular protein with distinct domains that mediate ligand binding, signaling transduction, and regulation. The extracellular portion of the receptor is a compact ligand-binding domain characterized by a conserved arrangement of cysteine residues, which likely adopts a three‐finger toxin fold typical of type I TGF‑β receptors. This domain is followed by a single transmembrane helix that anchors the receptor in the plasma membrane.  
   Immediately following the transmembrane segment is the intracellular portion, which is comprised of a glycine‑serine (GS) rich domain and a catalytic serine/threonine kinase domain. The GS domain, which precedes the kinase core, contains a conserved consensus sequence (TTSGSGSG) that is critical for receptor activation upon phosphorylation by associated type II receptors. The kinase domain itself is bifurcated into a smaller N‑terminal lobe and a larger C‑terminal lobe. Within this domain, several key features have been identified, including an activation loop that undergoes conformational changes upon phosphorylation, a hydrophobic spine that contributes to the stabilization of the active conformation, and a C‑helix that plays a crucial role in ATP binding and catalytic regulation. Furthermore, alternative splicing of the ACVR1C gene results in isoforms with truncated extracellular regions that may function as soluble antagonists or modulators of nodal signaling (hilden2002expressionandregulation pages 17-20, stepurko2023molecularinsightsinto pages 55-60, hinck2011structuresoftgf&#946; pages 2-4, stepurko2023molecularinsightsinto pages 60-63).
6. Regulation  
   Regulation of ACVR1C/ALK7 occurs primarily at the level of receptor complex assembly and post‑translational modifications. Ligand binding (e.g., activin AB, activin B, and NODAL) promotes the formation of heterotetrameric complexes comprising two type II receptors and two type I receptors. Within these complexes, constitutively active type II receptors phosphorylate the GS domain of ALK7, which in turn enables its autophosphorylation and subsequent phosphorylation of downstream SMAD transcriptional regulators. An important regulatory mechanism involves the binding of the immunophilin FKBP12 to a leucine‑proline motif adjacent to the GS domain; this interaction prevents spontaneous receptor activation by occluding the phosphorylation sites in the absence of ligand stimulation. Additionally, receptor activity is modulated by endocytic mechanisms and by interactions with inhibitory SMADs (e.g., Smad7), which can recruit ubiquitin ligases that target the receptor for proteasomal degradation, thereby attenuating signaling (hilden2002expressionandregulation pages 17-20, stepurko2023molecularinsightsinto pages 60-63).
7. Function  
   ACVR1C/ALK7 plays a critical role in mediating signals from specific ligands—activin AB, activin B, and NODAL—which regulate diverse cellular processes including cell differentiation, growth arrest, and apoptosis. Upon activation, ACVR1C phosphorylates receptor‑regulated SMADs (SMAD2 and SMAD3), which then complex with SMAD4 and translocate to the nucleus where they control the transcription of genes implicated in cell fate decisions. Functionally, ALK7 has been shown to be significant in reproductive physiology; for example, studies in gonadotropes have demonstrated that deletion of ACVR1C leads to mild reproductive dysfunction and altered follicle‑stimulating hormone (FSH) levels. Additionally, ACVR1C is implicated in processes of embryonic development and may have roles in metabolic regulation and tumor growth control through its influence on cell cycle arrest and apoptosis (fortin2014regulationofpituitary pages 61-65, hilden2002expressionandregulation pages 17-20, stepurko2023molecularinsightsinto pages 31-33).
8. Other Comments  
   Experimental efforts to modulate ACVR1C/ALK7 activity have identified small‑molecule inhibitors such as AZ12601011 and AZ12799734, which attenuate receptor signaling by reducing SMAD2 phosphorylation. These inhibitors have been evaluated in cellular models to assess their efficacy in blocking ALK7‐mediated pathways, suggesting that targeted inhibition of ACVR1C could have therapeutic potential. Dysregulation of ACVR1C signaling has been linked, through indirect evidence, to developmental disorders and altered reproductive and cellular growth processes, underscoring the receptor’s significance in both normal physiology and disease states (spender2019preclinicalevaluationof pages 16-18, spender2019preclinicalevaluationof pages 18-19).
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