1. Phylogeny  
   Activin receptor type‑2B (ACVR2B), also known as Activin receptor type IIB, belongs to the transforming growth factor‑β (TGF‑β) superfamily of receptor serine/threonine kinases and is evolutionarily conserved across vertebrates (garciaaranda2019targetingreceptorkinases pages 4-5). It falls within the tyrosine kinase–like (TKL) family of serine/threonine kinases; this family is characterized by the presence of an extracellular ligand‑binding domain and a cytoplasmic catalytic domain that, although structurally similar to classical tyrosine kinases, lacks many of the tyrosine‐specific motifs (garciaaranda2019targetingreceptorkinases pages 4-5). Orthologs of ACVR2B are found in diverse mammalian species, underscoring its critical role in activin signaling pathways that regulate cellular proliferation, differentiation, and migration (garciaaranda2019targetingreceptorkinases pages 4-5). The receptor’s conservation throughout evolution implies an essential function in mediating extracellular activin signals to intracellular responses and situates ACVR2B within an ancient kinome module that has been maintained since the early divergence of eukaryotes (garciaaranda2019targetingreceptorkinases pages 4-5).
2. Reaction Catalyzed  
   ACVR2B functions as an ATP‑dependent serine/threonine kinase by catalyzing the transfer of the γ‑phosphate from ATP to specific serine or threonine residues on its substrate protein, which in the context of activin signaling is typically a type I receptor (garciaaranda2019targetingreceptorkinases pages 4-5). The enzymatic reaction can be summarized by the chemical equation:  
     ATP + [protein]‑OH → ADP + [protein]‑O‑phosphate + H⁺  
   This phosphorylation event is critical as it serves as an “on/off” regulatory switch that initiates downstream signal transduction through the activation of SMAD proteins (garciaaranda2019targetingreceptorkinases pages 4-5).
3. Cofactor Requirements  
   The kinase activity of ACVR2B requires ATP as a phosphate donor, and like many protein kinases, its catalytic mechanism is dependent on the presence of Mg²⁺ ions that coordinate with ATP to facilitate the phosphoryl transfer reaction (garciaaranda2019targetingreceptorkinases pages 4-5). The presence of Mg²⁺ is essential for stabilizing the negative charges on the phosphate groups of ATP, thereby ensuring efficient catalysis by the enzyme (garciaaranda2019targetingreceptorkinases pages 4-5).
4. Substrate Specificity  
   ACVR2B exhibits substrate specificity that is principally focused on its role within the activin receptor complex; upon activin ligand binding, ACVR2B interacts with and phosphorylates associated type I activin receptors (garciaaranda2019targetingreceptorkinases pages 10-11). Although no precise consensus phosphorylation motif has been delineated for ACVR2B itself, its kinase domain is evolutionarily optimized to recognize and transfer phosphate groups specifically to serine/threonine residues present in the intracellular domains of type I receptors, thereby ensuring faithful signal relay in the TGF‑β superfamily pathway (garciaaranda2019targetingreceptorkinases pages 10-11, garciaaranda2019targetingreceptorkinases pages 4-5).
5. Structure  
   ACVR2B is a multi‑domain transmembrane protein that comprises three distinct regions: an N‑terminal extracellular ligand‑binding domain, a single transmembrane segment, and a C‑terminal intracellular serine/threonine kinase domain (garciaaranda2019targetingreceptorkinases pages 4-5). The extracellular domain is responsible for binding activin ligands such as activin‑A, activin‑B, and related TGF‑β superfamily members; this interaction is the first step in the formation of a heterotetrameric receptor complex that includes type I receptor partners (garciaaranda2019targetingreceptorkinases pages 4-5). The single transmembrane helix serves primarily as an anchoring module, ensuring proper receptor localization within the cell membrane and facilitating the spatial organization required for subsequent receptor complex formation (garciaaranda2019targetingreceptorkinases pages 4-5). The intracellular kinase domain of ACVR2B contains a conserved protein kinase catalytic core that is structurally organized into an N‑terminal lobe (N‑lobe) and a larger C‑terminal lobe; the N‑lobe harbors the ATP‑binding pocket, while the C‑lobe includes the activation loop and key catalytic residues necessary for phosphoryl transfer (garciaaranda2019targetingreceptorkinases pages 4-5). Structural features such as the glycine‑rich loop within the N‑lobe and the arrangement of the catalytic motifs form a hydrophobic spine that is critical for achieving and maintaining the active conformation of the kinase (garciaaranda2019targetingreceptorkinases pages 4-5).
6. Regulation  
   The activity of ACVR2B is regulated through several mechanisms that ensure precise control over activin signal transduction. Ligand binding to the extracellular domain is the first regulatory step; upon activin engagement, ACVR2B forms a heterotetrameric complex with type I receptors, which is indispensable for initiating the phosphorylation cascade that leads to the activation of intracellular SMAD proteins (garciaaranda2019targetingreceptorkinases pages 10-11). In addition to extracellular regulation, the intracellular kinase domain of ACVR2B undergoes autophosphorylation and potential trans‑phosphorylation events that modulate its catalytic activity (garciaaranda2019targetingreceptorkinases pages 10-11). Endogenous inhibitory proteins such as follistatin can sequester activin ligands in the extracellular space, thereby reducing the availability of ligand for receptor binding and attenuating subsequent signal transduction (garciaaranda2019targetingreceptorkinases pages 10-11). Further regulation may occur via receptor internalization and degradation, processes that are often mediated by ubiquitin ligases; these mechanisms serve to fine‑tune the duration and intensity of the signal (garciaaranda2019targetingreceptorkinases pages 10-11). Such tightly orchestrated regulatory events ensure that ACVR2B-mediated signaling is responsive to physiological cues and that aberrant activation, which is implicated in oncogenic transformation and cancer progression, is minimized (garciaaranda2019targetingreceptorkinases pages 10-11).
7. Function  
   ACVR2B is a central mediator in the activin signaling pathway, playing a pivotal role in transducing extracellular signals into intracellular responses that regulate a variety of cellular processes. Upon binding activin ligands, ACVR2B forms a receptor complex with type I receptors, facilitating the phosphorylation and activation of receptor‑regulated SMAD proteins (primarily SMAD2 and SMAD3) (garciaaranda2019targetingreceptorkinases pages 10-11). The phosphorylated SMADs then complex with the common mediator SMAD4 and translocate to the nucleus, where they modulate the transcription of genes involved in cell proliferation, differentiation, adhesion, and migration (garciaaranda2019targetingreceptorkinases pages 10-11). In the context of carcinogenesis, dysregulation of ACVR2B signaling has been linked to oncogenic transformation and cancer progression, as alterations in TGF‑β receptor activity contribute to aberrant cell growth and metastatic behavior (garciaaranda2019targetingreceptorkinases pages 10-11). Although ACVR2B has been associated with a range of physiological processes—including roles in wound healing, extracellular matrix production, and immunosuppression—the peer‑reviewed evidence from colorectal cancer research underscores its critical involvement in modulating cellular responses that are central to tumor biology (garciaaranda2019targetingreceptorkinases pages 10-11). This multifunctional receptor is thus instrumental in integrating extracellular activin signals with intracellular transcriptional programs that determine cell fate and behavior under both normal and pathological conditions (garciaaranda2019targetingreceptorkinases pages 10-11).
8. Other Comments  
   Inhibition of ACVR2B represents a promising therapeutic strategy in oncology given its central role in modulating TGF‑β superfamily signaling; experimental approaches have focused on the development of small molecule inhibitors and monoclonal antibodies that selectively target its kinase domain (garciaaranda2019targetingreceptorkinases pages 10-11). Such inhibitors have demonstrated potential in modulating aberrant receptor activity, thereby impeding cancer cell proliferation and metastasis in preclinical models (garciaaranda2019targetingreceptorkinases pages 10-11). Additionally, alterations in ACVR2B expression or function have been associated with dysregulated cellular processes, including loss of proper cell adhesion, enhanced migratory capacity, and altered differentiation, all of which are hallmarks of malignancy (garciaaranda2019targetingreceptorkinases pages 10-11). The receptor’s involvement in immunosuppressive processes and extracellular matrix remodeling further broadens its potential as a target not only in cancer therapy but also in conditions where tissue repair and fibrosis are dysregulated (garciaaranda2019targetingreceptorkinases pages 10-11). Future research aimed at elucidating the precise structural determinants and regulatory mechanisms of ACVR2B will be crucial for the design of more effective and selective therapeutic agents, with the goal of mitigating its contribution to disease pathogenesis while preserving normal physiological functions (garciaaranda2019targetingreceptorkinases pages 10-11).
9. References  
   [1] Marilina García‑Aranda and Maximino Redondo. Targeting receptor kinases in colorectal cancer. Cancers, 11:433, Mar 2019 (garciaaranda2019targetingreceptorkinases pages 3-4, garciaaranda2019targetingreceptorkinases pages 4-5, garciaaranda2019targetingreceptorkinases pages 10-11).

References

1. (garciaaranda2019targetingreceptorkinases pages 10-11): Marilina García-Aranda and Maximino Redondo. Targeting receptor kinases in colorectal cancer. Cancers, 11:433, Mar 2019. URL: https://doi.org/10.3390/cancers11040433, doi:10.3390/cancers11040433. This article has 78 citations and is from a peer-reviewed journal.
2. (garciaaranda2019targetingreceptorkinases pages 4-5): Marilina García-Aranda and Maximino Redondo. Targeting receptor kinases in colorectal cancer. Cancers, 11:433, Mar 2019. URL: https://doi.org/10.3390/cancers11040433, doi:10.3390/cancers11040433. This article has 78 citations and is from a peer-reviewed journal.
3. (garciaaranda2019targetingreceptorkinases pages 3-4): Marilina García-Aranda and Maximino Redondo. Targeting receptor kinases in colorectal cancer. Cancers, 11:433, Mar 2019. URL: https://doi.org/10.3390/cancers11040433, doi:10.3390/cancers11040433. This article has 78 citations and is from a peer-reviewed journal.