## Phylogeny

TGFBR2 is classified within the Tyrosine Kinase-Like (TKL) group and the STRK (Serine/Threonine Receptor Kinase) family, which includes activin and TGF-beta receptors (manning2002theproteinkinase pages 3-3). The TKL group is specific to metazoans and is required for signaling related to development and intercellular communication (manning2002evolutionofprotein pages 1-2). In hierarchical clustering analysis of the human kinome, TGFBR2 is placed among the TGF-beta receptor kinases within a larger cluster labeled ‘LKB/CAMKK’ (johnson2023anatlasof pages 4-5). Significant sequence and structural homology exists between type II and type I TGFβ receptor kinases, with conservation extending to bacteria (zimmermann2017molecularmodelingand pages 2-3). The STRK family has invertebrate homologs that lack kinase domains (manning2002theproteinkinase pages 3-3).

## Reaction Catalyzed

The kinase catalyzes the transfer of a γ-phosphate group from ATP to the hydroxyl side chain of serine or threonine residues on a protein substrate, yielding a phosphoprotein and ADP (johnson2023anatlasof pages 1-2, horbelt2010quantitativeanalysisof pages 7-8, johnson2023anatlasof pages 4-5).

## Cofactor Requirements

The catalytic activity of TGFBR2 is dependent on divalent metal ion cofactors, such as Mg²⁺ or Mn²⁺, which coordinate ATP binding and facilitate phosphate transfer (johnson2023anatlasof pages 4-5, horbelt2010quantitativeanalysisof pages 7-8, johnson2023anatlasof pages 1-2, zimmermann2017molecularmodelingand pages 2-3).

## Substrate Specificity

The specific consensus substrate motif for TGFBR2 is not detailed in the provided context (johnson2023anatlasof pages 4-5, johnson2023anatlasof pages 1-2). TGFBR2 is classified within a group of kinases characterized by a preference for phosphorylation motifs rich in serine/threonine residues (johnson2023anatlasof pages 4-5).

## Structure

TGFBR2 is a transmembrane protein with three primary domains: an extracellular ligand-binding domain, a single transmembrane domain, and a cytoplasmic/intracellular serine/threonine kinase domain essential for its signaling function (gordon2008roleoftransforming pages 20-21, harradine2006mutationsoftgfbeta pages 4-5, gordon2008roleoftransforming pages 1-2, harradine2006mutationsoftgfbeta pages 1-2, stheneur2008identificationof23 pages 12-12). The kinase domain is composed of N- and C-lobes with an ATP binding pocket situated at their interface (zimmermann2017molecularmodelingand pages 2-3). Key structural features of the kinase domain include an activation loop critical for catalysis and an α-helix F, which is important for positioning catalytic residues and substrate binding (zimmermann2017molecularmodelingand pages 2-3, horbelt2010quantitativeanalysisof pages 7-8).

## Regulation

TGFBR2 activity is modulated by post-translational modifications (PTMs), including phosphorylation, ubiquitination, and sumoylation (gordon2008roleoftransforming pages 20-21, massague2023tgfβsignalingin pages 6-8, santibanez2011tgfβtgfβreceptorsystem pages 4-6). The kinase domain is constitutively active and undergoes autophosphorylation on serine, threonine, and tyrosine residues, which is essential for its catalytic activity (gordon2008roleoftransforming pages 1-2, horbelt2010quantitativeanalysisof pages 7-8). Ubiquitination and sumoylation regulate receptor stability and availability (massague2023tgfβsignalingin pages 6-8, santibanez2011tgfβtgfβreceptorsystem pages 4-6). Smurf ubiquitin ligases can target the receptor for degradation (santibanez2011tgfβtgfβreceptorsystem pages 4-6).

Regulation also occurs via ligand availability, which is controlled by the proteolytic activation of latent TGF-β complexes and sequestration by extracellular matrix proteins (gordon2008roleoftransforming pages 20-21, harradine2006mutationsoftgfbeta pages 1-2, santibanez2011tgfβtgfβreceptorsystem pages 4-6). Receptor activity is influenced by its expression level and interaction with co-receptors such as endoglin, ALK1, and betaglycan, which modulate ligand binding (gordon2008roleoftransforming pages 20-21, massague2023tgfβsignalingin pages 6-8). Signaling is subject to negative feedback by inhibitory SMADs (SMAD6, SMAD7), which bind to the receptor complex and inhibit R-SMAD phosphorylation (massague2023tgfβsignalingin pages 6-8, santibanez2011tgfβtgfβreceptorsystem pages 4-6).

## Function

TGFBR2 is widely expressed in tissues, with prominent expression noted in endothelial cells, fibroblasts, vascular smooth muscle cells (VSMCs), and tissues critical for development, such as the palatal medial edge epithelium and neural crest-derived osteoprogenitors (gordon2008roleoftransforming pages 20-21, harradine2006mutationsoftgfbeta pages 4-5, iwata2012modulationofnoncanonical pages 13-13, schepers2018amutationupdate pages 10-14).

Upon binding TGF-β ligands, TGFBR2 forms a heteromeric complex with the type I receptor, TGFBR1 (also known as ALK5) (gordon2008roleoftransforming pages 20-21, harradine2006mutationsoftgfbeta pages 4-5, iwata2012modulationofnoncanonical pages 13-13). As a constitutively active kinase, TGFBR2 phosphorylates and activates TGFBR1 (gordon2008roleoftransforming pages 1-2, massague2023tgfβsignalingin pages 6-8). Activated TGFBR1 then phosphorylates receptor-regulated SMADs (R-SMADs), primarily Smad2 and Smad3 (gordon2008roleoftransforming pages 20-21, schepers2018amutationupdate pages 10-14). These phosphorylated R-SMADs form a complex with the common-mediator Smad4, which translocates to the nucleus to regulate target gene transcription (gordon2008roleoftransforming pages 20-21, harradine2006mutationsoftgfbeta pages 4-5, gordon2008roleoftransforming pages 1-2). TGFBR2 signaling also involves non-canonical pathways, including the activation of TAK1, p38 MAPK, ERK, JNK, and RhoA (iwata2012modulationofnoncanonical pages 13-13, schepers2018amutationupdate pages 10-14, gordon2008roleoftransforming pages 1-2).

The pathway regulates cellular processes such as proliferation, differentiation, migration, apoptosis, wound healing, extracellular matrix production, immune regulation, and morphogenesis (harradine2006mutationsoftgfbeta pages 4-5, horbelt2010quantitativeanalysisof pages 1-2, iwata2012modulationofnoncanonical pages 13-13, gordon2008roleoftransforming pages 1-2, schepers2018amutationupdate pages 10-14).

## Inhibitors

Therapeutic and experimental inhibitors of TGF-β signaling involving TGFBR2 include neutralizing antibodies that block ligand-receptor interaction and soluble receptors or ligand traps that sequester TGF-β ligands (gordon2008roleoftransforming pages 20-21, harradine2006mutationsoftgfbeta pages 4-5, gordon2008roleoftransforming pages 1-2, schepers2018amutationupdate pages 10-14). Small molecule inhibitors have been developed that either prevent TGF-β binding to TGFBR2 or target the kinase activity of TGFBR1 and TGFBR2 (gordon2008roleoftransforming pages 20-21, harradine2006mutationsoftgfbeta pages 4-5, massague2023tgfβsignalingin pages 6-8). The agent losartan has been shown to reduce pathological TGF-β signaling mediated via TGFBR2 in certain diseases (gordon2008roleoftransforming pages 20-21).

## Other Comments

Mutations in the *TGFBR2* gene are associated with hereditary connective tissue disorders, including Loeys-Dietz syndrome (LDS), Marfan syndrome type 2 (MFS2), and familial thoracic aortic aneurysms and dissections (TAAD) (gordon2008roleoftransforming pages 20-21, harradine2006mutationsoftgfbeta pages 4-5, horbelt2010quantitativeanalysisof pages 1-2, santibanez2011tgfβtgfβreceptorsystem pages 4-6). Somatic loss-of-function mutations are also implicated in various cancers (massague2023tgfβsignalingin pages 6-8, harradine2006mutationsoftgfbeta pages 1-2).

Disease-associated mutations are frequently heterozygous, missense variants located in highly conserved residues of the kinase domain, such as R460, R528, and R537 (harradine2006mutationsoftgfbeta pages 4-5, horbelt2010quantitativeanalysisof pages 1-2, horbelt2010quantitativeanalysisof pages 7-8). These mutations can impair receptor kinase activity, stability, and internalization, leading to dysregulated TGF-β signaling (harradine2006mutationsoftgfbeta pages 4-5, horbelt2010quantitativeanalysisof pages 1-2). Loss-of-function mutations in *TGFBR2* have been reported to paradoxically cause an increase in TGF-β signaling output and downstream gene expression, which may be due to the loss of canonical pathway feedback inhibition (schepers2018amutationupdate pages 10-14). However, other analyses indicate no immediate paradoxical activation of TGF-β signaling by these mutations (horbelt2010quantitativeanalysisof pages 1-2). These genetic defects result in clinical phenotypes such as aortic aneurysms, skeletal abnormalities, and craniofacial defects (harradine2006mutationsoftgfbeta pages 4-5, iwata2012modulationofnoncanonical pages 13-13).

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