## Phylogeny

G protein-coupled receptor kinase 3 (GRK3), also known as ADRBK2, is a Ser/Thr protein kinase classified within the AGC kinase group, which also includes PKA, PKG, and PKC (manning2002theproteinkinase pages 1-2, schumacher2017noncanonicalrolesof pages 1-2). It is a member of the GRK family, further categorized into the GRK2-like subfamily (also referred to as the β-adrenergic receptor kinase or βARK subfamily), alongside its close homolog GRK2 (mushegian2012theoriginand pages 1-2, evron2012grk2multipleroles pages 1-2, ferrero2022grk2incardiovascular pages 3-4, premont1995proteinkinasesthat pages 1-2). Evolutionarily, the GRK family diverged into two main clades, GRKa (containing GRK1, 4, 5, 6, 7) and GRKb (containing GRK2, 3), prior to the emergence of metazoans (mushegian2012theoriginand pages 10-11). GRK2 and GRK3 arose from gene duplication events within the GRKb lineage (mushegian2012theoriginand pages 10-11). The kinase domain of GRKs is related to that of the ribosomal protein S6 kinase (RPSK) family (mushegian2012theoriginand pages 7-10). Orthologs of GRK3 are conserved across metazoans, including invertebrates like *Caenorhabditis elegans* and *Drosophila*, as well as in some unicellular opisthokonts, but are not found in plants, fungi, or amoebozoa (mushegian2012theoriginand pages 1-2, mushegian2012theoriginand pages 10-11, manning2002theproteinkinase pages 2-3).

## Reaction Catalyzed

GRK3 catalyzes the ATP-dependent phosphoryl transfer from ATP to serine or threonine residues on the intracellular domains, specifically the third intracellular loop or C-terminus, of agonist-activated G protein-coupled receptors (GPCRs) (evron2012grk2multipleroles pages 1-2, ferrero2022grk2incardiovascular pages 4-6, ribas2007thegproteincoupled pages 1-3).

## Cofactor Requirements

The catalytic activity of GRK3 requires ATP as the phosphate donor cofactor (ferrero2022grk2incardiovascular pages 4-6, ribas2007thegproteincoupled pages 1-3). The kinase also requires the divalent cation Mg²⁺ to coordinate the phosphate groups of ATP in the active site, which is essential for the phosphoryl transfer reaction (singh2008structuresofrhodopsin pages 3-4).

## Substrate Specificity

GRK3 phosphorylates serine/threonine residues within specific sequence motifs on activated GPCRs (evron2012grk2multipleroles pages 1-2). An atlas of substrate specificities for the human kinome generated position-specific scoring matrices (PSSMs) for kinase motifs spanning positions -5 to +4 relative to the phospho-acceptor site (johnson2023anatlasof pages 2-3). Based on this analysis, GRK3 substrate motifs show selectivity for basic residues near the phosphorylation site, particularly N-terminal to it (johnson2023anatlasof pages 2-3). While the study provides detailed motif logos showing amino acid preferences at each position, the explicit consensus sequence for GRK3 is not stated in the provided text (johnson2023anatlasof pages 2-3, johnson2023anatlasof pages 3-4). Another study suggests that the substrate-binding channel in the GRK family prefers acidic substrates, targeting serine and threonine residues within receptor C-terminal regions rich in acidic amino acids (singh2008structuresofrhodopsin pages 3-4).

## Structure

GRK3 is a multidomain protein composed of a conserved central AGC-type kinase domain (~270 amino acids) flanked by an N-terminal domain (~185 aa) and a C-terminal domain (mushegian2012theoriginand pages 1-2, ribas2007thegproteincoupled pages 3-4, guccione2016gproteincoupledreceptorkinase pages 4-5). The N-terminus contains a regulator of G protein signaling (RGS) homology domain (~120 aa) involved in receptor recognition and interaction with Gαq subunits (ribas2007thegproteincoupled pages 3-4, penela2019gproteincoupledreceptor pages 1-2). Unique to GRK2 and GRK3 is a C-terminal pleckstrin homology (PH) domain, which binds membrane phospholipids (PIP2) and free Gβγ subunits to facilitate membrane localization (mushegian2012theoriginand pages 10-11, ferrero2022grk2incardiovascular pages 4-6, ribas2007thegproteincoupled pages 3-4). Crystal structures of the close homolog GRK2 show the kinase domain adopts an inactive ‘open’ conformation that transitions to a ‘closed’ active state (guccione2016gproteincoupledreceptorkinase pages 4-5). This conformational change involves key regulatory elements such as the activation loop, the αC-helix, and the hydrophobic spine (guccione2016gproteincoupledreceptorkinase pages 4-5).

## Regulation

The activity of GRK3 is allosterically regulated by its interaction with G protein βγ-subunits (Gβγ), which serve as allosteric effectors (watari2014multiplefunctionsof pages 1-2, penela2019gproteincoupledreceptor pages 1-2). Gβγ binding to the PH domain facilitates GRK3 translocation to the plasma membrane and enhances its kinase activity (schumacher2017noncanonicalrolesof pages 2-4, ribas2007thegproteincoupled pages 3-4). In its basal state, GRK3 is maintained in an inactive conformation by intramolecular interactions that are relieved upon binding to Gβγ or an activated receptor (ribas2007thegproteincoupled pages 3-4). GRK3 activity can also be modulated by phosphorylation by other kinases such as MAPK, PKA, and c-Src, which affects its activity, stability, and protein interactions (ribas2007thegproteincoupled pages 3-4).

## Function

GRK3 is ubiquitously expressed in mammalian tissues (evron2012grk2multipleroles pages 1-2, ribas2007thegproteincoupled pages 3-4, watari2014multiplefunctionsof pages 1-2). Its primary role is to phosphorylate activated GPCRs, which promotes the binding of β-arrestin, leading to G protein signal desensitization and receptor internalization (evron2012grk2multipleroles pages 1-2, watari2014multiplefunctionsof pages 1-2). GRK3 also participates in β-arrestin-mediated signaling pathways that are distinct from G protein-dependent pathways (watari2014multiplefunctionsof pages 1-2). Interacting partners of GRK3 include Gαq, Gβγ, PI3K, clathrin, caveolin, AKT, GIT, and MEK (ribas2007thegproteincoupled pages 3-4). Beyond GPCRs, GRK3 can phosphorylate non-receptor substrates like tubulin (ribas2007thegproteincoupled pages 3-4).

## Inhibitors

GRK activity can be endogenously modulated by the Raf kinase inhibitor protein (RKIP) (ribas2007thegproteincoupled pages 1-3). Several small-molecule inhibitors have been characterized for the highly homologous GRK2, which stabilize the kinase in various conformational states; these include balanol (PDB: 3KRX), CMPD101 (PDB: 3PVU), paroxetine (PDB: 3V5W), and GSK180736A (PDB: 4PNK) (guccione2016gproteincoupledreceptorkinase pages 4-5).

## Other Comments

Dysregulation of GRK3 has been implicated in pathological conditions including heart failure, asthma, and autoimmune disorders (watari2014multiplefunctionsof pages 1-2). The kinase also has a role in blood pressure regulation and other cardiovascular functions (schumacher2017noncanonicalrolesof pages 1-2). Notably, the coding region of the human *GRK3* gene has no known genetic variations, and no disease-associated mutations or polymorphisms affecting the protein’s structure or sequence have been documented (lymperopoulos2012pharmacogenomicsofthe pages 13-15).

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