1. Phylogeny  
   GRK6 is an evolutionarily conserved member of the G protein-coupled receptor kinase family that is expressed in all examined mammalian species. It belongs to the non‐visual GRK subgroup and is classified within the GRK4 subfamily together with GRK4 and GRK5, thereby distinguishing it from the visual kinases (GRK1 and GRK7) as well as from the GRK2/3 subfamily that harbors unique Gβγ‐binding domains (gurevich2012gproteincoupledreceptor pages 1-2, gurevich2012gproteincoupledreceptor pages 2-4, gurevich2012gproteincoupledreceptor pages 25-27).
2. Reaction Catalyzed  
   GRK6 catalyzes the transfer of a phosphate group from adenosine triphosphate (ATP) to serine and threonine residues located in the cytoplasmic regions of activated G protein-coupled receptors; the overall reaction can be summarized as follows: ATP + protein–OH → ADP + protein–O–PO3²⁻ + H⁺ (gurevich2012gproteincoupledreceptor pages 1-2, gurevich2012gproteincoupledreceptor pages 57-59).
3. Cofactor Requirements  
   The kinase activity of GRK6 is strictly dependent on ATP as the phosphate donor and requires divalent metal ions, particularly magnesium (Mg²⁺), to facilitate proper coordination of ATP binding and phosphate transfer (gurevich2012gproteincoupledreceptor pages 25-27, gurevich2012gproteincoupledreceptor pages 59-62).
4. Substrate Specificity  
   GRK6 displays a substrate preference predominantly for activated G protein-coupled receptors; it phosphorylates serine and threonine residues that are frequently organized in clusters within the receptor’s intracellular loops and carboxyl-terminal tail. Although a strict consensus motif for GRK6 has not been fully delineated, its activity is confined to receptors that have undergone an agonist-induced conformational change, and it is also capable in vitro of phosphorylating non-GPCR substrates such as rhodopsin, LRP6, and synucleins (gurevich2012gproteincoupledreceptor pages 1-2, gurevich2012gproteincoupledreceptor pages 8-9, pronin2000synucleinsarea pages 1-1).
5. Structure  
   GRK6 is organized into several distinct domains essential for its function. It possesses an N-terminal region of approximately 25 residues that is critical for receptor docking and proper alignment of the catalytic domain. This is followed by a regulator of G protein signaling (RGS) homology domain which, although homologous to domains in receptors that bind Gα subunits, in GRK6 appears to serve a regulatory role in maintaining the correct conformation of the kinase. Central to the protein is the catalytic serine/threonine kinase domain characteristic of the AGC kinase family; this domain contains conserved motifs including an activation loop, a hydrophobic C-helix, and a critical lysine residue required for ATP binding. The C-terminal region of GRK6 contains positively charged lipid-binding elements and, in certain splice variants (e.g., GRK6A), palmitoylation sites that enhance membrane association. Structural studies indicate that GRK6 can adopt an “open” conformation that transitions to a closed, active conformation upon interaction with activated receptors, thereby positioning its catalytic elements optimally for substrate phosphorylation (gurevich2012gproteincoupledreceptor pages 4-5, gurevich2012gproteincoupledreceptor pages 6-8, gurevich2012gproteincoupledreceptor pages 57-59).
6. Regulation  
   The regulation of GRK6 is mediated by several mechanisms that control its catalytic activity and subcellular localization. Primarily, GRK6 is activated through direct interaction with agonist-bound GPCRs; receptor docking induces an allosteric change from an inactive “open” state to a catalytically active “closed” conformation. Post-translational modifications also play a role in its regulation; for example, alternative splicing generates isoforms (GRK6A, GRK6B, and GRK6C) that differ in their C-terminal sequences and consequently in their membrane-targeting properties. For GRK6A, palmitoylation enhances plasma membrane association, while other isoforms utilize basic amino acid patches for effective localization. Unlike GRK2 and GRK3, GRK6 does not possess a specific Gβγ-binding domain, and its recruitment to the membrane is predominantly governed by its lipid-binding elements and receptor-induced conformational shifts. Additional regulatory influences, such as interactions with molecular chaperones (e.g., Hsp90) and potential modulation at the transcriptional level, further refine its functional output (gurevich2012gproteincoupledreceptor pages 1-2, gurevich2012gproteincoupledreceptor pages 4-5, gurevich2012gproteincoupledreceptor pages 10-12, gurevich2012gproteincoupledreceptor pages 15-16).
7. Function  
   GRK6 functions by phosphorylating activated G protein-coupled receptors, an event that promotes the binding of beta-arrestins to the receptor. This beta-arrestin recruitment results in receptor desensitization, internalization via clathrin-dependent pathways, and the initiation of alternative, beta-arrestin-dependent signaling cascades. GRK6 is specifically involved in the regulation of D2-like dopamine receptors in the striatum, where its activity limits receptor sensitivity, and it also modulates chemokine receptor signaling (for example, CXCR4) that is critical for CXCL12-induced chemotaxis. In vitro studies have demonstrated that GRK6 can phosphorylate rhodopsin as well as LRP6, a protein involved in Wnt signaling, thereby extending its functional repertoire beyond classical GPCR substrates. GRK6 is widely expressed across tissues, with notable expression in the brain, immune cells, and other non-visual tissues; this broad distribution underscores its central role in the fine-tuning of receptor-mediated signaling in both neuronal and immune contexts (gurevich2012gproteincoupledreceptor pages 1-2, gurevich2012gproteincoupledreceptor pages 27-28, gurevich2012gproteincoupledreceptor pages 41-42).
8. Other Comments  
   Dysregulation of GRK6 activity has been linked to a number of pathological conditions. Altered expression or activity of GRK6 is associated with abnormal dopaminergic signaling exemplified by receptor supersensitivity in the striatum, a phenomenon that has been implicated in Parkinson’s disease and in the development of L-DOPA-induced dyskinesia. In immune cells, GRK6 modulates chemokine receptor desensitization, with consequences for leukocyte chemotaxis and inflammatory responses. Although several inhibitors have been developed for members of the GRK family, selective inhibition of GRK6 remains an ongoing area of investigation, and current pharmacological tools typically do not discriminate robustly between GRK isoforms. Moreover, the existence of multiple splice variants of GRK6 adds additional complexity to its regulatory landscape and may influence tissue-specific functional outcomes (gurevich2012gproteincoupledreceptor pages 27-28, gurevich2012gproteincoupledreceptor pages 37-38, sato2015theevolvingimpact pages 18-19, raghuwanshi2012thechemokinereceptors pages 7-9).
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