## Phylogeny

Cyclin G-associated kinase (GAK) is a serine/threonine kinase belonging to the numb-associated kinase (NAK) family, which also includes adaptor-associated kinase (AAK1), STK16/MPSK1, and BMP-2 inducible kinase (BIKE) (asquith2018identificationandoptimization pages 1-2, asquith2019sgcgak1achemical pages 1-3, kovackova2015selectiveinhibitorsof pages 1-3). It has also been classified within the Ark family of kinases due to its homology with actin regulating kinase (ARK-1) (emsleyleik2009theeffectof pages 47-50). According to the kinome classification by Manning et al., 2002, GAK is placed in the NAK subfamily (asquith2018identificationandoptimization pages 1-2, asquith2019sgcgak1achemical pages 1-3). The kinase domain shows similarity to Nek1, CDK2, Plk, and Tsk-1 but lacks the canonical PSTAIR motif found in CDKs (kanaoka1997gakacyclin pages 1-2, kanaoka1997gakacyclin pages 5-7).

Known orthologs include Auxilin-related kinase (Ark) in mice, Auxilin (dAux) in *Drosophila*, and zGAK in zebrafish (chaikuad2014structureofcyclin pages 2-2, greener2000roleofcyclin pages 3-4, bai2010disruptionofzebrafish pages 5-7). The mouse ortholog shares high sequence homology with human GAK, and both zebrafish and mammalian GAK can rescue defects from dAux mutations in *Drosophila* (kanaoka1997gakacyclin pages 5-7, bai2010disruptionofzebrafish pages 5-7).

## Reaction Catalyzed

GAK catalyzes the transfer of the γ-phosphate group from ATP to serine or threonine residues on substrate proteins (asquith2018identificationandoptimization pages 1-2, asquith2019sgcgak1achemical pages 8-9, chaikuad2014structureofcyclin pages 10-10). The general reaction is: Protein + ATP → Phosphoprotein + ADP.

## Cofactor Requirements

The kinase activity of GAK requires ATP as the phosphate donor cofactor (asquith2018identificationandoptimization pages 1-2, asquith2019sgcgak1achemical pages 1-3, kovackova2015selectiveinhibitorsof pages 1-3). The catalytic activity also requires magnesium ions (Mg²⁺) to facilitate ATP binding and phosphate transfer (chaikuad2014structureofcyclin pages 10-10).

## Substrate Specificity

I cannot answer. The provided context, including excerpts from the priority publication *Johnson, J. L., et al. (2023). An atlas of substrate specificities for the human serine/threonine kinome*, states that the consensus substrate motif for GAK is not detailed or available (johnson2023anatlasof pages 1-2, johnson2023anatlasof pages 2-3, johnson2023anatlasof pages 4-5, johnson2023anatlasof pages 9-10).

## Structure

GAK is a 144-160 kDa protein with a multi-domain architecture (asquith2018identificationandoptimization pages 1-2, emsleyleik2009theeffectof pages 47-50, kovackova2015selectiveinhibitorsof pages 1-3). Its key domains are: - **N-terminal kinase domain:** This domain is responsible for the catalytic serine/threonine kinase activity (asquith2019sgcgak1achemical pages 6-8, emsleyleik2009theeffectof pages 47-50). It phosphorylates substrates such as histone H1 and the μ2 subunit of the AP-2 complex (emsleyleik2009theeffectof pages 47-50, greener2000roleofcyclin pages 4-6). - **Central PTEN-like (tensin/auxilin-like) domain:** This domain is implicated in regulatory functions and clathrin-mediated membrane trafficking (asquith2019sgcgak1achemical pages 6-8, kanaoka1997gakacyclin pages 5-7). Although structurally similar to the PTEN tumor suppressor, it lacks phosphatase activity (greener2000roleofcyclin pages 6-7). - **C-terminal J-domain:** This domain functions as a co-chaperone that directly interacts with the heat shock protein Hsc70, stimulating its ATPase activity to drive the uncoating of clathrin-coated vesicles (asquith2019sgcgak1achemical pages 6-8, greener2000roleofcyclin pages 3-4, kanaoka1997gakacyclin pages 5-7). - **Clathrin-binding domain:** Located in the C-terminal region, this domain induces clathrin polymerization (emsleyleik2009theeffectof pages 47-50, greener2000roleofcyclin pages 1-1).

Key structural features include a regulatory spine (R-spine), a conserved set of hydrophobic residues that assembles to stabilize the active conformation of the kinase domain (asquith2019sgcgak1achemical pages 6-8, emsleyleik2009theeffectof pages 47-50). Structurally, GAK differs from other NAK family members by having a deeper substrate binding cleft, which is due to an extended loop between helices αF and αG (sorrell2016familywidestructuralanalysis pages 5-6). Nanobody-trapped crystal structures reveal that GAK can adopt different conformations and may form a homodimer via activation segment exchange, potentially representing an inactive state (asquith2019sgcgak1achemical pages 8-9, sorrell2016familywidestructuralanalysis pages 5-6).

## Regulation

GAK activity is regulated through multiple mechanisms: - **Allosteric Regulation:** The J-domain of GAK is essential for its function in clathrin uncoating and acts as an allosteric regulator. It stimulates the binding of Hsc70 to clathrin baskets in the presence of ATP, which in turn facilitates the uncoating reaction (greener2000roleofcyclin pages 4-6, greener2000roleofcyclin pages 6-7). - **Post-Translational Modification:** The kinase domain of GAK is constitutively active and does not require phosphorylation of its activation loop, as its regulatory spine is pre-assembled in the active conformation (sorrell2016familywidestructuralanalysis pages 5-6). An experimentally verified autophosphorylation site at Ser433 is critical for modulating kinase activity and its function in vesicle uncoating (greener2000roleofcyclin pages 6-7). - **Other Mechanisms:** GAK activity may be regulated by homodimerization, which is proposed to induce an inactive conformation (sorrell2016familywidestructuralanalysis pages 5-6). Alternative splicing of transcripts involving exon 26 (clathrin-binding domain) and exon 28 (J-domain) may also influence its function (dumitriu2011cyclingassociatedkinasemodifies pages 5-6).

## Function

GAK is a ubiquitously expressed protein with the highest levels in the testes; it localizes to the cytoplasm, nucleus, Golgi complex, and perinuclear regions (asquith2019sgcgak1achemical pages 1-3, emsleyleik2009theeffectof pages 47-50). Its primary function is the regulation of clathrin-mediated trafficking in both endocytic and secretory pathways (kovackova2015selectiveinhibitorsof pages 1-3). It acts as a homolog of the neuronal protein auxilin in non-neuronal cells, facilitating the uncoating of clathrin-coated vesicles by cooperating with Hsc70 (greener2000roleofcyclin pages 1-1, emsleyleik2009theeffectof pages 47-50).

GAK phosphorylates specific substrates, including the T156 residue on the μ2 subunit of the adaptor protein-2 (AP-2) complex to regulate cargo internalization and the Thr104 residue on the B’γ subunit of protein phosphatase 2A (PP2A) to regulate its activity (asquith2018identificationandoptimization pages 1-2, naito2012cyclingassociatedkinase pages 1-3). GAK interacts with cyclin G, CDK5, clathrin, Hsc70, and pre-cathepsin D (CTSD) (emsleyleik2009theeffectof pages 47-50, kanaoka1997gakacyclin pages 2-5, dumitriu2011cyclingassociatedkinasemodifies pages 1-2). It is also involved in modulating α-synuclein expression and toxicity; GAK reduction leads to increased α-synuclein accumulation (dumitriu2011cyclingassociatedkinasemodifies pages 1-1, dumitriu2011cyclingassociatedkinasemodifies pages 2-3, dumitriu2011cyclingassociatedkinasemodifies pages 4-5). Furthermore, GAK plays roles in cell cycle progression, mitosis, and centrosome maturation (asquith2018identificationandoptimization pages 1-2, sorrell2016familywidestructuralanalysis pages 1-3).

## Inhibitors

Known inhibitors of GAK include 4-anilinoquinolines and gefitinib, a type I kinase inhibitor that binds to the ATP-binding site (asquith2018identificationandoptimization pages 1-2, asquith2019sgcgak1achemical pages 8-9, ohbayashi2018structuralbasisfor pages 1-2). SGC-GAK-1 is a selective chemical probe developed to study its kinase domain biology (asquith2019sgcgak1achemical pages 6-8).

## Other Comments

GAK is implicated in several diseases, including Parkinson’s disease (PD), prostate cancer, and osteosarcoma (dumitriu2011cyclingassociatedkinasemodifies pages 1-1, asquith2019sgcgak1achemical pages 6-8, asquith2019sgcgak1achemical pages 8-9). A single nucleotide polymorphism (SNP), rs1564282, within the GAK gene is significantly associated with an increased risk for familial PD (dumitriu2011cyclingassociatedkinasemodifies pages 1-1, dumitriu2011cyclingassociatedkinasemodifies pages 2-3). The minor allele of this SNP is associated with reduced expression of GAK exon 28 (dumitriu2011cyclingassociatedkinasemodifies pages 5-6). GAK expression levels also correlate with prostate cancer progression (asquith2019sgcgak1achemical pages 6-8). In animal models, knockout mice expressing a kinase-dead version of GAK exhibit neonatal lethality due to pulmonary dysfunction (asquith2019sgcgak1achemical pages 8-9, sorrell2016familywidestructuralanalysis pages 12-12).

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