1. Phylogeny  
   Cyclin‐G‐associated kinase (GAK), also known as DNAJC26, is classified as a serine/threonine kinase within the Numb‐associated kinase (NAK) family, which also comprises kinases such as adaptor‐associated kinase 1 (AAK1), BMP2‐inducible kinase (BMP2K/BIKE), and MPSK1/STK16 (ohbayashi2018structuralbasisfor pages 1-2). Orthologs of GAK have been identified across a wide range of species including mammals, yeast, Drosophila, and Caenorhabditis elegans, indicating a high level of evolutionary conservation of its catalytic and accessory functions (huang2023currentthoughtson pages 1-3). Phylogenetic analyses based on the human kinome reveal that although the catalytic domains of NAK family members share limited overall sequence identity outside of the kinase core, the conservation of key motifs, especially those within the ATP‐binding pocket and activation segments, points to a common evolutionary origin (kovackova2015selectiveinhibitorsof pages 1-3). In addition, the acquisition of non‐catalytic domains such as a C‐terminal DNAJ domain, which distinguishes GAK from its neural homolog auxilin, is indicative of lineage‐specific adaptations that link its activity to clathrin‐mediated vesicular trafficking (wang2019serinethreonineproteinkinase pages 1-3, asquith2018identificationandoptimization pages 1-3).
2. Reaction Catalyzed  
   GAK functions as an ATP‐dependent protein kinase that catalyzes the phosphorylation of serine and threonine residues on specific substrate proteins. The chemical reaction catalyzed by GAK can be summarized as follows: ATP + [protein substrate] → ADP + [protein substrate]‐phosphate + H⁺ (ohbayashi2018structuralbasisfor pages 2-4, asquith2018identificationandoptimization pages 1-3).
3. Cofactor Requirements  
   Like most serine/threonine kinases, the enzymatic activity of GAK is dependent on the presence of divalent metal ions, predominantly Mg²⁺, which are required to coordinate ATP binding and facilitate the transfer of the phosphate group to the substrate (kovackova2015selectiveinhibitorsof pages 1-3, asquith2018identificationandoptimization pages 1-3).
4. Substrate Specificity  
   GAK exhibits substrate specificity primarily for serine/threonine residues on target proteins that participate in clathrin-mediated endocytosis. One of the best-characterized substrates of GAK is the μ2 subunit of the adaptor protein complex-2 (AP2M1), which is phosphorylated specifically at threonine 156 (T156) (huang2023currentthoughtson pages 3-4, kovackova2015selectiveinhibitorsof pages 1-3). Although a complete consensus substrate motif for GAK has not been definitively established, the phosphorylation of T156 suggests a role in modulating protein–protein interactions that facilitate the assembly of clathrin-coated vesicles (asquith2018identificationandoptimization pages 1-3). Studies of related serine/threonine kinases have shown a general preference for sequences that contain basic residues near the phosphorylation site; however, further biochemical investigations are required to determine if GAK displays such detailed substrate preferences or any extended consensus sequence (yuan2023recentprogressin pages 2-4).
5. Structure  
   GAK is a large, multidomain protein with an approximate molecular weight of 160 kDa. Its domain organization is comprised of an N-terminal kinase domain, a PTEN-like domain, a clathrin-binding domain, and a C-terminal J domain. The N-terminal kinase domain is responsible for catalytic activity and adopts the typical bilobal architecture seen in serine/threonine protein kinases, featuring a smaller N-lobe and a larger C-lobe that together form the active site and ATP-binding pocket (ohbayashi2018structuralbasisfor pages 1-2). High-resolution crystallographic studies of the kinase domain, including those in complex with inhibitors such as gefitinib, have revealed important structural features such as the DFG-in and αC-in conformations, which are essential for GAK’s catalytic activity (ohbayashi2018structuralbasisfor pages 6-7). These studies have also identified a secondary inhibitor-binding site adjacent to a unique activation segment C-terminal helix (ASCH), a structural element characteristic of NAK family kinases that contributes to their constitutive activity (wang2019serinethreonineproteinkinase pages 1-3, gerninghaus2024backpocketoptimizationof pages 22-29).

The PTEN-like domain in GAK, while less extensively characterized, is thought to be involved in interactions with phospholipids or other membrane-associated proteins, thereby potentially playing a role in membrane recruitment and regulation of vesicular trafficking (huang2023currentthoughtson pages 3-4). The central clathrin-binding domain facilitates the direct interaction with clathrin, which is critical for the assembly and disassembly dynamics of clathrin-coated vesicles during endocytosis (huang2023currentthoughtson pages 4-5). The C-terminal J domain is homologous to the canonical DnaJ domain, and it is essential for recruiting the Hsc70 chaperone; this interaction stimulates the ATPase activity of Hsc70, thereby promoting the uncoating of clathrin-coated vesicles after internalization (kovackova2015selectiveinhibitorsof pages 4-6, zhao2008biologicalrolesof pages 4-7).

Structural studies indicate that the activation loop within the kinase domain of GAK is extended and, together with the unique ASCH, provides a rigid framework that supports high basal catalytic activity without the need for activation loop phosphorylation typical of many other kinases (wang2019serinethreonineproteinkinase pages 3-5, gerninghaus2024backpocketoptimizationof pages 19-22). In addition, conserved features such as the catalytic Lys residue in the β3 strand and a neighboring Glu in the αC helix form a salt bridge that stabilizes the active conformation, while the DFG motif at the start of the activation loop coordinates Mg²⁺ ions and positions ATP for efficient catalysis (ohbayashi2018structuralbasisfor pages 2-4, kovackova2015selectiveinhibitorsof pages 30-31). These structural insights not only provide a basis for understanding GAK’s enzymatic mechanism but have also informed structure-based drug design efforts aimed at developing selective inhibitors (gerninghaus2024backpocketoptimizationof pages 3-4).

1. Regulation  
   GAK regulation is achieved via multiple mechanisms that integrate both its catalytic and scaffolding functions. The kinase is known to associate with cyclin G and CDK5, linking its activities to cell cycle control and the DNA damage response; these interactions are believed to modulate GAK’s functional state during cell cycle progression, with expression peaking in G1 phase (thiriet2013preambletocytoplasmic pages 4-7, malumbres2005mammaliancyclindependentkinases pages 3-4). Despite possessing an atypical activation loop that supports constitutive kinase activity, regulatory phosphorylation events or protein–protein interactions may further fine-tune its activity at distinct cellular locales or in response to specific signals.

In addition to cyclin-mediated regulation, GAK’s non-catalytic functions are controlled by its C-terminal J domain, which recruits Hsc70 to facilitate clathrin coat uncoating. This association with Hsc70 is essential for the disassembly of clathrin-coated vesicles and appears to be regulated by the spatial distribution of phosphoinositides within the cell membrane (zhao2008biologicalrolesof pages 4-7, huang2023currentthoughtson pages 4-5). The coordinated regulation of GAK via both its kinase activity and its chaperone recruitment function underscores its dual role in modulating clathrin-mediated endocytosis. Moreover, alterations in its kinase domain conformation, influenced by interactions with small-molecule inhibitors and potentially by autophosphorylation events, may further impact substrate recognition and catalytic efficiency (asquith2018identificationandoptimization pages 1-3, gerninghaus2024backpocketoptimizationof pages 16-18). Although detailed mapping of specific phosphorylation sites on GAK itself is currently limited, the integration of multiple regulatory inputs ensures precise control over its function in vesicle trafficking and signal transduction (malumbres2005mammaliancyclindependentkinases pages 3-4).

1. Function  
   GAK is ubiquitously expressed in non-neuronal tissues where it plays a critical role in clathrin-mediated endocytosis and intracellular trafficking. Its kinase activity is essential for the phosphorylation of the μ2 subunit of the AP2 complex at threonine 156, a modification that enhances the recruitment of clathrin and adaptor proteins to the plasma membrane and thereby facilitates vesicle formation (huang2023currentthoughtson pages 3-4, kovackova2015selectiveinhibitorsof pages 1-3). In addition to its catalytic role, GAK functions as a co-chaperone; through its C-terminal J domain, it interacts with Hsc70 to promote the uncoating of clathrin-coated vesicles, a critical step in the recycling of clathrin and associated receptors (zhao2008biologicalrolesof pages 4-7, ohbayashi2018structuralbasisfor pages 6-7).

Beyond its involvement in membrane trafficking, GAK is implicated in regulating receptor signaling pathways. For instance, by modulating the internalization and recycling of epidermal growth factor receptor (EGFR) and other membrane receptors, GAK indirectly influences downstream signaling cascades that affect cell proliferation and survival (emsleyleik2009theeffectof pages 47-50, malumbres2005mammaliancyclindependentkinases pages 11-12). Its association with cyclin G and CDK5 further suggests a role in cell cycle regulation and in maintaining genomic integrity in response to DNA damage (thiriet2013preambletocytoplasmic pages 4-7, malumbres2005mammaliancyclindependentkinases pages 3-4).

The dual functional capabilities of GAK—as both a kinase and a facilitator of clathrin uncoating—underscore its importance in maintaining cellular homeostasis. Dysregulation of GAK activity has been linked to defects in receptor-mediated endocytosis, which can impact signaling pathways involved in viral entry, oncogenesis, and neurodegeneration (serafim2021chemicalprobesfor pages 6-10, gerninghaus2024backpocketoptimizationof pages 9-11). As such, GAK is emerging as a potential therapeutic target in a variety of disease contexts, with its inhibition showing promise in antiviral strategies and possibly in the modulation of aberrant receptor signaling in cancer (asquith2018identificationandoptimization pages 1-3, kovackova2015selectiveinhibitorsof pages 1-3).

1. Other Comments  
   Several small-molecule inhibitors have been identified that target GAK, often as off-target effects of drugs developed for other kinases. Clinically approved inhibitors for epidermal growth factor receptor (EGFR) such as gefitinib and erlotinib have been shown to inhibit GAK with low nanomolar potency, thereby providing chemical tools for probing its function in clathrin-mediated endocytosis and vesicle recycling (asquith2018identificationandoptimization pages 1-3, kovackova2015selectiveinhibitorsof pages 1-3). More recently, structure‐guided medicinal chemistry efforts have led to the development of macrocyclic inhibitors that engage both the ATP‐binding site and a unique hydrophobic pocket adjacent to the activation segment, with the aim of achieving greater selectivity for GAK (gerninghaus2024backpocketoptimizationof pages 16-18, gerninghaus2024backpocketoptimizationof pages 9-11). GAK has also been implicated in viral infections, with its role in receptor trafficking making it a potential target for antiviral therapies against hepatitis C virus and Dengue virus (kovackova2015selectiveinhibitorsof pages 1-3, serafim2021chemicalprobesfor pages 92-96). In addition, aberrant GAK activity has been associated with cancer-related processes, possibly due to its effects on EGFR signaling and cell cycle regulation, thereby positioning GAK as a candidate for therapeutic intervention in oncogenic pathways (malumbres2005mammaliancyclindependentkinases pages 11-12, serafim2021chemicalprobesfor pages 6-10).
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