1. Phylogeny  
   5′-AMP-activated protein kinase catalytic subunit alpha‑1 (PRKAA1, also known as AMPK1) is a highly evolutionarily conserved serine/threonine kinase found in all eukaryotes, from yeast to mammals. Its catalytic domain shares high sequence homology with the α subunit of the yeast SNF1 complex, indicating that the kinase originated early in eukaryotic evolution and has been maintained as part of an ancestral energy‐sensing module through the Last Eukaryotic Common Ancestor (LECA) or earlier (cox2003proteinkinasesand pages 53-57, hardie2007ampactivatedsnf1proteinkinases pages 1-2). Within the human kinome, in accordance with the classification by Manning and colleagues, PRKAA1 is grouped with the AMPK family, which forms an evolutionarily conserved regulatory branch distinct from other serine/threonine kinases. This subgroup is part of the metabolic regulatory core that includes kinases such as LKB1, AKT, and mTOR, whose functions are interlinked in energy homeostasis and nutrient signaling (hardie2007ampactivatedsnf1proteinkinases pages 1-2, cox2003proteinkinasesand pages 53-57). In mammals, AMPK exists as a heterotrimer composed of various isoforms of the catalytic (α1 and α2), regulatory β (β1 and β2), and γ (γ1, γ2, and γ3) subunits, and PRKAA1 encodes the predominant catalytic isoform present in many tissues such as liver, muscle, and brain. The conservation of these isoforms across species underscores the central role of AMPK in cellular energy sensing and metabolism regulation (hardie2007ampactivatedsnf1proteinkinases pages 1-2, cox2003proteinkinasesand pages 53-57).
2. Reaction Catalyzed  
   AMPKα1 catalyzes the transfer of a phosphate group from ATP to specific serine/threonine residues on its target protein substrates. The canonical reaction can be represented as: ATP + [protein]-(L-serine or L-threonine) → ADP + [protein]-(L-serine/threonine)-phosphate + H⁺. This phosphorylation event is fundamental to switching various metabolic enzymes and regulatory proteins on or off, thereby modulating catabolic and anabolic processes in response to changes in cellular energy status (hardie2004ampactivatedproteinkinase pages 2-3, kemp2003ampactivatedproteinkinase pages 3-6).
3. Cofactor Requirements  
   The kinase activity of AMPKα1 is dependent on the presence of divalent metal ions, predominantly Mg²⁺, which serve as essential cofactors for ATP binding and catalysis. In addition, the regulatory mechanism relies on binding of adenine nucleotides such as AMP (and to a lesser extent ADP) which promote allosteric activation and protect the activating phosphorylation site on the α subunit from dephosphorylation. The requirement for Mg²⁺ ensures proper alignment of ATP within the catalytic pocket and facilitates the transfer of the phosphate group during the phosphorylation reaction (hardie2004ampactivatedproteinkinase pages 2-3, russell2020ampactivatedproteinkinase pages 2-4).
4. Substrate Specificity  
   AMPKα1 preferentially phosphorylates serine or threonine residues within substrates that display specific consensus motifs. Detailed studies have indicated that the substrate motif often features hydrophobic residues at the –5 and +4 positions relative to the phosphoacceptor site, along with basic residues (typically arginine, lysine, or histidine) at positions such as –4 and –3. The resulting preferred sequence may be summarized as hyd-X-bas-XXSXXX-hyd (where “bas” represents a basic residue and “hyd” represents a hydrophobic residue) (cox2003proteinkinasesand pages 57-61). Recent phosphoproteomic studies on the human serine/threonine kinome corroborate that AMPK exhibits a distinct set of substrate preferences corresponding to these sequence features (Johnson2023Example pages 1-4). Although AMPK primarily functions as a serine/threonine kinase, its substrate specificity categorizes it within a broader class of kinases that includes enzymes with similar consensus motifs, ensuring that its targets encompass key metabolic enzymes such as acetyl-CoA carboxylase, hormone-sensitive lipase, and various transcription regulators (cox2003proteinkinasesand pages 57-61, michell1996isoformspecificpurificationand pages 3-4).
5. Structure  
   The structure of AMPKα1 is defined by a modular organization that includes an N-terminal serine/threonine kinase domain, an autoinhibitory domain (AID), and a C-terminal domain (CTD) responsible for interaction with regulatory subunits. The kinase domain comprises a two-lobed structure: a smaller N-terminal lobe containing β-sheets important for ATP binding and a larger C-terminal lobe that houses catalytic residues and the active site. Within this domain, the conserved activation loop contains threonine 172—a critical residue whose phosphorylation by upstream kinases is essential for full catalytic activation (hardie2004ampactivatedproteinkinase pages 2-3, hardie2007ampactivatedsnf1proteinkinases pages 3-4). The AID, located immediately C-terminal to the kinase domain, exerts an inhibitory effect in the absence of allosteric activators and is relieved upon AMP binding to the regulatory complex. The C-terminal region also mediates the interaction with the β and γ subunits, allowing the assembly of a heterotrimeric complex. Structural models and crystallographic data, including those derived from AlphaFold predictions, reveal a tight configuration of the catalytic domain along with a prominent hydrophobic spine and an appropriately positioned C-helix that play roles in substrate alignment and catalytic efficiency (hardie2007ampactivatedsnf1proteinkinases pages 3-4, witczak2008ampactivatedproteinkinase pages 3-4, russell2020ampactivatedproteinkinase pages 4-6). The overall three-dimensional conformation is critical for both the enzymatic function and the regulation by nucleotides, with the Bateman domains present in the γ subunit binding AMP/ADP and transmitting allosteric signals that modulate the conformation of the catalytic α subunit (witczak2008ampactivatedproteinkinase pages 4-6).
6. Regulation  
   Regulation of AMPKα1 activity is achieved by a combination of post-translational modifications and allosteric mechanisms. One of the most critical regulatory events is the phosphorylation of Thr172 within the activation loop by upstream kinases such as LKB1 and CaMKKβ; this phosphorylation increases AMPK activity several hundred- to thousand-fold (hardie2007ampactivatedproteinkinase pages 1-3, hardie2011ampactivatedproteinkinase pages 3-4). AMP binding to the γ subunit of AMPK allosterically activates the enzyme, stimulates further phosphorylation of Thr172, and prevents its dephosphorylation by protein phosphatases (PP2C among others) (hardie2004ampactivatedproteinkinase pages 2-3, russell2020ampactivatedproteinkinase pages 23-24). In addition, regulatory phosphorylation at other serine residues (for example, serine 485 in the α1 isoform) has been reported to exert inhibitory effects, potentially mediated by kinases such as protein kinase B (PKB/Akt). These multiple layers of regulation, which include nucleotide binding, phosphorylation by specific upstream kinases, and protective interactions with regulatory subunits, enable AMPKα1 to function precisely as a sensor of cellular energy status (cox2003proteinkinasesand pages 61-64, hardie2007ampactivatedproteinkinase pages 1-3, hardie2011ampactivatedproteinkinase pages 3-4, russell2020ampactivatedproteinkinase pages 23-24).
7. Function  
   AMPKα1 plays a central role in maintaining cellular energy homeostasis by modulating key metabolic pathways in response to changes in the intracellular energy charge. Under conditions of energy stress—such as hypoxia, nutrient deprivation, or muscle contraction—the intracellular concentration of AMP increases relative to ATP. This shift in the AMP:ATP ratio triggers the activation of AMPKα1, which in turn phosphorylates metabolic enzymes to inhibit ATP-consuming anabolic pathways, including fatty acid, cholesterol, protein, and carbohydrate synthesis (cox2003proteinkinasesand pages 53-57, hardie2007ampactivatedproteinkinase pages 1-3). Concurrently, AMPKα1 activation enhances ATP-generating catabolic processes such as fatty acid oxidation, glucose uptake, glycolysis, and autophagy. For instance, phosphorylation of acetyl-CoA carboxylase (ACACA and ACACB) by AMPK reduces malonyl-CoA levels, thereby removing the inhibition of mitochondrial fatty acid import and oxidation. In skeletal muscle, AMPK facilitates the translocation of the glucose transporter GLUT4 to the plasma membrane—via phosphorylation of proteins such as TBC1D4/AS160—thereby enhancing glucose uptake (cox2003proteinkinasesand pages 57-61, hardie2007ampactivatedproteinkinase pages 1-3, russell2020ampactivatedproteinkinase pages 2-4).  
   In the liver, AMPKα1 phosphorylates regulatory proteins such as CRTC2/TORC2, causing its sequestration in the cytoplasm and leading to a reduction in gluconeogenic gene expression, thereby contributing to glucose homeostasis. AMPKα1 also modulates lipid metabolism by phosphorylating and inactivating enzymes involved in lipogenesis such as HMG-CoA reductase (HMGCR) and by promoting lipolysis through effects on hormone-sensitive lipase (LIPE) (cox2003proteinkinasesand pages 57-61, hardie2011ampactivatedproteinkinase pages 10-10, russell2020ampactivatedproteinkinase pages 23-24).  
   Beyond its immediate metabolic functions, AMPKα1 influences gene expression through phosphorylation of transcriptional regulators such as FOXO3, ChREBP, and p53, thereby integrating acute metabolic responses with longer-term transcriptional adaptations. It also plays a role in regulating cell growth and proliferation by impacting the mTORC1 pathway; for example, AMPK-mediated phosphorylation of TSC2 and the RPTOR subunit of mTORC1 results in suppression of anabolic and growth-promoting signals during energy stress (cox2003proteinkinasesand pages 61-64, hardie2011ampactivatedproteinkinase—an pages 4-5, russell2020ampactivatedproteinkinase pages 2-4). AMPKα1 is expressed ubiquitously, yet tissue-specific isoform distributions (for instance, a higher relative content of α1 in some tissues compared to α2) suggest differential roles in various cell types, such as skeletal muscle, liver, adipose tissue, and the brain (cox2003proteinkinasesand pages 53-57, hardie2007ampactivatedsnf1proteinkinases pages 1-2).
8. Other Comments  
   Several pharmacological agents are known to modulate AMPK activity. Indirect activators such as metformin and AICAR have been employed extensively in both research and clinical settings to harness AMPK’s metabolic benefits in conditions like type 2 diabetes and metabolic syndrome by creating a cellular environment that mimics energy stress (russell2020ampactivatedproteinkinase pages 23-24, hardie2011ampactivatedproteinkinase pages 10-10). In addition, there are direct activators such as A-769662, which interact with regulatory subunits, and experimental inhibitors that have been used to study AMPK function. Inhibition of AMPK has also been associated with increased anabolic activity and cell proliferation in certain contexts, pointing to its potential role as a tumor suppressor. Alterations in AMPK signaling have been linked to a variety of disease states, including cardiac hypertrophy, insulin resistance, and even aspects of cancer progression via its actions on cell growth pathways. Notably, mutations affecting AMPK regulatory subunits (and by extension its activation) have been associated with disorders of glycogen storage and arrhythmias. AMPKα1 is also described to have tau-protein kinase activity in response to amyloid beta exposure; however, the in vivo relevance of this function remains to be fully clarified (cox2003proteinkinasesand pages 61-64, hardie2007ampactivatedsnf1proteinkinases pages 1-2, russell2020ampactivatedproteinkinase pages 23-24). The wide-ranging substrate portfolio of AMPKα1 includes transcription regulators, metabolic enzymes, and proteins involved in autophagy and mitophagy, which further emphasizes its role as a master regulator of cellular energy and homeostasis (steinberg2023newinsightsinto pages 9-13, hardie2011ampactivatedproteinkinase pages 10-10).
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