1. Phylogeny  
   AKT3 (also known as Protein kinase B gamma, RAC‐PK‐γ, or STK-2) is one of three highly homologous isoforms within the AKT family, which forms part of the AGC kinase group. It is evolutionarily conserved across eukaryotes and can be found in a broad range of species from yeast to mammals. In mammals, orthologs of AKT3 have been identified in primates and rodent models, underlining its conservation and significance. Gene duplication events early in eukaryotic evolution gave rise to the three AKT isoforms (AKT1, AKT2, and AKT3), with each isoform subsequently acquiring partially distinct tissue expression patterns and functional roles. AKT3 in particular is noted for its predominant expression in the brain and its implication in neural development, distinguishing it within this conserved kinase family (mcdowell2011targetingtheakt pages 1-2, toker2014signalingspecificityin pages 7-8, rakshambikai2015typicalandatypical pages 9-11).
2. Reaction Catalyzed  
   The catalytic reaction carried out by AKT3 involves the transfer of the γ-phosphate from ATP to the hydroxyl group of serine or threonine residues on substrate proteins. In chemical terms, the reaction is:  
     ATP + [protein]-(L-serine or L-threonine) → ADP + [protein]-(L-serine/threonine)-phosphate + H⁺.  
   This phosphorylation event is central to the modulation of downstream signaling events and serves as the fundamental biochemical activity of the kinase (fabbro2015tenthingsyou pages 1-2, mcdowell2011targetingtheakt pages 9-10).
3. Cofactor Requirements  
   The enzymatic activity of AKT3 requires ATP as a phosphate donor and is dependent on divalent metal ions for proper catalytic function. Magnesium ions (Mg²⁺) are the principal cofactors that facilitate the coordination of ATP within the active site, thereby ensuring efficient phosphotransfer to substrate proteins (fabbro2015tenthingsyou pages 1-2, surucu2010regulationofprotein pages 12-17).
4. Substrate Specificity  
   AKT3 phosphorylates a wide array of proteins on serine and threonine residues. Although more than 100 substrate candidates have been reported, no unique consensus sequence specific to AKT3 has been definitively established due to the considerable overlap with substrates of AKT1 and AKT2. In general, AKT substrates are known to contain motifs that often conform to a consensus such as RXRXXS/T. This requirement for specific basic or hydrophobic residues in defined positions aids in substrate recognition; however, isoform‐specific substrate determinants for AKT3 remain an area for ongoing research (toker2014signalingspecificityin pages 8-10, mcdowell2011targetingtheakt pages 4-5, rakshambikai2015typicalandatypical pages 9-11).
5. Structure  
   AKT3 exhibits a modular structure that is characteristic of AKT isoforms. Its organization comprises three principal domains:

  • The N-terminal pleckstrin homology (PH) domain: This domain is responsible for binding phosphoinositides (e.g., phosphatidylinositol (3,4,5)-trisphosphate or PIP₃) at the plasma membrane, a critical step for its activation. The PH domain confers both membrane localization and plays a role in the conformational regulation of the kinase (rakshambikai2015typicalandatypical pages 4-6, toker2014signalingspecificityin pages 3-5).

  • The central kinase catalytic domain: This domain adopts the typical bilobal architecture observed in protein kinases. The smaller N-terminal lobe, principally composed of β-sheets, and the larger C-terminal lobe, which is enriched in α-helices, together create the active site cleft where ATP binds and the phosphoryl transfer reaction occurs. Within this domain, key structural features such as the activation loop, the C-helix, and elements of the hydrophobic spine are critical to achieving and maintaining an active conformation (fabbro2015tenthingsyou pages 7-9, mcdowell2011targetingtheakt pages 9-10).

  • The C-terminal regulatory tail: Although less well characterized than the other domains, this region is believed to contribute to substrate binding and may contain auto-inhibitory elements that modulate kinase activity under basal conditions. The interplay between the regulatory tail and the catalytic domain is important for fine-tuning the enzyme’s activation status (mcdowell2011targetingtheakt pages 4-5, toker2014signalingspecificityin pages 8-10).

1. Regulation  
   AKT3 is subject to complex regulatory mechanisms that ensure its activity is tightly controlled. Initially maintained in an inactive state by intramolecular interactions that mask its catalytic domain, AKT3 becomes activated upon recruitment to the plasma membrane via its PH domain binding to PIP₃, a product of phosphatidylinositol 3-kinase (PI3K) activity (mcdowell2011targetingtheakt pages 1-2, toker2014signalingspecificityin pages 3-5). Once localized to the membrane, AKT3 undergoes conformational changes that expose critical phosphorylation sites:

  • Phosphorylation of the activation loop by phosphoinositide-dependent kinase 1 (PDK1) is necessary for achieving an active conformation. This event is analogous to the phosphorylation seen in other AKT isoforms and is indispensable for catalytic activity (surucu2010regulationofprotein pages 12-17, mcdowell2011targetingtheakt pages 9-10).

  • A second phosphorylation event occurs at the hydrophobic motif—typically equivalent to the Ser473 residue in AKT1—mediated by the mTOR complex 2 (mTORC2) or, under certain stress conditions, by DNA-dependent protein kinase (DNA-PK). This phosphorylation further stabilizes the active conformation and enhances substrate binding (surucu2010regulationofprotein pages 12-17, mcdowell2011targetingtheakt pages 9-10).

Additional layers of regulation arise from phosphatases such as PHLPP, which dephosphorylate AKT3 to terminate signaling, and from interactions with various adaptor proteins that may influence its subcellular localization and substrate specificity. This regulation by phosphorylation/dephosphorylation cycles is central to controlling the magnitude and duration of AKT3 signaling (toker2014signalingspecificityin pages 1-3, mcdowell2011targetingtheakt pages 2-3).

1. Function  
   AKT3 plays a pivotal role in integrating multiple extracellular signals with intracellular responses. It is involved in controlling processes such as metabolism, cell proliferation, survival, growth, and angiogenesis by phosphorylating an extensive network of substrates. In particular, AKT3 has been highlighted for its critical functions in the following contexts:

  • Brain development: AKT3 is highly expressed in neuronal tissues and is essential for proper brain formation. Genetic studies have revealed that disruption of AKT3 expression leads to a reduction in brain size, reflecting its importance in neural growth and development (mcdowell2011targetingtheakt pages 1-2, toker2014signalingspecificityin pages 7-8).

  • Tumor cell viability: In malignant gliomas, AKT3 supports cell survival and proliferation. Its kinase activity contributes to the maintenance of oncogenic signaling networks, making it a potential therapeutic target in glioblastoma and other brain cancers (mcdowell2011targetingtheakt pages 1-2, mcdowell2011targetingtheakt pages 9-10).

  • Mitochondrial biogenesis and apoptosis: AKT3 is required for the coordination of mitochondrial biogenesis with growth factor–induced increases in cellular energy demands. It also regulates the phosphorylation of the pro-apoptotic protein BAD; down-regulation of AKT3 results in diminished levels of phosphorylated BAD, leading to the activation of caspase-dependent cell death pathways (rakshambikai2015typicalandatypical pages 9-11, surucu2010regulationofprotein pages 12-17).

  • Extracellular matrix modulation: There is evidence that AKT3 may be involved in the regulation of matrix metalloproteinase 13 (MMP13) via interleukin 13–mediated pathways, potentially impacting tissue remodeling and cancer invasiveness (rakshambikai2015typicalandatypical pages 9-11).

1. Other Comments  
   AKT3 is recognized as the least studied isoform among the AKT family, and ongoing investigations aim to clarify its unique roles relative to AKT1 and AKT2. Several small molecule inhibitors targeting the PI3K/AKT signaling pathway, including both ATP-competitive agents and allosteric modulators, have been developed and show promise in preclinical models, particularly in the context of glioblastoma. However, compounds with high specificity for AKT3 remain limited, underscoring the need for further research and development in this area (serafim2021chemicalprobesfor pages 66-71, mcdowell2011targetingtheakt pages 10-10). Dysregulation of AKT3 is associated with a range of pathologies, most notably in neurological disorders and cancers involving aberrant cell survival and proliferation mechanisms. In malignant gliomas, for instance, elevated AKT3 activity contributes to tumor cell viability and resistance to apoptotic signals. Moreover, RNA interference studies have demonstrated that down-regulation of AKT3 reduces phosphorylated BAD levels, thereby triggering caspase-dependent apoptosis—highlighting its critical role in cell survival pathways (rakshambikai2015typicalandatypical pages 9-11, mcdowell2011targetingtheakt pages 1-2).
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