## Phylogeny

• AKT1 is a member of the AGC kinase group and forms the AKT sub-family together with the closely related isoforms AKT2 and AKT3, all sharing PH, catalytic and hydrophobic-motif domains (kumar2005aktcrystalstructure pages 2-3).  
• Orthologous Akt1 proteins are documented in Mus musculus and Rattus norvegicus, reflecting strong conservation across mammals (unknownauthors2010physiologicalregulationof pages 1-3).  
• Invertebrate orthologs exist in Drosophila melanogaster Akt1 and Caenorhabditis elegans akt-1, indicating retention of PI3K→AKT signaling from invertebrates to vertebrates (lawlor2001pkbaktakey pages 4-5).  
• Kinome dendrogram analyses cluster AKT1 within the conserved AGC clade, distinct from PKA, PKC and S6K branches but sharing the catalytic core architecture (armenta2020statisticalmethodsto pages 40-43).

## Reaction Catalyzed

ATP + protein-Ser/Thr → ADP + phospho-protein-Ser/Thr (kumar2025structuralinsightsof pages 18-19).

## Cofactor Requirements

• Catalysis requires a divalent cation; Asp292 of the DFG motif coordinates Mg²⁺, and Mn²⁺ can substitute in vitro (kumar2025structuralinsightsof pages 14-15).

## Substrate Specificity

• Preferred consensus motif: Arg-X-Arg-X-X-Ser/Thr-Φ, where Arg at −5/−3 and a bulky hydrophobic residue (Φ) at +1 are critical for efficient phosphorylation (alessi1996molecularbasisfor pages 4-5).  
• Kinome-wide profiling assigns AKT1 to the canonical RxRxxS/TΦ preference characteristic of AGC kinases (armenta2020statisticalmethodsto pages 40-43).

## Structure

• Domain organisation: N-terminal PH domain (residues 1–≈107), central kinase domain (149–408) and C-terminal extension containing the hydrophobic motif (409–480) (kumar2005aktcrystalstructure pages 2-3).  
• Autoinhibited PH-in conformation sequesters the activation loop; PIP₃ binding induces a ~23° PH-out rotation that exposes Thr308 for phosphorylation (truebestein2021structureofautoinhibited pages 3-4).  
• Active kinase displays DFG-in and αC-in geometry with a Lys179–Glu198 salt bridge and assembled catalytic (Val164/Ala177/Met281) and regulatory (Leu202/Leu213/Tyr272/Phe293/Asp331) spines (kumar2025structuralinsightsof pages 8-9).  
• Phospho-Thr308 is stabilised by His194, Arg273 and Lys297; phospho-Ser473 in the hydrophobic motif interacts with the PH-kinase linker to lock the active state (kumar2025structuralinsightsof pages 14-15).  
• Gatekeeper residue Met227 modulates ATP-site accessibility and inhibitor sensitivity (kumar2025structuralinsightsof pages 8-9).  
• Oncogenic E17K in the PH domain disrupts the PH-kinase interface, increases affinity for PIP₃/PIP₂ and biases the enzyme toward the active conformation (truebestein2021structureofautoinhibited pages 7-8).

## Regulation

• Phosphorylation  
– Thr308 in the activation loop by PDK1 is essential for catalytic competence (hart2011phosphorylationofakt pages 1-2).  
– Ser473 in the hydrophobic motif by mTORC2 maximises activity (hart2011phosphorylationofakt pages 1-2).  
– Thr450 in the turn motif by mTORC2 supports protein stability (truebestein2021structureofautoinhibited pages 7-7).  
– Tyr176 phosphorylation by Src family kinases augments membrane localisation (chan2014posttranslationalregulationof pages 2-3).  
• Dephosphorylation  
– PP2A removes phosphates from Thr308 and Ser473, attenuating signalling (chan2014posttranslationalregulationof pages 1-2).  
– PHLPP specifically dephosphorylates Ser473, thereby inactivating AKT1 (unknownauthors2010physiologicalregulationof pages 3-5).  
• Ubiquitination  
– K63-linked ubiquitination by E3 ligase NEDD4-1 promotes membrane recruitment and activation (chan2014posttranslationalregulationof pages 1-2).  
• Acetylation  
– PCAF-mediated acetylation fine-tunes kinase output (chan2014posttranslationalregulationof pages 1-2).  
• Lipid binding & autoinhibition  
– PH domain recognition of PIP₃ relieves PH-in autoinhibition and enables activation loop phosphorylation (truebestein2021structureofautoinhibited pages 3-4).  
– The unphosphorylated C-tail can dock into the PIF pocket to stabilise an inactive state; allosteric inhibitors mimic this interaction (truebestein2021structureofautoinhibited pages 7-8).

## Function

• AKT1 is ubiquitously expressed and is indispensable for cell survival, proliferation and metabolism across tissues (unknownauthors2010physiologicalregulationof pages 1-3).  
• Upstream regulators: receptor tyrosine kinases → PI3K → PIP₃, with subsequent activation by PDK1 and mTORC2 (bae2022phdomainmediatedautoinhibition pages 9-16).  
• Downstream substrates include GSK3β, FOXO1/3, TSC2, BAD, PRAS40, MDM2, eNOS and AS160, controlling metabolism, apoptosis, cell cycle and angiogenesis (lawlor2001pkbaktakey pages 4-5, iksen2021targetingthepi3kaktmtor pages 4-5).  
• Phosphorylation-dependent binding of 14-3-3 sequesters substrates such as FOXO, while HSP90 stabilises AKT1 itself (unknownauthors2010physiologicalregulationof pages 1-3).  
• Activated AKT1 drives the PI3K-AKT-mTOR axis to promote proliferation, migration, metabolic adaptation and resistance to apoptosis (davies2015tumorswithakt1e17k pages 1-5).

## Inhibitors

• AZD5363 (capivasertib): ATP-competitive inhibitor; 0.1 µM reduces colony formation >80 % and achieves 76–89 % tumour growth inhibition in AKT1-E17K breast explants (davies2015tumorswithakt1e17k pages 13-16).  
• MK-2206: allosteric inhibitor stabilising the PH-in state; produces 56–58 % tumour inhibition and robust downstream substrate suppression in AKT1-E17K models (davies2015tumorswithakt1e17k pages 13-16).  
• Miransertib (ARQ 092) and ARQ 751: allosteric inhibitors with biochemical IC₅₀ values of 5–16 nM against AKT isoforms; block Ser473 phosphorylation and membrane translocation of AKT1-E17K (yu2015targetingakt1e17kand pages 7-9).  
• GSK690693: ATP-competitive inhibitor; IC₅₀ 180 nM for AKT1 and evaluated in solid and haematologic tumours (iksen2021targetingthepi3kaktmtor pages 8-10).

## Other Comments

• The E17K hotspot in the PH domain occurs in 1–8 % of breast, colorectal, lung, prostate and bladder cancers and in ~90 % of Proteus syndrome cases, conferring constitutive membrane localisation and pathway hyper-activation (chen2020effectofakt1 pages 2-3, boormans2010e17ksubstitutionin pages 3-4, yu2015targetingakt1e17kand pages 24-25).  
• AKT1-E17K enhances downstream phosphorylation of PRAS40, GSK3β and S6, promotes anchorage-independent growth and renders tumours sensitive to AKT inhibitors (davies2015tumorswithakt1e17k pages 1-5).  
• Additional activating or destabilising mutations cluster at the PH-kinase interface and activation loop, driving growth-factor-independent signalling (truebestein2021structureofautoinhibited pages 3-4).

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