Phylogeny  
AKT3 (Protein Kinase B γ) is placed within the AGC kinase group, Protein Kinase B subfamily, in the human kinome catalogue of Manning et al. 2002 (degan2021emergingrolesfor pages 1-2). Human paralogs are AKT1 and AKT2, each sharing greater than 80 % amino-acid identity with AKT3 (kumar2005aktcrystalstructure pages 2-3). Orthologous genes are recorded in mouse, rat, zebrafish, Drosophila melanogaster and Caenorhabditis elegans, demonstrating broad metazoan conservation (unknownauthors2018noncanonicalpi3kinasesignaling pages 66-71).

Reaction Catalyzed  
ATP + protein L-serine/threonine ⇌ ADP + protein O-phospho-L-serine/threonine (unknownauthors2010physiologicalregulationof pages 1-3, kumar2025structuralinsightsof pages 1-3).

Cofactor Requirements  
Catalytic activity requires divalent cations; Mg²⁺ is essential and Mn²⁺ can substitute in vitro (degan2021emergingrolesfor pages 1-2, mundi2016aktincancer pages 1-4).

Substrate Specificity  
AKT3 recognizes the consensus motif RXRXXS/TΦ, favouring arginine at –5 and –3, a bulky hydrophobic residue at +1 (Φ), and proline at +2 to enhance 14-3-3 binding (toker2014signalingspecificityin pages 3-5, degan2021emergingrolesfor pages 1-2).

Structure  
Domain organisation – N-terminal pleckstrin homology (PH) domain (~5–108) binds PtdIns(3,4,5)P₃/PtdIns(3,4)P₂ via Lys14, Arg23 and Arg86; a poorly conserved PH-kinase linker (~108–148); a bilobal kinase domain (~149–405) containing the Gly-rich loop (GKGTFG), gatekeeper Met227, catalytic loop YRDLKLEN, Mg²⁺-binding DFG motif Asp292-Phe293-Gly294 and aligned regulatory/catalytic hydrophobic spines; and a C-terminal extension (~409–480) harbouring the FPQFSY motif with Ser472 (kumar2025structuralinsightsof pages 3-4, kumar2025structuralinsightsof pages 8-9, unknownauthors2016studiesoncell pages 12-14).  
Three-dimensional organisation – Structural studies reveal an autoinhibited “PH-in” conformation; lipid binding induces a “PH-out” rotation exposing Thr305 for phosphorylation (calleja20093dstructureand pages 15-15, kumar2025structuralinsightsof pages 3-4). Activation pulls the αC-helix inward, locks the DFG motif “in” and completes R-spine assembly to form an active catalytic cleft (kumar2025structuralinsightsof pages 9-10). A Val228 substitution in the Gly-rich loop is unique to AKT3 and may influence nucleotide or inhibitor accommodation (kumar2025structuralinsightsof pages 4-8).

Regulation  
Phosphorylation – PDK1 phosphorylates Thr305 in the activation loop, priming catalytic activity (kumar2025structuralinsightsof pages 3-4). mTORC2 phosphorylates Ser472 in the hydrophobic motif for maximal activity (toker2014signalingspecificityin pages 1-3). TORC2 also phosphorylates Thr450 co-translationally, increasing protein stability (toker2014signalingspecificityin pages 1-3). Stimulus-dependent phosphorylation of Ser477 and Thr479 provides an additional activation layer (hassan2024aktkinasesas pages 3-6).  
Ubiquitination – TRAF6 attaches Lys63-linked chains to Lys8 and Lys14 within the PH domain, facilitating membrane recruitment (hassan2024aktkinasesas pages 3-6, unknownauthors2018noncanonicalpi3kinasesignaling pages 66-71).  
Dephosphorylation – PP2A removes pThr305, whereas PHLPP1 selectively dephosphorylates pSer472 to terminate signalling (toker2014signalingspecificityin pages 3-5, degan2021emergingrolesfor pages 1-2).  
Allosteric control – Binding of PtdIns(3,4,5)P₃ to the PH domain releases autoinhibition; the oncogenic E17K mutation enhances lipid affinity, driving constitutive activation (yu2015targetingakt1e17kand pages 24-25, toker2014signalingspecificityin pages 1-3).

Function  
Expression – Highest in brain and testes, with lower levels in lung and mammary tissue (kumar2025structuralinsightsof pages 1-3, hassan2024aktkinasesas pages 1-2).  
Upstream signalling – Class I PI3-kinase generates PtdIns(3,4,5)P₃; PTEN antagonises this signal; PDK1 and mTORC2 confer activating phosphorylations (toker2014signalingspecificityin pages 3-5, unknownauthors2010physiologicalregulationof pages 1-3).  
Downstream actions – AKT3 phosphorylates BAD, procaspase-9, FOXO transcription factors, GSK3 and TSC2, promoting survival, metabolism and proliferation (mundi2016aktincancer pages 4-8).  
Physiological and pathological roles – AKT3 supports post-natal brain growth, coordinates mitochondrial biogenesis and maintains glioma cell viability; it modulates IL-13-induced MMP13 expression in inflammatory contexts (degan2021emergingrolesfor pages 1-2).

Inhibitors  
MK-2206 is an allosteric pan-AKT inhibitor that suppresses AKT3 activity (mundi2016aktincancer pages 27-33). Capivasertib (AZD5363) and GSK690693 are ATP-competitive inhibitors with documented potency against AKT3 (kumar2005aktcrystalstructure pages 2-3, mundi2016aktincancer pages 27-33).

Other Comments  
Akt3-null mice display approximately 25 % reduced brain mass, indicating a non-redundant neurodevelopmental role (mundi2016aktincancer pages 4-8). Hyperactivation of AKT3 caused by PTEN loss or PI3K pathway mutations contributes to oncogenesis and therapy resistance, particularly in glioblastoma (romano2013theroleof pages 1-2, kumar2005aktcrystalstructure pages 2-3). The E17K PH-domain mutation confers constitutive activation and imparts resistance to certain allosteric inhibitors (yu2015targetingakt1e17kand pages 24-25, degan2021emergingrolesfor pages 1-2). Copy-number gains or activating mutations of AKT3 are reported in sporadic tumours and overgrowth syndromes (menges2024alterationsofthe pages 1-4).

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