1. Phylogeny  
   AKT1 (also known as Protein kinase B alpha, PKBα, or RAC‐PK‐alpha) is an evolutionarily conserved serine/threonine protein kinase that belongs to the AGC family of kinases. Orthologs of AKT1 are found in a wide range of eukaryotic species, from invertebrates such as C. elegans to vertebrates including mammals, demonstrating a high level of amino acid conservation in both the regulatory pleckstrin homology (PH) domain and the catalytic kinase domain (hanada2004structureregulationand pages 1-2, lindsley2010theaktpkbfamily pages 1-2). Phylogenetic studies show that the AKT family, which includes AKT1, AKT2, and AKT3, emerged early during metazoan evolution and has maintained nearly identical domain architectures across species. The conservation of the catalytic core and regulatory modules in AKT1 underscores its central role in fundamental signaling pathways such as those regulating metabolism, cell survival, and proliferation (scheeff2005structuralevolutionof pages 2-3, hanada2004structureregulationand pages 1-2). Numerous analyses of the human kinome further position AKT1 within the evolutionary core set of AGC kinases alongside PDK1, S6K, RSK, and SGK, highlighting its importance from the Last Eukaryotic Common Ancestor through to modern vertebrates (hanada2004structureregulationand pages 1-2, lindsley2010theaktpkbfamily pages 1-2).
2. Reaction Catalyzed  
   AKT1 catalyzes the phosphorylation of serine and threonine residues on substrate proteins by transferring the γ-phosphate from ATP. The general reaction can be written as:  
     ATP + [protein]-(L-serine/L-threonine) → ADP + [protein]-(L-serine/threonine)-phosphate + H⁺  
   This phosphorylation reaction is central to the modulation of numerous downstream signaling proteins involved in processes such as cell growth, metabolism, and survival (barnett2005theaktpkbfamily pages 14-14, manning2007aktpkbsignalingnavigating pages 5-6).
3. Cofactor Requirements  
   The catalytic activity of AKT1 depends on the presence of Mg²⁺, which acts as a cofactor to coordinate ATP in the active site and to facilitate the phosphoryl transfer reaction. ATP itself is essential as the phosphate donor in this reaction, and the Mg²⁺ ion is required to stabilize the transition state during catalysis (scheeff2005structuralevolutionof pages 2-3, newton2003regulationofthe pages 2-3).
4. Substrate Specificity  
   AKT1 exhibits substrate specificity defined by its preference for phosphorylating serine/threonine residues that are embedded in a specific consensus motif. The most commonly recognized motif by AKT1 is generally denoted as R-X-R-X-X-[S/T], where the presence of basic residues upstream of the target serine or threonine is critical for substrate recognition (manning2007aktpkbsignalingnavigating pages 4-5, hanada2004structureregulationand pages 14-14). Although over 100 candidate substrates have been reported, many share this minimal recognition motif, and the lack of absolute isoform specificity among the substrates suggests that factors such as subcellular localization and additional protein-protein interactions modulate AKT1 substrate selection (barnett2005theaktpkbfamily pages 2-3, manning2007aktpkbsignalingnavigating pages 4-5).
5. Structure  
   AKT1 is organized into distinct functional domains. At its N-terminus, it possesses a pleckstrin homology (PH) domain that mediates interaction with phosphoinositide lipids (such as PtdIns(3,4,5)P₃), which is imperative for its recruitment to the plasma membrane and subsequent activation. Central to the protein is the catalytic kinase domain, which adopts the typical bilobed structure observed in all protein kinases; this domain contains the ATP-binding cleft, the activation loop, and the αC-helix that are critical for enzymatic activity (hanada2004structureregulationand pages 2-4, newton2003regulationofthe pages 2-3). A short regulatory tail at the C-terminus, though less well structured, is involved in modulating kinase activity. Essential regulatory phosphorylation sites are located in the activation loop at Thr308 and in the hydrophobic motif at Ser473, both of which must be phosphorylated for full AKT1 activation (hanada2004structureregulationand pages 14-14, manning2017aktpkbsignalingnavigating pages 28-29). The overall three-dimensional organization, as determined by crystallographic studies and supported by AlphaFold models, reveals that the PH domain and the kinase domain can engage in an intramolecular interaction that maintains AKT1 in an autoinhibited conformation in the absence of membrane-bound phosphoinositides (manning2017aktpkbsignalingnavigating pages 3-4, lindsley2010theaktpkbfamily pages 17-17).
6. Regulation  
   AKT1 is regulated by multiple mechanisms that converge to control its activation and deactivation. Under resting conditions, AKT1 remains in the cytosol in an autoinhibited state, with its PH domain masking the catalytic activity of the kinase domain. Following stimulation by growth factors or insulin, class I phosphoinositide 3-kinases (PI3K) are activated and generate phosphoinositide lipids such as PtdIns(3,4,5)P₃, which bind the PH domain of AKT1 and facilitate its translocation to the plasma membrane (hanada2004structureregulationand pages 1-2, vanhaesebroeck2000thepi3k–pdk1connection pages 3-4). At the membrane, AKT1 undergoes critical phosphorylation events: PDK1 phosphorylates Thr308 within the activation loop, and mTOR complex 2 (mTORC2) phosphorylates Ser473 in the hydrophobic motif. These phosphorylation events are indispensable for full catalytic activation and result in substantial conformational rearrangements that enable substrate binding (manning2017aktpkbsignalingnavigating pages 3-4, lindsley2010theaktpkbfamily pages 17-17). Negative regulatory mechanisms include the action of phosphatases such as PTEN, which dephosphorylates PtdIns(3,4,5)P₃, thereby reducing membrane localization of AKT1, and PHLPP, which specifically dephosphorylates Ser473, leading to attenuation of AKT1 activity (lindsley2010theaktpkbfamily pages 19-20, manning2017aktpkbsignalingnavigating pages 25-26). Allosteric inhibition is another modality by which AKT1 activity can be modulated; certain small molecule inhibitors bind to the interface between the PH domain and the kinase domain, locking AKT1 in an inactive conformation without competing with ATP (kung2016structuralbasisfor pages 3-4, barnett2005theaktpkbfamily pages 6-7).
7. Function  
   AKT1 is a central mediator in signaling pathways that control vital cellular processes. It phosphorylates a large array of proteins involved in cell survival, growth, and metabolism, thereby influencing apoptosis, cell cycle progression, and protein synthesis. A key role of AKT1 is its involvement in insulin signaling, where it facilitates the insulin-induced translocation of the GLUT4 glucose transporter to the cell surface and promotes glycogen synthesis through the inactivation of glycogen synthase kinase 3 (GSK3) (manning2007aktpkbsignalingnavigating pages 19-22, manning2017aktpkbsignalingnavigating pages 22-23). In addition, AKT1 regulates angiogenesis through phosphorylation of substrates such as endothelial nitric oxide synthase (eNOS), which is critical for nitric oxide production and vascular homeostasis (manning2017aktpkbsignalingnavigating pages 28-29, lindsley2010theaktpkbfamily pages 17-17). AKT1 is also implicated in cell proliferation and survival by phosphorylating transcription factors (e.g., FOXO proteins), thereby inhibiting pro-apoptotic gene expression, and by activating mTORC1 signaling to stimulate protein synthesis (barnett2005theaktpkbfamily pages 14-14, manning2007aktpkbsignalingnavigating pages 19-22). Its broad substrate specificity and integration into numerous signaling cascades underscore the importance of AKT1 in maintaining cellular homeostasis; dysregulation of its activity is commonly associated with oncogenic transformation and metabolic disorders (manning2017aktpkbsignalingnavigating pages 25-26, barnett2005theaktpkbfamily pages 14-14).
8. Other Comments  
   Several small molecule inhibitors targeting AKT1 have been identified in preclinical studies, including both ATP-competitive inhibitors and allosteric inhibitors that exploit conformational differences conferred by the PH domain. For example, compounds such as MK-2206 have been shown to effectively inhibit AKT isoforms by binding to the inactive conformation and preventing the necessary phosphorylation events for full activation (lindsley2010theaktpkbfamily pages 17-17, barnett2005theaktpkbfamily pages 6-7). AKT1 has been implicated in various pathological conditions, most notably in cancer, where activating mutations—such as the E17K substitution in the PH domain—lead to constitutive membrane localization and aberrant kinase activity (manning2017aktpkbsignalingnavigating pages 25-26, vanhaesebroeck2000thepi3k–pdk1connection pages 6-6). Abnormal AKT1 signaling due to overactivation or loss of negative regulation (for instance, through PTEN mutation) is a frequent finding in many human tumors and has spurred the development of targeted therapies aimed at dampening AKT activity (barnett2005theaktpkbfamily pages 14-14, manning2007aktpkbsignalingnavigating pages 19-22). Clinical investigations continue to assess the efficacy of these inhibitors, with the goal of reducing oncogenic signaling while minimizing adverse effects related to interference with normal metabolic pathways (manning2017aktpkbsignalingnavigating pages 25-26, lindsley2010theaktpkbfamily pages 15-16).
9. References
10. Barnett, S., Bilodeau, M., & Lindsley, C. (2005). The akt/pkb family of protein kinases: a review of small molecule inhibitors and progress towards target validation. Current Topics in Medicinal Chemistry, 5:109-125. https://doi.org/10.2174/1568026053507714
11. Hanada, M., Feng, J., & Hemmings, B. A. (2004). Structure, regulation and function of pkb/akt—a major therapeutic target. Biochimica et Biophysica Acta (BBA) - Proteins and Proteomics, 1697:3-16. https://doi.org/10.1016/j.bbapap.2003.11.009
12. Lindsley, C. (2010). The akt/pkb family of protein kinases: a review of small molecule inhibitors and progress towards target validation: a 2009 update. Current Topics in Medicinal Chemistry, 10:458-477. https://doi.org/10.2174/156802610790980602
13. Manning, B. D., & Cantley, L. C. (2007). Akt/pkb signaling: navigating downstream. Cell, 129:1261-1274. https://doi.org/10.1016/j.cell.2007.06.009
14. Manning, B. D., & Toker, A. (2017). Akt/pkb signaling: navigating the network. Cell, 169:381-405. https://doi.org/10.1016/j.cell.2017.04.001
15. Newton, A. C. (2003). Regulation of the ABC kinases by phosphorylation: protein kinase C as a paradigm. Biochemical Journal, 370:361-371. https://doi.org/10.1042/bj20021626
16. Vanhaesebroeck, B., & Alessi, D. R. (2000). The PI3K–PDK1 connection: more than just a road to PKB. Biochemical Journal, 346:561-576. https://doi.org/10.1042/bj3460561
17. Bain, J., et al. (2007). The selectivity of protein kinase inhibitors: a further update. Biochemical Journal, 408:297-315. https://doi.org/10.1042/bj20070797
18. Scheeff, E. D., & Bourne, P. E. (2005). Structural evolution of the protein kinase–like superfamily. PLoS Computational Biology, 1(6):e49. https://doi.org/10.1371/journal.pcbi.0010049
19. (Additional details on evolutionary conservation and domain architecture are supported by the integration of data from hanada2004structureregulationand pages 1-2, lindsley2010theaktpkbfamily pages 1-2, and newton2003regulationofthe pages 2-3.)

References

1. (barnett2005theaktpkbfamily pages 14-14): Stanley Barnett, Mark Bilodeau, and Craig Lindsley. The akt/pkb family of protein kinases: a review of small molecule inhibitors and progress towards target validation. Current Topics in Medicinal Chemistry, 5:109-125, Apr 2005. URL: https://doi.org/10.2174/1568026053507714, doi:10.2174/1568026053507714. This article has 205 citations and is from a peer-reviewed journal.
2. (hanada2004structureregulationand pages 1-2): Masahito Hanada, Jianhua Feng, and Brian A Hemmings. Structure, regulation and function of pkb/akt—a major therapeutic target. Biochimica et Biophysica Acta (BBA) - Proteins and Proteomics, 1697:3-16, Mar 2004. URL: https://doi.org/10.1016/j.bbapap.2003.11.009, doi:10.1016/j.bbapap.2003.11.009. This article has 1100 citations.
3. (lindsley2010theaktpkbfamily pages 1-2): Craig Lindsley. The akt/pkb family of protein kinases: a review of small molecule inhibitors and progress towards target validation: a 2009 update. Current Topics in Medicinal Chemistry, 10:458-477, Mar 2010. URL: https://doi.org/10.2174/156802610790980602, doi:10.2174/156802610790980602. This article has 163 citations and is from a peer-reviewed journal.
4. (lindsley2010theaktpkbfamily pages 17-17): Craig Lindsley. The akt/pkb family of protein kinases: a review of small molecule inhibitors and progress towards target validation: a 2009 update. Current Topics in Medicinal Chemistry, 10:458-477, Mar 2010. URL: https://doi.org/10.2174/156802610790980602, doi:10.2174/156802610790980602. This article has 163 citations and is from a peer-reviewed journal.
5. (lindsley2010theaktpkbfamily pages 19-20): Craig Lindsley. The akt/pkb family of protein kinases: a review of small molecule inhibitors and progress towards target validation: a 2009 update. Current Topics in Medicinal Chemistry, 10:458-477, Mar 2010. URL: https://doi.org/10.2174/156802610790980602, doi:10.2174/156802610790980602. This article has 163 citations and is from a peer-reviewed journal.
6. (manning2017aktpkbsignalingnavigating pages 3-4): Brendan D. Manning and Alex Toker. Akt/pkb signaling: navigating the network. Cell, 169:381-405, Apr 2017. URL: https://doi.org/10.1016/j.cell.2017.04.001, doi:10.1016/j.cell.2017.04.001. This article has 3789 citations and is from a highest quality peer-reviewed journal.
7. (newton2003regulationofthe pages 2-3): Alexandra C. NEWTON. Regulation of the abc kinases by phosphorylation: protein kinase c as a paradigm. Biochemical Journal, 370:361-371, Mar 2003. URL: https://doi.org/10.1042/bj20021626, doi:10.1042/bj20021626. This article has 1070 citations and is from a domain leading peer-reviewed journal.
8. (barnett2005theaktpkbfamily pages 2-3): Stanley Barnett, Mark Bilodeau, and Craig Lindsley. The akt/pkb family of protein kinases: a review of small molecule inhibitors and progress towards target validation. Current Topics in Medicinal Chemistry, 5:109-125, Apr 2005. URL: https://doi.org/10.2174/1568026053507714, doi:10.2174/1568026053507714. This article has 205 citations and is from a peer-reviewed journal.
9. (barnett2005theaktpkbfamily pages 6-7): Stanley Barnett, Mark Bilodeau, and Craig Lindsley. The akt/pkb family of protein kinases: a review of small molecule inhibitors and progress towards target validation. Current Topics in Medicinal Chemistry, 5:109-125, Apr 2005. URL: https://doi.org/10.2174/1568026053507714, doi:10.2174/1568026053507714. This article has 205 citations and is from a peer-reviewed journal.
10. (hanada2004structureregulationand pages 14-14): Masahito Hanada, Jianhua Feng, and Brian A Hemmings. Structure, regulation and function of pkb/akt—a major therapeutic target. Biochimica et Biophysica Acta (BBA) - Proteins and Proteomics, 1697:3-16, Mar 2004. URL: https://doi.org/10.1016/j.bbapap.2003.11.009, doi:10.1016/j.bbapap.2003.11.009. This article has 1100 citations.
11. (hanada2004structureregulationand pages 2-4): Masahito Hanada, Jianhua Feng, and Brian A Hemmings. Structure, regulation and function of pkb/akt—a major therapeutic target. Biochimica et Biophysica Acta (BBA) - Proteins and Proteomics, 1697:3-16, Mar 2004. URL: https://doi.org/10.1016/j.bbapap.2003.11.009, doi:10.1016/j.bbapap.2003.11.009. This article has 1100 citations.
12. (lindsley2010theaktpkbfamily pages 15-16): Craig Lindsley. The akt/pkb family of protein kinases: a review of small molecule inhibitors and progress towards target validation: a 2009 update. Current Topics in Medicinal Chemistry, 10:458-477, Mar 2010. URL: https://doi.org/10.2174/156802610790980602, doi:10.2174/156802610790980602. This article has 163 citations and is from a peer-reviewed journal.
13. (manning2007aktpkbsignalingnavigating pages 19-22): Brendan D. Manning and Lewis C. Cantley. Akt/pkb signaling: navigating downstream. Cell, 129:1261-1274, Jun 2007. URL: https://doi.org/10.1016/j.cell.2007.06.009, doi:10.1016/j.cell.2007.06.009. This article has 7670 citations and is from a highest quality peer-reviewed journal.
14. (manning2007aktpkbsignalingnavigating pages 4-5): Brendan D. Manning and Lewis C. Cantley. Akt/pkb signaling: navigating downstream. Cell, 129:1261-1274, Jun 2007. URL: https://doi.org/10.1016/j.cell.2007.06.009, doi:10.1016/j.cell.2007.06.009. This article has 7670 citations and is from a highest quality peer-reviewed journal.
15. (manning2007aktpkbsignalingnavigating pages 5-6): Brendan D. Manning and Lewis C. Cantley. Akt/pkb signaling: navigating downstream. Cell, 129:1261-1274, Jun 2007. URL: https://doi.org/10.1016/j.cell.2007.06.009, doi:10.1016/j.cell.2007.06.009. This article has 7670 citations and is from a highest quality peer-reviewed journal.
16. (manning2017aktpkbsignalingnavigating pages 22-23): Brendan D. Manning and Alex Toker. Akt/pkb signaling: navigating the network. Cell, 169:381-405, Apr 2017. URL: https://doi.org/10.1016/j.cell.2017.04.001, doi:10.1016/j.cell.2017.04.001. This article has 3789 citations and is from a highest quality peer-reviewed journal.
17. (manning2017aktpkbsignalingnavigating pages 25-26): Brendan D. Manning and Alex Toker. Akt/pkb signaling: navigating the network. Cell, 169:381-405, Apr 2017. URL: https://doi.org/10.1016/j.cell.2017.04.001, doi:10.1016/j.cell.2017.04.001. This article has 3789 citations and is from a highest quality peer-reviewed journal.
18. (manning2017aktpkbsignalingnavigating pages 28-29): Brendan D. Manning and Alex Toker. Akt/pkb signaling: navigating the network. Cell, 169:381-405, Apr 2017. URL: https://doi.org/10.1016/j.cell.2017.04.001, doi:10.1016/j.cell.2017.04.001. This article has 3789 citations and is from a highest quality peer-reviewed journal.
19. (vanhaesebroeck2000thepi3k–pdk1connection pages 3-4): Bart VANHAESEBROECK and Dario R. ALESSI. The pi3k–pdk1 connection: more than just a road to pkb. Biochemical Journal, 346:561-576, Mar 2000. URL: https://doi.org/10.1042/bj3460561, doi:10.1042/bj3460561. This article has 2253 citations and is from a domain leading peer-reviewed journal.
20. (vanhaesebroeck2000thepi3k–pdk1connection pages 6-6): Bart VANHAESEBROECK and Dario R. ALESSI. The pi3k–pdk1 connection: more than just a road to pkb. Biochemical Journal, 346:561-576, Mar 2000. URL: https://doi.org/10.1042/bj3460561, doi:10.1042/bj3460561. This article has 2253 citations and is from a domain leading peer-reviewed journal.
21. (kung2016structuralbasisfor pages 3-4): Jennifer E. Kung and Natalia Jura. Structural basis for the non-catalytic functions of protein kinases. Structure, 24 1:7-24, Jan 2016. URL: https://doi.org/10.1016/j.str.2015.10.020, doi:10.1016/j.str.2015.10.020. This article has 184 citations and is from a domain leading peer-reviewed journal.
22. (scheeff2005structuralevolutionof pages 2-3): Eric Scheeff and Philip Bourne. Structural evolution of the protein kinase–like superfamily. PLoS Computational Biology, Sep 2005. URL: https://doi.org/10.1371/journal.pcbi.0010049, doi:10.1371/journal.pcbi.0010049. This article has 354 citations and is from a highest quality peer-reviewed journal.