Molecular Modeling Studies of the Akt PH Domain and Its Interaction with Phosphoinositides

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The serine-threonine protein kinase Akt is a direct downstream target of phosphatidylinositol 3-kinase (PI3-K). The PI3-K-generated phospholipids regulate Akt activity via directly binding to the Akt PH domain. The binding of PI3-K-generated phospholipids is critical to the relocation of Akt to the plasma membrane, which plays an important role in the process of Akt activation. Activation of the PI3-K/Akt signaling pathway promotes cell survival. To elucidate the structural basis of the interaction of PI3-K-generated phospholipids with the Akt PH domain with the objective of carrying out structure-based drug design, we modeled the three-dimensional structure of the Akt PH domain. Comparative modeling-based methods were employed, and the modeled Akt structure was used in turn to construct structural models of Akt in complex with selected PI3-K-generated phospholipids using the computational docking approach. The model of the Akt PH domain consists of seven $\beta$-strands forming two antiparallel $\beta$-sheets capped by a C-terminal $\alpha$-helix. The $\beta_1-\beta_2$, $\beta_3-\beta_4$, and $\beta_6-\beta_7$ loops form a positively charged pocket that can accommodate the PI3-K-generated phospholipids in a complementary fashion through specific hydrogen-bonding interactions. The residues Lys14, Arg25, Tyr38, Arg48, and Arg86 form the bottom of the binding pocket and specifically interact with the 3- and 4-phosphate groups of the phospholipids, while residues Thr21 and Arg23 are situated at the wall of the binding pocket and bind to the 1-phosphate group. The predicted binding mode is consistent with known site-directed mutagenesis data, which reveal that mutation of these crucial residues leads to the loss of Akt activity. Moreover, our model can be used to predict the binding affinity of PI3-K-generated phospholipids and rationalize the specificity of the Akt PH domain for PI(3,4)P2, as opposed to other phospholipids such as PI(3)P and PI(3,4,5)P3. Taken together, our modeling studies provide an improved understanding of the molecular interactions present between the Akt PH domain and the PI3-K-generated phospholipids, thereby providing a solid structural basis for the design of novel, high-affinity ligands useful in modulating the activity of Akt.

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