Regulation of human Akt1 by phosphatidylinositol (3,4,5)-trisphosphate lipid species

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Akt1 is a membrane-associated serine/threonine-protein kinase known to mediate the phosphorylation of more than 100 metabolic and mitogenic substrates regulating growth, proliferation, protein synthesis, or glucose metabolism. Akt1 activation is coupled to the accumulation of phosphatidylinositol (3,4,5)-trisphosphate ($PI(3,4,5)P_3$) in the cytosolic leaflet of the plasma membrane. Akt1 binds to $PI(3,4,5)P_3$ through its lipid binding Pleckstrin Homology (PH) domain. However, $PI(3,4,5)P_3$ is actually a class of lipids consisting, in fact, of species of various acyl chain compositions, which differ in terms of length and saturation. Thus, a question arises if this variability plays a role in modulating the interactions between the Akt1 and $PI(3,4,5)P_3$ and, therefore, could influence the signaling outcomes.

To address this question, a bottom-up approach with purified components was applied. Purified full-length Akt1 interactions with membrane systems containing different $PI(3,4,5)P_3$ species was assessed by complementary biochemical and biophysical techniques. Our results show that Akt1 membrane translocation is associated with significant conformational change. We also show that Akt1-membrane binding affinity is $PI(3,4,5)P_3$ species dependent. Additionally, Akt1 binding to different $PI(3,4,5)P_3$ species influences its kinase activity. Thus, our work demonstrates that the $PI(3,4,5)P_3$ acyl chain composition can modulate Akt1 membrane binding and, consequently, its kinase activity. It, therefore, suggests an additional layer of complexity regarding the ability of cells to manipulate enzymatic activities and selective downstream signaling pathways.