Testing of parameters for a biologically accurate brain membrane and molecular dynamics simulations exploration of membrane interactions and conformational changes exhibited by p110α and its oncogenic mutants

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Abstract

Phosphatidylinositide 3-kinases are a family of enzymes which are involved in the regulation of cell growth and proliferation via signalling pathways. This, in turn, means they are linked with cancer development through mutations borne by the genes which encode them. One of these oncogenes, PIK3CA, encodes the catalytic subunit of p110α. This study will focus on p110α's interaction with a phospholipid bilayer, using computational techniques, in an effort to better understand this protein and the effect the cancer-related mutations have on its activity.

In order to model the phospholipid bilayer in a biologically and physiologically accurate manner, with all key components present in their correct proportions, model parameters for the components had to be produced and tested in small binary systems. The components of the membrane used include the phospholipids POPC, POPE, POPS and PIP_2, as well as sphingomyelin and cholesterol.

Using these new parameters for the components of a phospholipid bilayer, molecular dynamics simulations were run of the activated p110α subunit and two of its oncogenic mutants (E545K, H1047R) in the presence of a realistic brain lipid membrane. The results will pave the way to the development of drugs which will serve to inhibit the pathway when necessary, in an effort to control and reduce the incidence of cancer.

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