S1-2

Crystal Structure of the PTEN Tumor Suppressor: Implications for Its Phosphoinositide Phosphatase Activity and Membrane Association

Jie-Oh Lee*, Haijuan Yang[1] and Nikola Pavletich[1]

Department of Chemistry, Korea Advanced Insititute of Sciecne and Technology

[1] Memorial Sloan Kettering Cancer Center and Howard Hughes Medical Institute

The PTEN tumor suppressor is mutated in diverse human cancers and in hereditary cancer predisposition syndromes. PTEN is a phosphatase that can act on both polypeptide and phosphoinositide substrates in vitro. The PTEN structure reveals a phosphatase domain similar to protein phosphatases but having an enlarged active site important for the accommodation of the phosphoinositide substrate. The structure also reveals that PTEN has a C2 domain. The PTEN C2 domain binds phospholipid membranes in vitro and mutation of lysine residues that could mediate this reduces PTEN's membrane affinity and its ability to suppress the growth of glioblastoma tumor cells. The phosphatase and C2 domains associate across an extensive interface, suggesting that the C2 domain may serve to productively position the catalytic domain
on the membrane.