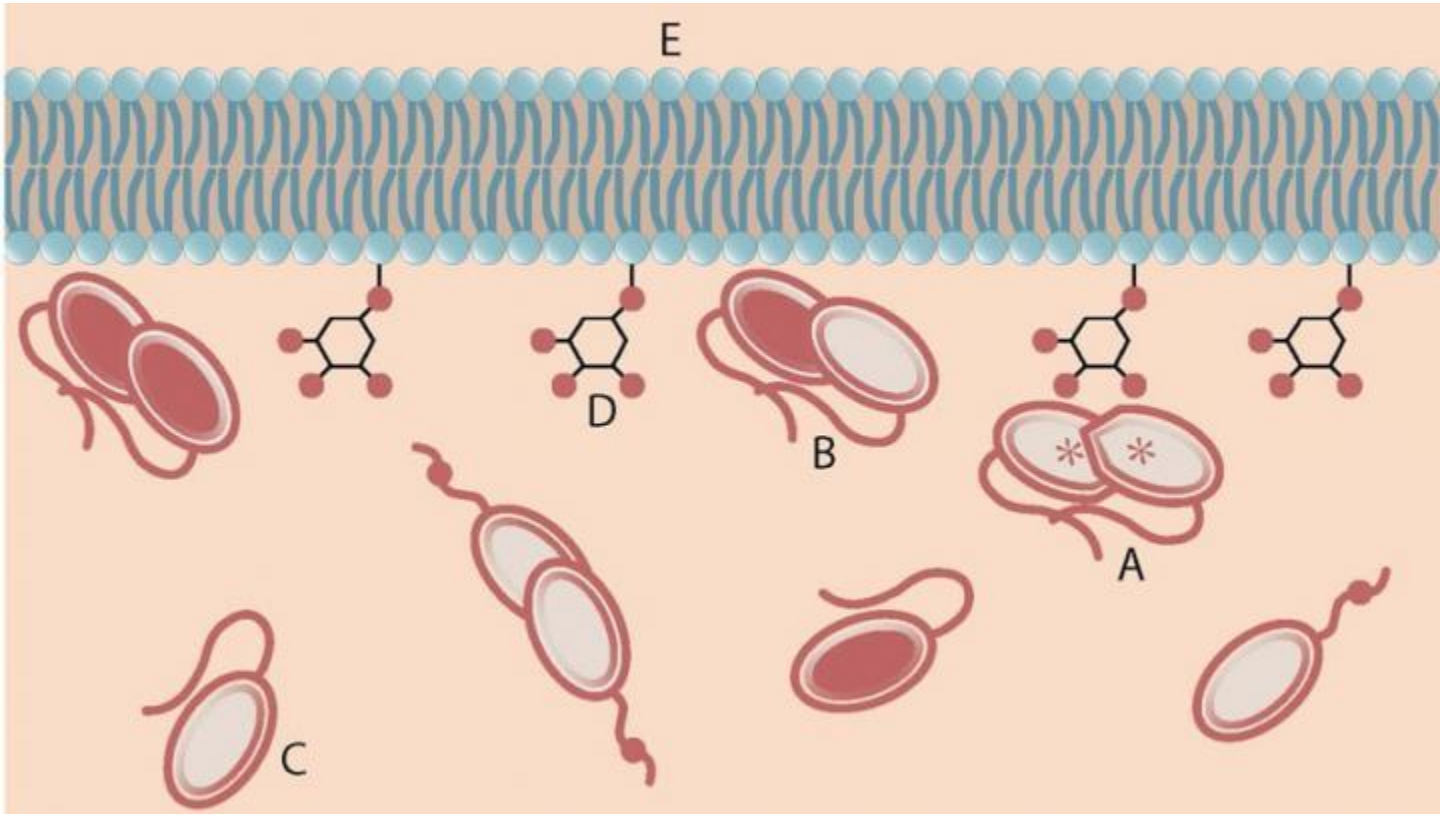
Identifying the Structure of a Tumor-Suppressing Protein



An activated PTEN dimer that contains two non-mutant proteins (A) can transform the functional lipid (D) on the cellular membrane (E) into a chemical form that tunes down cancer predilection. Dimers that contain a mutated protein (B), or PTEN monomers cannot transform the functional lipid. Image: Carnegie Mellon University

The dimer structure of an important tumor-suppressing protein, phosphatase and tensin homolog (PTEN), the second most frequently mutated protein found in human cancer, has been established by an international group of researchers carrying out studies using the BioCAT beamline 18ID at the U.S. Department of Energy's Advanced Photon Source (APS), an Office of Science user facility. Their findings provide new insights into how the protein regulates cell growth and how mutations in the gene that encodes the protein can lead to cancer. The study was published online in *Structure*, and will appear in the October 6, 2015 issue.

Phosphatase and tensin homolog is a known tumor suppressing protein that is encoded by the PTEN gene. When expressed normally, the protein acts as an enzyme at the cell membrane, instigating a complex biochemical reaction that regulates the cell cycle and prevents cells from growing or dividing in an unregulated fashion. Each cell in the body contains two copies of the PTEN gene, one inherited from each parent. When there is a mutation in one or both of the PTEN genes, it interferes with the protein's enzymatic activity and, as a result inhibits its tumor suppressing ability.

Membrane-incorporated and membrane-associated proteins like PTEN make up one-third of all proteins in our body; many important functions in health and disease depend on their proper

functioning. Despite PTEN's importance in human physiology and disease, there is a critical lack of understanding of the complex mechanisms that govern its activity.

Recently, researchers at Harvard Medical School found that PTEN's tumor suppressing activity becomes elevated when two copies of the protein bind together, forming a dimeric protein. PTEN dimerization may be the key to understanding an individual's susceptibility for PTEN-sensitive tumors

In order to reveal how dimerization improves PTEN's ability to thwart tumor development, the researchers in this study, from Carnegie Mellon University, the National Institute of Standards and Technology, the Center for Synchrotron Radiation Research and Instrumentation, the Illinois Institute of Technology, Monash University, Harvard Medical School, the University of Massachusetts Medical School, and Worcester Polytechnic Institute needed to establish the protein's dimeric structure. Normally, protein structure is identified using crystallography, but attempts to crystallize the PTEN dimer had failed.

So the team used a different technique called small-angle x-ray scattering (SAXS), which gains information about a protein's structure by scattering x-rays through a solution containing the protein. This experimentation was carried out at the Biophysics Collaborative Access Team 18-ID-D x-ray beamline at the Argonne APS. They then used computer modeling to establish the dimer's structure.

They found that in the PTEN dimers, the C-terminal tails of the two proteins may bind the protein bodies in a cross-wise fashion, which makes them more stable. As a result, they can more efficiently interact with the cell membrane, regulate cell growth and suppress tumor formation.

Now that more is known about the structure of the PTEN dimer, researchers will be able to use molecular biology tools to investigate the atomic-scale mechanisms of tumor formation facilitated by PTEN mutations. The researchers also hope that their findings will offer up a new avenue for cancer therapeutics.

See: Frank Heinrich[1,2], Srinivas Chakravarthy[3,4], Hirsh Nanda[1,2], Antonella Papa[5,6], Pier Paolo Pandolfi[6], Alonzo H. Ross[7], Rakesh K. Harishchandra[8], Arne Gericke[8], and Mathias Lösche[1,2]*, “The PTEN Tumor Suppressor Forms Homodimers in Solution,” Structure (2015), in press, published on-line in advance of print. DOI: 10.1016/j.str.2015.07.012

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