Quick guide

PTEN

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What is it? PTEN stands for **p**hosphatase and **ten**sin homolog deleted on chromosome 10, a tumor suppressor gene located in a region of human chromosome 10 that is commonly deleted as many human tumors progress.

What does it look like? PTEN looks just like a tyrosine phosphatase, an exciting discovery as many tumors are caused by too much tyrosine kinase activity. However, it dephosphorylates tyrosine-phosphorylated proteins only very poorly although a couple of putative subtrates have been identified. But in 1998, Jack Dixon's group showed that PTEN could dephosphorylate a particular phospholipid, phosphatidylinositol 3,4,5 trisphosphate or PtdIns(3,4,5)P_3.

Is lipid phosphatase activity important? Yes! PtdIns(3,4,5)P_3 is produced by phosphoinositide 3-kinase (PI3K), which is important for insulin signaling, cytoskeletal rearrangements, differentiation, migration, proliferation, survival… So PTEN antagonizes PI3K by converting PtdIns(3,4,5)P_3 to an inactive state. The lipid phosphatase activity is probably more important than the protein tyrosine phosphatase activity for PTEN's role as a tumor suppressor: some PTEN mutants found in tumors lack lipid phosphatase activity but retain tyrosine phosphatase activity. Recently PTEN2 was described, which is a membrane-associated, testis-specific isoform. This enzyme also dephosphorylates PtdIns(3,4,5)P_3, but seems to have a preference for the related lipid PtdIns(3,5)P_2, thereby complicating matters.

What types of cancer do people with PTEN mutations get? Sporadic PTEN mutation occurs in more than 30% of advanced brain and prostate cancers, and endometrial cancers, and in a range of others at lower frequency. The overall frequency of mutation in human cancer is similar to that of the most famous tumor suppressor protein p53. Germline PTEN mutations are also found in some patients who develop benign lesions throughout their bodies, with an increased incidence of breast, uterus and thyroid cancers. Mice lacking both copies of the gene die early in embryogenesis, but heterozygote animals develop a broad range of tumours similar to the neoplasias seen in humans with one mutated copy of PTEN. Interestingly, heterozygote mice also develop an autoimmune disorder through the impaired death of activated T cells.

How is PTEN regulated? Hmmm... Despite more than 500 papers, there is very little information on the regulation of PTEN expression, localization or activity. PTEN is phosphorylated near its carboxyl terminus on serine and threonine, perhaps by casein kinase 2, which may decrease its stability. The carboxyl terminus of PTEN contains a PDZ-binding domain, which may regulate its localization to the plasma membrane, where its substrate lipid resides.

Where can I find out more?

Cantley LC, Neel BG: New insights into tumor suppression: PTEN suppresses tumor formation by restraining the phosphoinositide 3-kinase/AKT pathway. *Proc Natl Acad Sci USA* 1999, 96:4240-4245.

Di Christofano A, Pandolfi PP: The multiple roles of PTEN in tumor suppression. *Cell* 2000, 100:387-390.

Simpson L, Parsons R: PTEN: Life as a tumour suppressor. *Exp Cell Res* 2001, 264:29-41.

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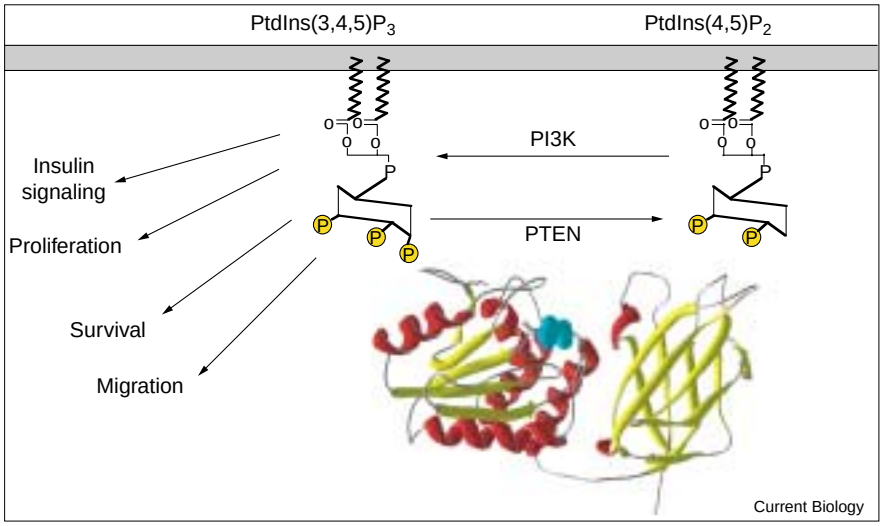

PTEN converts the biologically active lipid PtdIns(3,4,5)P_3 to PtdIns(4,5)P_2. The ribbon diagram of the PTEN structure (Lee *et al.*, *Cell* 1999, 99:323-334) is shown with the active site in light blue. PtdIns(3,4,5)P_3 produced by PI3K has a wide range of biological effects.