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TUMOUR SUPPRESSORS

PTEN surprise

> PTEN-Long led to tumour regression

Although the PTEN phosphatase, which inhibits PI3K signalling, has been intensively studied since its discovery in 1997, it seems that we are still unaware of certain fundamental aspects of the function of this tumour suppressor. In a paper in *Science*, Ramon Parsons and colleagues have shown that a translational variant of PTEN is secreted and taken up by cells, where it can affect signalling and induce tumour regression.

Looking carefully at the *PTEN* mRNA transcript, the authors found an alternative translation initiation codon (CUG) 5′ of and in-frame with the normal initiation codon; this PTEN-Long variant was predicted to contain an additional 173 amino acids at the amino terminus of the canonical PTEN protein. Transfection of PTEN-Long cDNA into *PTEN*-null cells indicated that both PTEN-Long and PTEN were translated, and that PTEN-Long had phosphatase activity and inhibited PI3K signalling in the cells in which it was expressed. The PTEN-Long variant was also expressed in PTEN wild-type cells.

Modelling of the unique PTEN-Long N-terminal domain indicated that it contained a secretion signal, so the authors examined whether PTEN-Long was present outside cells. PTEN-Long was present in conditioned medium from cells expressing PTEN-Long but not from cells expressing PTEN-Long with a mutated secretion signal, and inhibition of transport from the endoplasmic reticulum to the Golgi blocked PTEN-Long secretion. Does secreted PTEN-Long have any biological function? An evolutionarily conserved poly-arginine stretch, similar to that in the cell-penetrating transactivator of transcription (TAT) protein from HIV, was present in the PTEN-Long N-terminal domain, suggesting that secreted PTEN-Long might be able to enter cells. Indeed, fluorescently tagged PTEN-Long that was exogenously added to cells could be detected inside the cells, and this was blocked by the removal of the arginine residues. Uptake of PTEN-Long could also affect signalling, as cells incubated with purified PTEN-Long had reduced PI3K signalling, which was indicated by decreased phosphorylation of AKT, forkhead box O (FOXO) and the AKT substrate PRAS40. PTEN-Long also increased the cleavage of caspase 3 and induced cell death.

What might PTEN-Long do *in vivo?* Following intraperitoneal injection of purified PTEN-Long, the variant was detected and was able to reduce PI3K signalling in several mouse tissues, as well as in a xenograft tumour. In addition, intraperitoneally injected PTEN-Long led to tumour regression in several xenograft models (with the exception of tumours derived from HCT116 colon cancer cells), and this depended on PTEN-Long phosphatase activity. PTEN-Long also induced tumour regression in a syngeneic mouse model of glioblastoma derived from *Pten*$^{-/-}$, *Trp53*$^{-/-}$ and platelet-derived growth factor-overexpressing cells. Finally, the authors identified five somatic missense mutations of PTEN-Long in tumour samples using the Catalogue of Somatic Mutations in Cancer database, and these mutants had a reduced ability to affect PI3K signalling, suggesting that PTEN-Long mutation might be advantageous during tumour evolution.

Not only does this work highlight the surprising function of a protein that we thought we knew well, but it also raises the interesting question of whether purified PTEN-Long might have therapeutic applications.

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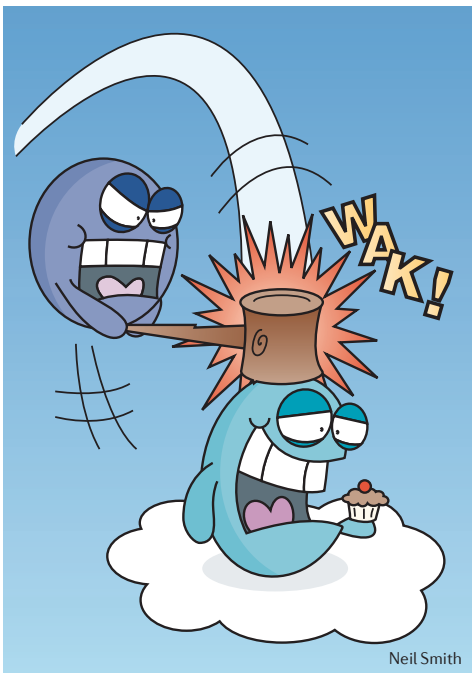
ORIGINAL RESEARCH PAPER Hopkins, B. D. *et al.* A secreted PTEN phosphatase that enters cells to alter signaling and survival. *Science* http://dx.doi.org/10.1126/science.1234907 (2013)



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