TUMOUR SUPPRESSORS

Self-restraint

The PTEN phosphatase has long been known to have tumour-suppressive activity through its ability to antagonize the phosphatidylinositol 3-kinase (PI3K)–AKT signalling pathway. Its loss in many cancers upregulates the pathway and leads to increased cell growth, proliferation and survival. Recently, PTEN has been implicated in another common function of cancer cells — cell migration — and Alan Hall and colleagues now show that the C2 domain of PTEN controls this process.

As glioma cells are invasive and lack expression of PTEN, the authors used them in wound-healing assays to investigate how PTEN regulates migration. Cells engineered to express wild-type PTEN did not migrate and were overtaken by control cells, indicating that PTEN inhibits motility. A PTEN mutant that lacked lipid-phosphatase activity could also inhibit migration, indicating that this effect is not regulated by the PI3K–AKT pathway. However, mutants lacking protein-phosphatase activity or the C2 domain of PTEN could not prevent cell movement and were therefore required for this property of PTEN. Expression of C2 domains derived from other proteins had no effect on migration, indicating that this inhibition requires the presence of the C2 domain of PTEN. As both the phosphatase catalytic domain and the C2 domain are required for PTEN to inhibit migration, might they somehow work together?

The authors mutated the phosphate sites in the carboxyl terminus that control PTEN phosphatase activity, and found that mutation of threonine 383 completely restored the ability of catalytically inactive PTEN to prevent migration. So, in the wild-type protein, Thr383 must be dephosphorylated for PTEN to inhibit migration, and this process is dependent on protein-phosphatase acitivity. Intramolecular interaction between the C2 and phosphatase domains of PTEN has been observed by X-ray crystallography, and Thr383 phosphorylation might prevent this interaction. Immunoprecipitation experiments showed that the carboxyl and amino termini of PTEN could, in fact, co-precipitate, but only if an intact C2 domain was present within the C terminus. This interaction was unaffected, however, by phosphorylation status.

Instead, Thr383 phosphorylation seems to be directly controlled by the phosphatase activity — catalytically inactive PTEN is phosphorylated at Thr383, whereas wild-type PTEN is not. These results indicate that the C2 domain of PTEN is inactive when it is phosphorylated and activation by dephosphorylation of Thr383 enables PTEN to interfere with migration. This ability to control cell migration might have important implications for tumour progression.

Emma Croager

References and links

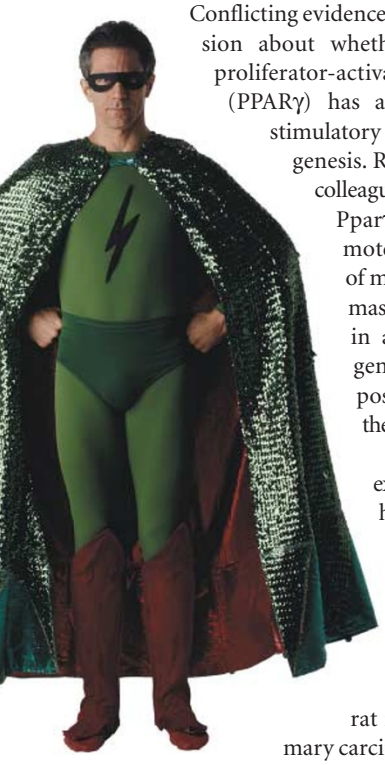
ORIGINAL RESEARCH PAPER Raftopoulou, M., Etienne-Manneville, S., Self, A., Nicholls, S. & Hall, A. Regulation of cell migration by the C2 domain of the tumor suppressor PTEN. *Science* **303**, 1179–1181 (2004)

WEB SITE

Alan Hall's home page:
http://www.ucl.ac.uk/LMCB/pages/hall.html

TUMORIGENESIS

Hero or villain?



Conflicting evidence has led to confusion about whether peroxisome-proliferator-activated receptor-γ (PPARγ) has an inhibitory or stimulatory effect on tumorigenesis. Ronald Evans and colleagues now show that Pparγ signalling promotes the formation of mammary carcinomas in mice, but only in animals that are genetically predisposed to developing these tumours.

PPARγ is overexpressed in several human cancers, including mammary tumours. Activators of this receptor inhibit tumour development in rat models of mammary carcinoma, indicating that stimulating PPARγ signalling might be a useful anticancer treatment. However, PPARγ activators can suppress proliferation even in cells in which the receptor is not expressed and can cause increased tumour development in mouse models of colon cancer. This confusion necessitates a greater understanding of how PPARγ signalling contributes to the development of different tumour types.

Evans and colleagues generated transgenic mice that express a constitutively active form of Pparγ in breast epithelium. Mammary-gland development was normal in these animals and they showed no increased tendency to develop tumours. The authors then crossed these animals to mice that express the polyoma virus middle T antigen (PyV-MT) in mammary tissue, which rapidly develop tumours with an average time to detection of 57 days in female mice. Those that expressed both activated Pparγ and PyV-MT showed accelerated development of mammary tumours, with an average time to appearance of just 37 days. So, although increased Pparγ activation does not initiate tumour formation in normal mammary tissue, it promotes tumorigenesis on a tumour-susceptible background.

Increased Wnt signalling is implicated in the development of mammary carcinomas, so could Pparγ contribute to tumour development through activation of this pathway? The Wnt target genes cyclin D1 and c-*Myc* were shown to be upregulated in mice expressing PyV-MT and constitutively active Pparγ compared with mice expressing PyV-MT only. Increased expression was also seen for β-catenin, a component of the Wnt pathway, and for the Wnt receptor frizzled homologue 4, whereas Wnt5a, a negative regulator of Wnt signalling, was downregulated.

This study has made important progress in understanding the role of Pparγ in tumorigenesis, but several key questions remain. For example, why does Pparγ signalling only promote mammary tumour development in genetically susceptible cells and how does Pparγ interact with the Wnt signalling pathway? This work also strengthens the suggestion that the inhibition of tumorigenesis by Pparγ ligands in previous studies is due to receptor-independent effects of these proteins. Clearly, further investigation will be needed before a safe verdict on the connection between PPARγ and cancer can be reached.

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References and links

ORIGINAL RESEARCH PAPER Saez, E. *et al.* PPARγ signalling exacerbates mammary gland tumor development. *Genes Dev.* **18**, 528–540 (2004)

FURTHER READING Michalik, L., Desvergne, B. & Wahli, W. Peroxisome-proliferator-activated receptors and cancers: complex stories. *Nature Rev. Cancer* **4**, 61–70 (2004)

WEB SITE

Ronald Evans's lab:
http://www.salk.edu/faculty/faculty/details.php?id=21