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SIGNALLING

Follow your eNOS

The Achilles heel of many tumours is thought to be their 'addiction' to or dependence on specific factors and pathways, such as activation of the phosphatidylinositol 3-kinase (PI3K)–Akt signalling pathway in tumour cells expressing oncogenic Ras. But what is it about these factors that tumours can't live without? In *Nature*, Kian-Huat Lim *et al*. have identified endothelial nitric oxide synthase (eNOS or NOS3) as a target downstream of activated Ras and Akt that is required for tumour growth and maintenance.

When Akt is activated in otherwise normal cells, these cells become tumorigenic when they are mixed with other tumorigenic cells to form a tumour microenvironment. Lim *et al.* exploited this, and mixed cells with activated Akt that expressed short hairpin RNAs to knock down Akt targets (such as BAD, FOXO, IKKα, TCS2 and eNOS) with oncogenic HRAS-expressing cells. They looked for those cells that could no longer contribute to the tumour mass, and knockdown of eNOS had the greatest effect. Indeed, loss of eNOS expression reduced tumour growth even after tumours had already formed. Similarly, eNOS-null mice were resistant to chemical carcinogen-induced spontaneous Ras-driven tumours.

Image courtesy of Christopher Counter's laboratory

eNOS catalyses the synthesis of nitric oxide, which facilitates nitrosylation and activation of proteins such as HRAS. Lim *et al*. found that knockdown of endogenous HRAS or NRAS in oncogenic KRAS-expressing tumour cell lines had the same effects as knockdown of eNOS. Moreover, mutating the amino acid that is nitrosylated by nitric oxide inhibited the ability of HRAS and NRAS to promote tumour growth.

The authors conclude that the addiction of cancer cells to PI3K–Akt signalling in oncogenic Ras-driven tumour initiation and maintenance results from the phosphorylation and activation of eNOS, leading to the activation of other wild-type Ras family members. Therefore, inhibition of eNOS, possibly in conjunction with a Ras inhibitor, might prove useful in the clinic.

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ORIGINAL RESEARCH PAPER Lim, K-H., Ancrile, B. B., Kashatus, D. F. & Counter, C. M. Tumour maintenance is mediated by eNOS. *Nature* **452**, 646–649 (2008)