found that *Bim* is a direct transcriptional target of Myc.

Previously, this group demonstrated that the loss of one allele of *Bim* could correct many of the tissue defects within *Bcl2*-null animals, establishing Bim as a key physiological antagonist of Bcl2. Their most recent data, however, clearly show that the oncogenic impact of loss of Bim in the B-lymphoid compartment is not equivalent to gain of Bcl2. Unraveling this conundrum in the future will undoubtedly tell us more about the sophisticated circuitry regulating cell life and death during B-lymphoid differentiation.

Nicola McCarthy

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WEB SITE

Suzanne Cory's lab: http://www.wehi.edu.au/research/divisions/mgc/index.html

TUMORIGENESIS

Right place, wrong time

When members of the FOXO family of transcription factors are located in the nucleus, they activate expression of genes that prevent proliferation and promote apoptosis. Nuclear exclusion of FOXO can therefore contribute to cancer pathogenesis. Hu *et al.* have discovered a new mechanism that regulates this localization, reporting that the IκB kinase-β (IKKβ) regulates FOXO3A access to the nucleus and, therefore, tumorigenesis.

When cells are stimulated with growth factors, signalling pathways become activated that lead to phosphorylation of the kinase AKT (AKT-p), which in turn phosphorylates the transcription factors FOXO1, FOXO3A and FOXO4. This causes their localization to the cytoplasm and subsequent cell proliferation. In the absence of growth or survival signalling, however, AKT remains unphosphorylated and inactivated, resulting in the nuclear retention of FOXO factors and the inhibition of cell division — as well as tumour suppression.

Hu *et al.* investigated the relationships between AKT-p and FOXO3A localization in 131 primary breast tumour specimens. As expected, they observed that FOXO3A was mainly localized to the cytoplasm of tumour cells with a high level of AKT-p and in the nucleus of cells that were AKT-p negative. Surprisingly, they also found a significant number of tumour samples that lacked AKT-p, yet FOXO3A was still confined to the cytoplasm.

So is there an alternative mechanism by which cancer cells exclude FOXO3a from the nucleus? Another cancer-associated kinase that regulates nuclear–cytoplasmic localization of transcription factors is IKKβ, which controls NF-κB activity. When Hu *et al.* examined levels of IKKβ in the tumour samples, they found that the level of nuclear FOXO3A was inversely correlated with the level of this protein. A lack of IKKβ was also correlated with the survival rate of patients with breast cancer. So could IKKβ also contribute to tumorigenesis by keeping FOXO factors out of the nucleus?

Through immunoprecipitation studies, the authors showed that IKKβ physically interacts with and phosphorylates FOXO3A, independently of AKT. Furthermore, IKKβ phosphorylation of FOXO3A leads to its proteolysis through the ubiquitin-dependent proteasome pathway. Hu *et al.* engineered cells to constitutively express IKKβ and showed that this resulted in loss of FOXO3A activity. In these cells, FOXO3A was no longer present in the nucleus, and therefore did not activate transcription of its target genes. This led to cell-cycle progression and proliferation.

Is constitutive IKKβ activity sufficient to cause tumour formation *in vivo*? Injection of IKKβ-stably-transfected cells into the mammary fat pad of nude mice caused tumour formation at that location, whereas control cells did not. Re-expression of FOXO3A in these cells, however, suppressed *in vivo* tumour formation. Therefore, the mechanism underlying IKKβ-mediated tumorigenesis is likely to be through inhibition of FOXO3A.

Hu *et al.* conclude that as there is an inverse correlation between cytoplasmic FOXO3A in tumour cells and survival in patients with breast cancer, this transcription factor might be a useful prognostic factor, as well as a new tool for therapeutic intervention.

Kristine Novak

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Mien-Chie Hung's lab: http://www.bcrfcure.org/rese_meet_hung.html