WEB WATCH

Bringing mice together

- **http://tumor.informatics.jax.org/**

Studies of tumour development in mice are fundamental to cancer research and a wealth of information from this work has accumulated over the years. Founded in 1997 by The Jackson Laboratory, The Mouse Tumor Biology Database (MTB) brings together data from hundreds of mouse models, providing an essential resource for anyone interested in using mice to understand cancer.

The MTB contains data on inbred, hybrid and genetically engineered mouse strains that develop tumours. It also includes results from studies in which mice have been exposed to tumour-promoting conditions, including treatment with chemicals, growth factors and hormones, radiation exposure and viral infection. The information provided in the database includes details of organs and tissues affected, data on tumour frequency and latency, associated genetic factors, tumour pathology images and relevant references. The database can be searched in several ways: by tumour type, for specific strains or for lines carrying genetic aberrations that affect a gene of interest.

Because of the sheer volume of data available, the MTB isn't yet fully up to date with the most recently published literature. However, the database does contain a huge amount of information and is regularly updated, with priority given to those studies that are relevant to the most prevalent forms of human cancer in the United States.

Louisa Flintoft

ONCOGENES

Taking the direct route

TP53 mutations are associated with many cancers, but are surprisingly rare in acute promyelocytic leukaemia (APL). Work from PierGiuseppe Pelicci, Saverio Minucci and colleagues now shows that an APL-associated oncoprotein provides a direct mechanism of p53 inactivation by promoting its deacetylation and subsequent degradation.

Most cases of APL result from a chromosomal translocation that produces PML–RAR, a fusion of the PML and retinoic-acid receptor (RAR) proteins. This oncoprotein recruits histone deacetylases (HDACs) to chromatin to inhibit the expression of RAR target genes, predisposing cells to tumorigenesis. So, could PML–RAR also be responsible for p53 inactivation in APL? Pelicci, Minucci and colleagues showed that exposing mouse haematopoietic cells to genotoxic stress causes p53-dependent cell loss, but expression of PML–RAR protected cells from this effect. By contrast, no protection was provided by a mutant form of PML–RAR — known as the AHT mutant — that is unable to recruit HDACs. In addition, PML–RAR inhibited transcription from p53-responsive constructs *in vitro*, but transcription was restored using the AHT mutant.

But how does PML–RAR inhibit p53 activity? Exposure of wild-type mice to genotoxic stress leads to increased p53 levels because of decreased proteasomal degradation. However, p53 levels in APL mice were shown to remain low after exposure to X-rays, indicating that PML–RAR might promote p53 degradation. Consistent with this, treatment of X-ray-exposed APL animals with proteasome inhibitors led to increased p53 levels. The authors also showed that Mdm2, which targets p53 to the proteasome, is required for p53 downregulation by PML–RAR, as PML–RAR is unable to reduce p53 expression in *Mdm2*$^{-/-}$ cells. In addition, Arf, an Mdm2 inhibitor, restored p53 expression that was blocked by PML–RAR.

Acetylation is known to stabilize p53 in response to stress by inhibiting its proteasomal degradation. So, the authors tested whether HDAC recruitment by PML–RAR leads to deacetylation of p53. When wild-type mice are exposed to X-rays, acetylated p53 accumulates. However, this effect was not seen in APL animals, even when p53 was stabilized using a proteasome inhibitor. This inhibition of p53 acetylation requires HDAC recruitment, as treatment of APL mice with an HDAC inhibitor restored both total p53 and acetylated p53 to levels similar to those seen in wild-type mice.

So, PML–RAR stimulates p53 deacetylation and promotes its Mdm2-dependent proteasomal degradation. This is in contrast with the previously known function of PML–RAR in inhibiting gene expression by deacetylating chromatin. Interestingly, this newly discovered function of PML–RAR requires wild-type Pml, which binds p53 and is involved in its normal regulation. The authors showed that PML–RAR binds p53 only weakly and is unable to deacetylate p53 or protect cells from genotoxic stress in the absence of Pml. Interestingly, this is the first known example in which an oncoprotein is dependent on expression of the corresponding wild-type protein for its tumorigenic function.

Louisa Flintoft

References and links

ORIGINAL RESEARCH PAPER Insinga, A. *et al.* Impairment of p53 acetylation, stability and function by an oncogenic transcription factor. *EMBO J.* 19 Feb 2004 (doi:10.1038/sj.emboj.7600109)

WEB SITES

PierGiuseppe Pelicci's lab: www.ifom-ieo-campus.it/groups/pelicci.html
Saverio Minucci's lab: www.ifom-ieo-campus.it/groups/minucci.html