DNA METABOLISM

… and from repair to remodelling

The past ten years or so have seen many global boundaries come down — from economic and geographical borders to the Berlin wall. This is the case in science too, where the lines that have traditionally divided many areas of molecular and cell biology are beginning to blur.

Molecules identified in one process are increasingly being implicated in other — often unexpected — pathways. Take the TIP60 protein, for example. Originally isolated as a protein that interacts with HIV-1 Tat, it was subsequently shown to be a histone acetyltransferase. And now, according to a paper by Yoshihiro Nakatani and collaborators in *Cell*, TIP60 may also be involved in DNA repair and apoptosis.

The first step was purification of the TIP60 complex from HeLa cells. Initial studies of TIP60's histone acetyltransferase activity had used TIP60 monomers, and there was a problem with that — activity was detected only when free histones were used, and not with the more physiologically relevant nucleosomes. But Nakatani and colleagues showed that the TIP60 complex, which contains at least 14 subunits, can acetylate both substrates.

The authors then took a closer look at the complex. Using mass spectrometry they discovered that the two 54 kDa subunits, christened TAPs — for 'TIP60-associated proteins' — were familiar faces, corresponding to the eukaryotic RuvB-like proteins RUVBL1 and RUVBL2, respectively.

RuvB is a ring-shaped protein required for DNA recombination and repair in *Escherichia coli* (see the review by Hingorani and O'Donnell on page 22 for more information). Because RuvB has intrinsic ATPase and helicase activities, Nakatani and co-workers first confirmed that these are also functions of the TIP60 complex. Then, given that the TIP60 complex contains what seem to be functional counterparts of RuvB, the authors wondered whether it — and, specifically, its histone acetyltransferase activity — might have some function in DNA repair.

To test their idea, they ectopically expressed a mutated TIP60 with no acetyltransferase activity in HeLa cells. They then watched how these cells behaved after γ-irradiation, which generates double-stranded DNA breaks, compared with controls (cells expressing wild-type TIP60 or with no ectopic TIP60 at all). The result was that, in the controls, at least 40% of the breaks were repaired within 30 minutes of γ-irradiation. But only 5% of the damage in the mutant cells was mended over the same period.

Normally, in cells with irreparable DNA damage, an apoptotic death pathway is activated. So Nakatani and colleagues looked for evidence of this in the cells expressing mutated TIP60. But after 12 hours of γ-irradiation these cells showed no apoptosis at all, indicating that the suicide response was also affected by the TIP60 mutation. It's therefore likely that the TIP60 complex interacts with checkpoint proteins to activate a cellular suicide programme in response to DNA damage.

These results raise plenty of questions, but they could be a step towards understanding DNA repair and signalling pathways in the real world of chromosomes and chromatin. Many *in vitro* studies use naked DNA as a substrate, but in living cells the enzymes have nucleosomes to contend with. Until now histone acetyltransferases have been implicated mainly in transcriptional activation, where they are thought to relax the structure of the chromatin so that transcription factors can access the DNA. But DNA repair enzymes presumably face many of the same challenges, so it would make a lot of sense to have both activities in a single complex. It turns out that other subunits of the TIP60 complex have already turned up in several different chromatin-remodelling complexes, indicating that this may be a general phenomenon — maybe not a global one, but certainly one that blurs the boundary between chromatin biology and DNA metabolism.

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References and links

ORIGINAL RESEARCH PAPER Ikura, T. *et al*. Involvement of the TIP60 histone acetyltransferase complex in DNA repair and apoptosis. *Cell* **102**, 463–473 (2000)

REVIEW Sterner, D. E. & Berger, S. L. Acetylation of histones and transcription-related factors. *Microbiol. Mol. Biol. Rev.* **64**, 435–459 (2000)

WEB WATCH

Untangling inositol

Where do you turn if your research flings you into a completely new field? The story on page 6 will doubtless have experts in DNA repair grappling with *myo*-inositol and its extended family; but if you don't know your phytate from your pentakisphosphates, help is at hand.

Most of the researchers who study inositol phosphates view the calcium-releasing second messenger inositol-1,4,5-trisphosphate as the centre of their universe (see the review by Michael J. Berridge and colleagues on page 11 of this issue), but Stephen Shears at the US National Institute of Environmental Health Sciences has a different perspective: he has put together an online tutorial on the more-highly phosphorylated inositol polyphosphates, with inositol hexakisphosphate ($InsP_6$, also known as phytate) at its hub. The front page provides a map of inositol polyphosphate metabolism, and clicking on different sections of it takes you to reviews on the metabolism and functions of just about every inositol polyphosphate known to exist. There's some valuable historical background information (see, for example, the section on the $Ins(1,4,5)P_3$–$Ins(1,3,4,5)P_4$ cycle) and fascinating insights into the variety of cellular processes that these molecules have been implicated in. Each review has an extensive reference list and is regularly updated.

One thing that is missing, however, is a guide to their nomenclature. A *myo*-inositol guide written by the International Union of Biochemistry and Molecular Biology's committee of nomenclature experts explains all. It may shock you to learn that this was written in 1988, but it is comforting to know that one thing in this field has stayed the same for 12 years.

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