IN THE NEWS

All-in-one repair kit

DNA double-strand breaks (DSBs) often lead to incompatible chromosome ends that can be repaired by the complex, poorly understood, non-homologous end-joining (NHEJ) pathway. Now, reporting in *Science*, Aidan Doherty and colleagues have shown that, in *Mycobacterium tuberculosis*, just two proteins can carry out the gamut of processes that are required for NHEJ.

The researchers subjected the *M. tuberculosis* DNA ligase Mt-Lig to a range of *in vitro* assays to assess its usefulness in DNA repair. In a dazzling display of versatility, Mt-Lig showed competence as an RNA polymerase, a combined DNA polymerase and ligase, an RNA primase, a terminal transferase and even showed 3′→5′ single-stranded-DNA exonuclease activity. Interestingly, this resourceful protein used NTPs — the nucleotides that are incorporated into RNA — to correctly fill in an *in vitro* DSB. Also, co-transfection of Mt-Lig with another mycobacterial repair protein, Mt-Ku, restored NHEJ in a DNA-repair mutant yeast.

Referring to Mt-Lig, Steve Kowalczykowski from the University of California, USA, remarked that it was "…just amazing how there are so many activities in one protein", and was curious to find out "…how its component parts can catalyze so many different events typically separated in eukaryotes" (*The Scientist*, 25 October 2004). And, corresponding author, Aiden Doherty, from the University of Sussex, UK, highlighted the intriguing prospect that "…RNA could be used to repair DSBs probably as a short-term measure."

As well as shedding light on the NHEJ processes, molecular biologists are relishing the prospect of using this all-in-one repair kit to facilitate DNA cloning.

Shannon Amoils

ADHESION AND SIGNALLING

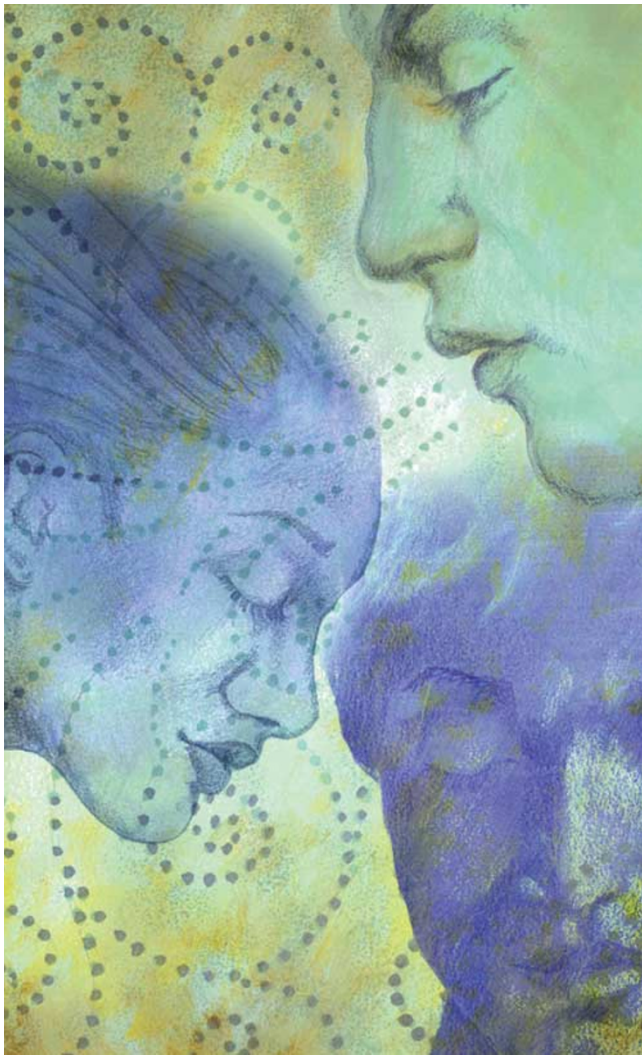
The many faces of β-catenin

To carry out its roles, β-catenin has two groups of business associates. In cell–cell adhesion, β-catenin binds to cadherin and α-catenin, whereas it interacts with the T-cell factor (TCF)–Lef complex in Wnt-mediated transcriptional activation. Whether it deals with both of them independently or with each one competitively has troubled researchers in both fields for some time. But Gottardi and Gumbiner now propose that the regulation of distinct molecular forms of β-catenin that differ in their binding properties controls the role that β-catenin carries out.

In studying the binding properties of β-catenin using a 'pull-down' assay, the authors found that β-catenin showed a preference for a TCF fusion protein over a fusion protein that contained the cytoplasmic domain of cadherin — but only when Wnt was present. How, then, might Wnt generate a TCF-selective form of β-catenin? The C terminus of β-catenin can bind to a region within β-catenin, which might prevent β-catenin binding to the cadherin cytoplasmic domain, so the authors surmised that a C-terminus-mediated 'closed' conformation might be incompatible with binding to cadherin, but not to TCF. Indeed, the authors found that, in cadherin-binding fractions of β-catenin, the β-catenin C terminus was much more accessible than in non-binding fractions. Consistent with a role for the C terminus of β-catenin in mediating binding selectivity, a C-terminal-deletion mutant bound equivalently to cadherin and TCF.

Next, Gottardi and Gumbiner carried out binding studies on different cytosolic fractions of β-catenin. Cadherin bound preferentially to a higher-molecular-weight fraction of β-catenin that co-fractionated with α-catenin, whereas TCF bound a lower-molecular-weight fraction that corresponded to monomeric β-catenin (although it could also bind β-catenin–α-catenin dimers). But what about the C-terminal epitope? The authors used antibodies that were designed to recognize specific conformations of β-catenin to show that this region was accessible in the dimeric β-catenin–α-catenin complexes, but not in the monomeric β-catenin form, consistent with their previous findings.

β-catenin is subject to post-translational modification — phosphorylation, for example, affects its stability. Gottardi and Gumbiner speculate that such modification influences the conformation that β-catenin adopts, and therefore its chosen binding partner. However, what this modification is and how it arises are unknown. The authors propose that cells contain several distinct forms of β-catenin: one that is N-terminally phosphorylated and subject to degradation; a closed form, which predominantly



interacts with TCF to mediate transcription; an open form, which binds both TCF and cadherin; a form that, by interacting with α-catenin, binds to cadherin and mediates adhesion; and, potentially, another form that is inactive.

In contrast to *Caenorhabditis elegans*, which has several β-catenin gene products that it uses to regulate adhesion and signalling, vertebrates only have one, so the authors propose that the "…generation and targeting of distinct molecular forms of β-catenin could ensure that adhesion and signaling are not always coupled, and when necessary, can be regulated independently of one another."

Katrin Bussell

References and links

ORIGINAL RESEARCH PAPER Gottardi, C. J. & Gumbiner, B. M. Distinct molecular forms of β-catenin are targeted to adhesive or transcriptional complexes. *J. Cell Biol.* **167**, 339–349 (2004)