

# HIGHLIGHTS

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## DNA REPAIR

# A molecular monkey wrench

You wouldn't call a doctor to fix a leaking tap, or a plumber to mend your car. The same is true in cells, where different mechanisms are used to repair DNA depending on the type of damage sustained. One such system is base-excision repair (BER), which is used to remove a variety of damaged bases. And a report in *Nature* by Kai-Ming Chou and Yung-Chi Cheng sheds new light on how this system might work.

The first step of BER is removal of the damaged base by a DNA glycosylase. The remaining 'abasic' site is recognized by an apurinic/apyrimidinic endonuclease (APE), which cleaves the phosphodiester bond 5' to the lesion. DNA polymerase  $\beta$  (pol  $\beta$ ) then replaces the missing base, and the final step involves resealing of the nick by a DNA ligase.

There's just one problem — pol  $\beta$  is notoriously error-prone, and misincorporates as many as one incorrect nucleotide per 4,000. So why does BER not result in numerous mutations? The answer, say Chou and Cheng, is that the human APE1 enzyme might also have a proofreading activity that increases the fidelity of BER.

As well as its endonuclease activity, APE1 is known to have a 3' to 5' exonuclease activity; that is, it can nibble back a DNA end in the 3' to 5' direction. Chou and Cheng studied this activity on various DNA substrates, and found that APE1

removed 3' mismatched nucleotides (T/G, for example) over 50 times more efficiently than correctly paired nucleotides (C/G).

The idea that APE1's exonuclease activity could be used to specifically remove an incorrect nucleotide was supported by findings from an *in vitro*-reconstituted BER system. Here, DNA ligase I works very inefficiently if the nucleotide pair at the 3' terminus of the nick is mismatched. The authors found that the addition of APE1 increased the efficiency of ligating 3' mispaired substrates in a concentration-dependent manner, yet had no effect when correctly paired substrates were used.

The story has a final twist, too. Certain nucleoside analogues such as 3'-azido-3'-deoxythymidine (AZT) are often used as antiviral agents to block viral DNA replication. Chou and Cheng found that APE1, in contrast to other cytosolic exonucleases tested, can remove this analogue from the 3' terminus of a nick. As APE1 is expressed constitutively in human cells, it could therefore be used to limit the cytotoxicity of AZT and other anti-HIV compounds.

Other 3' to 5' exonucleases — such as TREX1 — have previously been proposed to provide a proofreading function for pol  $\beta$ . However, Chou and Cheng's data, along with the fact that pol  $\beta$  and APE1 interact physically, and that APE1 localizes to the nucleus (where BER takes place),



make a strong case that APE1's exonuclease activity is a new mechanism for repairing mispaired DNA.

Alison Mitchell

## References and links

**ORIGINAL RESEARCH PAPER** Chou, K.-M. & Cheng, Y.-C. An exonucleolytic activity of human apurinic/apyrimidinic endonuclease on 3' mispaired DNA. *Nature* **415**, 655–659 (2002)

**FURTHER READING** Jiricny, J. An APE that proofreads. *Nature* **415**, 593–594 (2002)

## WEB SITE

Encyclopedia of Life Sciences:  
<http://www.els.net>  
DNA repair