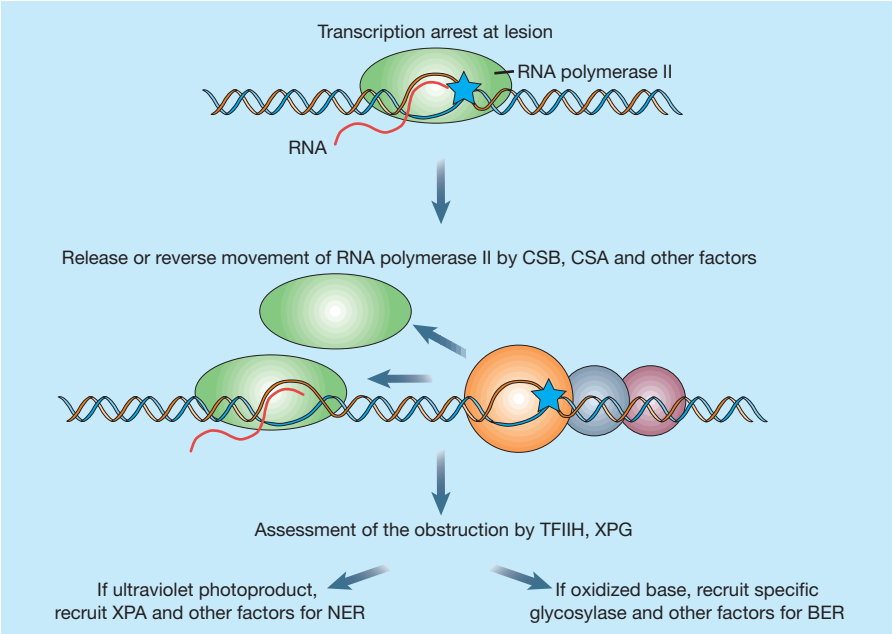


Figure 1 **The DNA-repair pathways meet. The results of Le Page *et al.*[1] lead to the following model for the repair of lesions in the transcribed strands of expressed genes. Top, RNA polymerase II transcribes DNA into RNA. If RNA polymerase II meets a lesion (asterisk) in the DNA strand, it will stop. Centre, repair of the lesion and further transcription is blocked until the polymerase is either released from the DNA or backed away from the lesion. Both TFIIH and XPG are then required before the lesions are repaired, perhaps to determine the nature of the obstruction. Bottom, enzymes of either the nucleotide-excision-repair (NER) or the base-excision-repair (BER) pathways are recruited, to remove the offending lesion and allow transcription to resume. The genes that can be mutated in Cockayne syndrome are required to remove the stalled polymerase, and to assess the nature of the damage.**

different roles in the TCR of oxidative damage and in NER.

Le Page *et al.* also turned their attention to another prominent oxidative lesion, 8-oxo-guanine. Using a shuttle vector, they introduced DNA containing 8-oxo-guanine residues into several human cell strains. They found that 8-oxo-guanine, like thymine glycol, is subject to TCR, but not significantly to NER — so it must be subject to BER instead. They also showed that 8-oxo-guanine (or 8-oxo-guanine plus a ligand) is an obstacle to the movement of RNA polymerase II, and that the arrested polymerase must be released to give the repair enzymes access to the site. So, not only is TCR missing in Cockayne syndrome, but the blocked RNA polymerase II prevents lesion recognition and repair by the global BER pathway as well.

Instead of being considered a subpathway of NER, it now seems that TCR is a process needed before either the BER or the NER pathway can repair oxidative damage to genes that are being transcribed, in which RNA polymerase is stalled at a lesion. TCR might be considered an 'obstacle-recognition' step, in which TFIIH and XPG may work together to assess the nature of the obstruction (Fig. 1). This obstruction might be removed only when the arrested RNA polymerase II has been moved away, which may be achieved by CSA and CSB, amongst other factors. TFIIH and XPG might then recruit the enzymes needed for BER or NER, as appropriate.

It is clear that an impasse provided by an arrested RNA polymerase II would severely affect transcription. In that sense, Cockayne syndrome could, indeed, be considered a 'transcription syndrome'. But the arrest of transcription also provides a strong signal for a cell-death (apoptosis) pathway[8]. So, Cockayne syndrome could also be characterized as a disease of excessive cell death by apoptosis — a disease that would affect rapidly metabolizing cells, such as neurons, that generate high levels of reactive oxygen species. The apoptosis model could also, in principle, explain the problems of stunted growth and neurological deterioration. It might also explain why Cockayne syndrome patients are not prone to skin cancer, even in the face of severe sunlight sensitivity — after all, dead cells do not form tumours. ■

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1. Le Page, F. *et al. Cell* **101,** 159–171 (2000).
2. Lindahl, T. & Wood, R. D. *Science* **285,** 1897–1905 (1999).
3. Tornaletti, S. & Hanawalt, P. C. *Biochimie* **81,** 139–148 (1999).
4. Bootsma, D. & Hoeijmakers, J. H. J. *Nature* **363,** 114–115 (1993).
5. Leadon, S. A. & Cooper, P. K. *Proc. Natl Acad. Sci. USA* **90,** 10499–10503 (1993).
6. Cooper, P. K. *et al. Science* **275,** 990–993 (1999).
7. Nouspikel, T. *et al. Proc. Natl Acad. Sci. USA* **94,** 3116–3121 (1997).
8. Ljungman, M. & Zhang, F. *Oncogene* **13,** 823–831 (1996).

**Daedalus**

## The depths of madness

**Protein molecules, folded so subtly, work all the enzymatic wonders of biochemistry. Heat can unfold and denature them — as all cooks know. But so can pressure. Raw egg white is opacified and hardened by a few thousand atmospheres (though it still tastes raw). Daedalus is now pondering the implications for deep-sea creatures.**

**A crucial problem for such creatures is to know how deep they are. Some rely on their eyes — daylight from the surface fades out with depth. Others have a swim-bladder, whose gas is compressed by the rising hydrostatic pressure as its owner sinks. But below 1 km or more, neither scheme works well. Daedalus reckons that whales, squid and other creatures who repeatedly patrol a wide vertical range exploit pressure-dependent protein folding. Some 'barometric enzyme' in their make-up changes its reactivity reversibly with pressure to register their depth.**

**So DREADCO trawlers are now lowering pressurized traps into the oceans, to snare abyssal creatures and haul them to the surface still under pressure. They will then be transferred to a pressurized aquarium for study. They, or perhaps their symbiotic and gut organisms, should harbour novel barometric enzymes which could throw new light on the protein-folding problem.**

**But this costly research programme has a greater goal. Daedalus argues that all the proteins of an abyssal creature must unfold somewhat in the deeps. And even if they fold again when their owner rises, very likely at least one molecule will do so wrongly. It will form a prion — and once one has formed, it will catalyse production of more prions the next time the creature dives. In the brain, proliferating prions pose a lethal threat. What protects a squid from 'mad squid disease'?**

**Whatever it is, Daedalus wants to know. For we also are vulnerable to malfolded proteins, not only as the brain plaques of Alzheimer's disease and CJD, but in the slow advance of wrinkled skin and hardened eye lenses and arteries. Somewhere in abyssal biochemistry, he hopes, is the crucial refolding reagent that prevents a protein from prionizing or forming a plaque, or even hauls it back from that doom. It could be an elixir of health and youth for all mankind. Daedalus cannot guess how it may work. But his team is on the look-out for any separated fraction that can unboil an egg.** **David Jones**

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