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Rubric: Idea to watch

A reverse gear for transcription coupled DNA repair? (Comment on DOI 10.1002/bies.201400106)

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The UvrD helicase protein participates in a diverse set of pathways that contribute to genome stability in bacteria [1]. In a Hypothesis paper in this issue of Bioessays, Vitaliy Epshteyn discusses the implications of his recent discovery that this multi-faceted enzyme can promote “backtracking” (sliding backwards) of RNA polymerase (RNAP) during transcription, and proposes that UvrD plays an important and unexpected role in transcription-coupled DNA repair (TCR) [2].

Accelerated repair of transcribed regions of the genome was first observed nearly 30 years ago, and it was subsequently found that only lesions in the strand used as a template by RNAP are repaired at an enhanced rate [3]. The strand specificity of TCR suggested that RNAP acts directly as a DNA damage sensor, because lesions within the template strand often stall RNAP. However, RNAP stalled on damaged DNA *in vitro* inhibits repair, rather than accelerating it, because the lesion is buried within the enzyme and inaccessible to repair proteins. This conundrum was resolved by the discovery of transcription-repair coupling factors [3].

The best characterised bacterial transcription-repair coupling factor is the Mfd protein, which pushes RNAP forward along DNA to release it from damage, and speeds up repair by interacting with the nucleotide excision repair machinery. Mfd catalyses TCR in a variety of experimental systems, and many details of its mechanism have been established [3]. However, although cells lacking Mfd are defective in TCR, they do not show the inhibition of template strand repair (and associated UV sensitivity) that would be expected if RNAP stalled at lesions could only be removed by Mfd [4].

Epshteyn’s hypothesis is that UvrD is also a transcription-repair coupling factor, sliding RNAP backwards away from DNA damage to unveil lesions for repair. A “two-tier” model of TCR is proposed, in which Mfd acts primarily to prioritise the repair of chronic, low levels, of DNA damage and the UvrD pathway takes over during periods of acute genotoxic stress. The model would explain why cells that lack Mfd have only a mild UV-sensitivity phenotype, and raises some pressing new questions. High amongst these is whether the role of UvrD is restricted to moving RNAP away from the damage so that repair is not impeded, or whether it actively stimulates repair. Moving RNAP away from the damage may be all that is required, because genotoxic stress triggers an “SOS-response” that increases the concentrations of repair proteins, and enables template and non-template strands to be repaired equally quickly, at least in some genes [5]. Alternatively, UvrD may cooperate with the transcription factor NusA to catalyse a “complete” Mfd-independent TCR pathway encompassing both RNAP removal and repair protein recruitment.

Understanding the interplay between the different pathways linking transcription to DNA repair will ultimately require the repair of multiple classes of damage to be analysed under a broad range of conditions. The question of whether UvrD actively promotes repair in association with NusA or other factors is amenable to biochemical analysis, but interpretation of the phenotype of mutants that lack UvrD is complicated by the concomitant loss of UvrD’s participation in the later stages of nucleotide excision repair and the resolution of replication-transcription conflicts [1]. Isolation of mutants that specifically disrupt backtracking activity would therefore greatly advance the prospects of unravelling the biological role of this intriguing aspect of UvrD’s enzymatic armoury.

- 1 **Dillingham MS.** 2011. Superfamily I helicases as modular components of DNA-processing machines. *Biochem Soc Trans* **39**: 413-23.
- 2 **Epshtein V.** 2015. UvrD helicase: An old dog with a new trick. *BioEssays* **37**: xxx – xxx <<note to typesetters: please insert page numbers at point of issue compilation>>
- 3 **Spivak G, Ganesan AK.** 2014. The complex choreography of transcription-coupled repair. *DNA Repair* **19**: 64-70.
- 4 **Mellon I, Champe GN.** 1996. Products of DNA mismatch repair genes mutS and mutL are required for transcription-coupled nucleotide-excision repair of the lactose operon in *Escherichia coli*. *Proc Natl Acad Sci U S A* **93**: 1292-7.
- 5 **Crowley DJ, Hanawalt PC.** 1998. Induction of the SOS Response Increases the Efficiency of Global Nucleotide Excision Repair of Cyclobutane Pyrimidine Dimers, but Not 6-4 Photoproducts, in UV-Irradiated *Escherichia coli*. *J Bacteriol* **180**: 3345-52.