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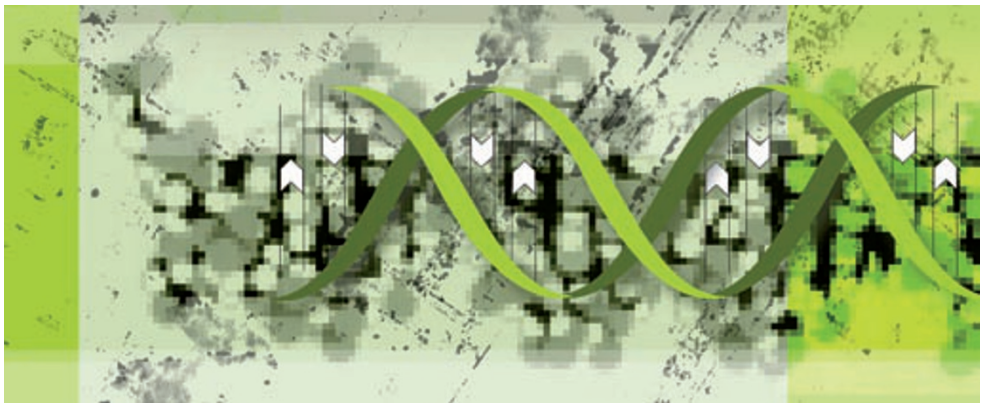

MECHANISMS OF DISEASE

A structural unwinding

Mutations in the human *XPD* helicase gene can cause one of three genetic disorders — the cancer-prone xeroderma pigmentosum (XP) or the ageing disorders Cockayne syndrome (CS) or trichothiodystrophy (TTD). *XPD* mutations have been difficult to understand as patient phenotypes cannot be predicted from the position of an individual mutation along the linear gene sequence; they are mainly single-point mutations that are sometimes located at adjacent residues, so how do they cause such strikingly different diseases? Fan *et al.* and Liu *et al.* now report the crystal structures of archaeal XPD, which, together with extensive biochemical studies, provide both a molecular basis for the mechanism of the enzyme and specific testable explanations for the wide spectrum of pathologies that arise from mutations of the gene.

XPD is a 5′ to 3′ DNA helicase that is an essential component of the transcription factor TFIIH, which plays a dual role in RNA polymerase II-mediated transcription initiation and nucleotide excision repair (NER). Although XPD helicase activity is not required for transcription initiation, mutations that reduce the XPD helicase activity cause defects in the NER pathway. Eukaryotic XPD is only fully active when assembled in the TFIIH complex; therefore, it has been impossible to distinguish between mutations that target the helicase activity directly and those that destabilize protein–protein interactions that are important for activity. The two groups took advantage of the archaeal XPD, which is fully functional in the absence of protein partners. Sequence analysis revealed that the archaeal XPD contains the XPD-conserved catalytic core, which consists of four domains: two Rad51/RecA-like domains (HD1 and HD2) with two other domains (the iron-sulphur cluster and Arch domains) inserted into HD1. These domains contain 22 out of the 26 known disease-causing point-mutation sites.

The structural analysis revealed that substrate-binding grooves separate HD1 and HD2 and an arch is formed by the iron-sulphur cluster and Arch domains. The positions of the Arch domain and iron-sulphur cluster domain argue strongly that single-stranded DNA is bound in the same orientation as in 3′ to 5′ enzymes and that the enzyme simply translocates in the opposite direction. So, helicase polarity is determined by the direction of translocation rather than the orientation of nucleic-acid binding.

Analysis of mutant enzyme activities showed that XP mutations map along the ATP-binding edge of HD1 and the DNA-binding channel of HD2, and impair helicase activity, which is essential for NER. By contrast, mutations that can cause XP and CS impair both helicase activity and the functional flexibility of HD1–HD2, which probably affects the protein–protein interactions within the TFIIH complex. Finally, TTD mutants either lose or retain helicase activity but map to sites in all four domains; these mutations are likely to impact on TFIIH stability. What is the role of the iron-sulphur cluster? Liu *et al.* suggest the cluster is a structural feature that stabilizes a small domain that physically separates the DNA-duplex strands, whereas Fan *et al.* additionally propose that the cluster position makes it an ideal candidate for efficient DNA-damage sensing.

These findings allow a molecular interpretation of human *XPD* mutations and broaden our understanding of how structural changes might impact cancer risks or result in ageing phenotypes.

Ekat Kritikou

> “…allow a molecular interpretation of human *XPD* mutations…”

ORIGINAL RESEARCH PAPERS Fan, L. *et al.* XPD helicase structures and activities: insights into the cancer and aging phenotypes from XPD mutations. *Cell* **133**, 789–800 (2008) | Liu, H. *et al.* Structure of the DNA repair helicase XPD. *Cell* **133**, 801–812 (2008)