

P024 Crystal structure of the FeS cluster-containing nucleotide excision repair helicase XPD

Wolski, Stefanie; Kuper, Jochen; Kisker, Caroline

*Rudolf Virchow Center for Experimental Biomedicine,
Institute for Structural Biology, University of Wuerzburg,
Germany*

DNA damage recognition by the nucleotide excision repair pathway requires an initial step identifying helical distortions in the DNA and a proofreading step verifying the presence of a lesion. This proofreading step is accomplished in eukaryotes by the TFIIH complex. The critical damage recognition component of TFIIH is the XPD protein, a 5'-3' DNA helicase that unwinds DNA and identifies the damage. We describe the three dimensional structure of an XPD protein from *Thermoplasma acidophilum* with high sequence identity to the human XPD protein which reveals how the structural framework is combined with additional elements for strand separation and DNA scanning.

The protein consists of two RecA-like helicase domains complemented by a 4Fe4S cluster domain, which has been implicated in damage recognition, and an additional α -helical domain. The first helicase domain together with the helical and 4Fe4S-cluster-containing domains form a central ring with a diameter sufficient in size to allow passage of single stranded DNA.

Based on our results we suggest a model how DNA is bound to the XPD protein. The structure also provides a framework to explain why some of the mutations in the human XPD gene lead to one of three severe diseases, xeroderma pigmentosum, Cockayne Syndrome, and trichothiodystrophy.