

P021 The structure and function of the archaeal XPD DNA helicase explain the phenotypes of *xpd* mutations in human

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The XPD helicase is a component of transcription factor IIH (TFIIH), which functions in transcription initiation and Nucleotide Excision Repair (NER) in eukaryotes, catalyzing DNA duplex opening localized to the transcription start site or site of DNA damage, respectively. XPD has a 5' to 3' polarity and the helicase activity is dependent on an iron-sulfur cluster binding domain, a feature that is conserved in related helicases such as FancJ. The *xpd* gene is the target of mutation in patients with xeroderma pigmentosum (XP), trichothiodystrophy (TTD) and combined XP with Cockayne's syndrome (XP/CS), characterized by a wide spectrum of symptoms ranging from cancer susceptibility to neurological and developmental defects.

This year, three archaeal crystal structures of XPD were obtained. In our lab, the structure of the crenarchaea *Sulfolobus tokodai*, together with detailed biochemical analyses, allows a molecular understanding of the structural basis for helicase activity and explains the phenotypes of *xpd* mutations in human. Furthermore, the functional DNA interactions of XPD have been studied on different DNA structures, as well as on damaged DNAs. Interestingly, XPD needs a 5' overhang of at least 12 nucleotides in length to display an activity whereas it's active on a 7 nucleotides bubble. This enzyme is also able to unwind efficiently DNA templates containing a damage. However, the presence of the single-strand DNA binding protein (ssb) inhibits the XPD activity, suggesting that these two factors cannot directly collaborate in an archaeal NER context.