Lesion Recognition By XPC, TFIIH And XPA In DNA Excision Repair

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Nucleotide excision repair (NER) removes DNA lesions caused by ultraviolet light (UV), cisplatin-like compounds and bulky adducts. After initial recognition by XPC in global genome repair (GGR) or a stalled RNA polymerase in transcription-coupled repair (TCR), damaged DNA is transferred to the seven-subunit TFIIH core complex (Core7) for verification and dual incisions by the XPF and XPG nucleases. Structures capturing lesion recognition by the yeast XPC-homolog Rad4 and TFIIH in transcription initiation or DNA repair have been separately reported. How two different lesion-recognition pathways converge and how the XPB and XPD helicases of Core7 move lesion DNA for verification are unclear. We report here structures revealing DNA-lesion recognition by human XPC and DNA-lesion handoff from XPC to Core7 and XPA. XPA, which binds between XPB and XPD, kinks the DNA duplex and shifts XPC and the DNA lesion by nearly a helical turn relative to Core7. The DNA lesion is thus positioned outside of Core7, as would occur with RNA polymerase. XPB and XPD, which track the lesion-containing strand but translocate DNA in opposite directions, push and pull the lesion-containing strand into XPD for verification.

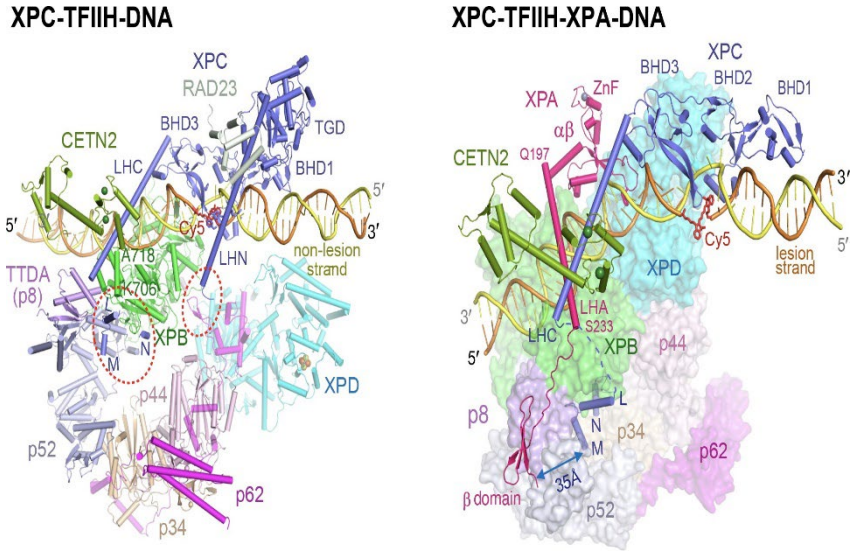

Figure 1