Recognition and Specificity in Base Excision Repair

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The Base excision repair (BER) system is a machinery of enzymes, recognising, removing, and correcting mispairs in the DNA. In the first step of the base excision repair system glycosylases recognise a damaged or mispaired base and remove it via glycosidic C1'-N1 bond hydrolysis. Apurinic/apyrimidinic endonuclease then cleaves the DNA backbone at the abasic site so as to allow subsequent insertion of a new, correct nucleotide by polymerase a and ultimately sealing of the backbone by a ligase enzyme. A crucial step in the base recognition and excision of mispared thymine (or damaged) bases by the BER enzyme human thymine DNA glycosylase (TDG) is the extrusion of the substrate base of the DNA helix and its "flip" into the active ste of the enzyme. The intrinsic conformational dynamics of mispaired DNA, exhibiting a partially-opened, partially flipped state [1], is exploited by the enzyme, stabilising this state over a closed state in the protein-DNA complex [2]. Further discrimination is achieved by the substrate base being better accommodated in the active site than non-cognate bases [2]. The glycosidic bond scission in the enzymatic complex is via a step-wise dissociative mechanism and largely facilitated by a proton transfer to the leaving base that is unlikely for intact cytosine bases. The chemical step can thus be understood as the last of several instances to protect intact DNA from base excision [3].

References

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