Biomolecular Simulation of Base Excision Repair

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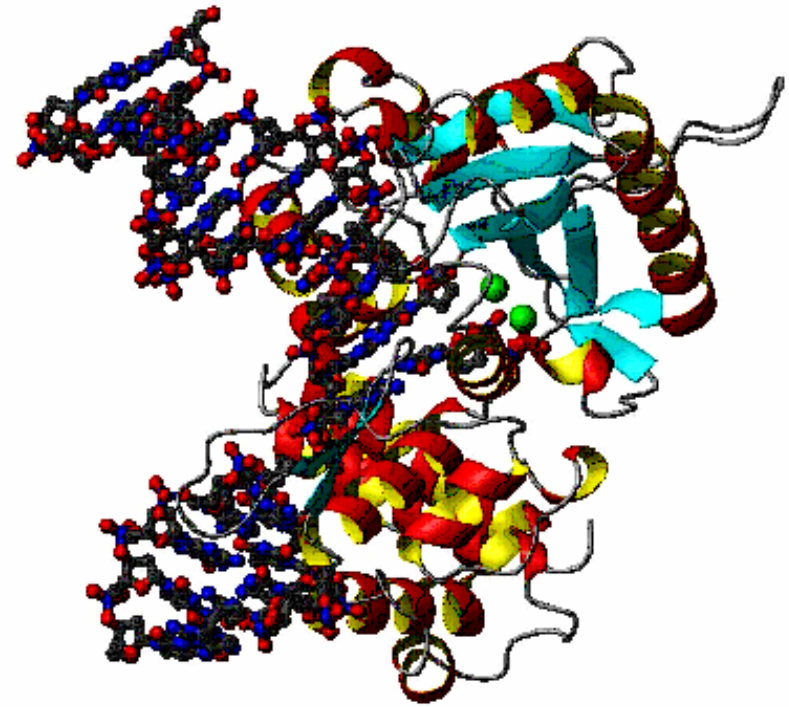

Closed conformation of the ternary complex of human polymerase-β (ribbons), gapped DNA (balls and sticks), and dCTP ternary complex. The dCTP substrate and magnesium ions (green) present in the active site can be seen in center of the picture.

Environmental factors including ionizing radiation contribute to continuous damage of cellular DNA, in addition to endogenous sources. The damage resulting from oxidative stress and ionizing radiation is primarily in the form of oxidized bases, single strand breaks, and loss of bases. These are the targets of the Base Excision Repair (BER) mechanism enzymes, including human polymerase-β.

A detailed understanding of the mechanism by which fidelity is assured by polymerase-β in the gap-filling DNA repair process requires a complete and accurate description of the polymerase-β active site in its active conformation just prior to the chemical nucleotidyl transfer step. Using the methods of molecular dynamics simulation and electronic structure calculations, we have been able to more fully characterize the active conformation of the polymerase-β active site.

R. C. Rittenhouse, W. K. Apostoluk, J. H. Miller, and T. P. Straatsma, “Characterization of the Active Site of DNA Polymerase β by Molecular Dynamics and Quantum Chemical Calculation”, PROTEINS 53 (3): 667-682 NOV 15 2003 .

Effects of 8-oxoguanine on DNA Bending

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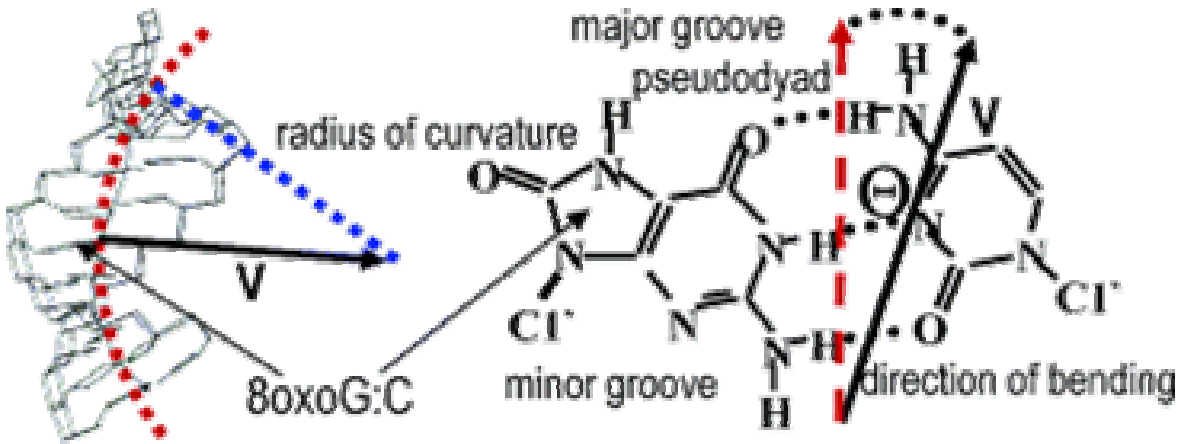

Molecular dynamics (MD) simulations were carried out on the DNA oligonucleotide GGGAA***C***AACTAG:CTAGTT***G***TTCCC in its native form and with guanine in the central G19:C6 base pair replaced by 8-oxoguanine (8oxoG). A box of explicit water molecules was used for solvation, and Na+ counterions were added to neutralize the system. The direction and magnitude of global bending were assessed by a technique used previously to analyze simulations of DNA containing a thymine dimer. The presence of 8oxoG did not greatly affect the magnitude of DNA bending; however, bending into the major groove was significantly more probable when 8oxoG replaced G19. Crystal structures of glycosylases bound to damaged-DNA substrates consistently show a sharp bend into the major groove at the damage site. We conclude that changes in bending dynamics that assist the formation of this kink are a part of the mechanism by which glycosylases of the base excision repair pathway recognize the presence of 8oxoG in DNA.

John H. Miller, Cheng-Chih P. Fan-Chiang, T. P. Straatsma, and Michael A. Kennedy , “8-Oxoguanine Enhances Bending of DNA that Favors Binding to Glycosylases ”, *J. Am. Chem. Soc.*, **125** (20), 6331 -6336, 2003 .