Poster 16

Solution Structures of the Mismatched Photoproduct Containing DNA Duplexes

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The pyrimidine(6-4)pyrimidone photoproduct is one of the major photoproducts induced by UV irradiation of DNA and occurs at TpT sites. The (6-4) adduct is highly mutagenic and leads most often to a 3′-T→C transition with 85% replicating error frequency. In contrast, its Dewar valence isomer is low mutagenic and produces a broad range of mutations with 42% replicating error frequency. In order to determine the origin of the mutagenic properties of these two photoproducts, we have used experimental NMR restraints and molecular dynamics to determine the solution structures of DNA decamer duplexes which contain mismatched base pairs between the 3′ T of two lesions and the opposite G residues. The O2 carbonyls of the 3′-T of both lesions form hydrogen bonds with the opposite G residues. In the case of the (6-4) lesion, the potential hydrogen bonding stabilizes the overall helix and restores the highly distorted conformation to the typical B-form-like DNA structure. This structural feature can explain the marked preference for the insertion of a G residue opposite the 3′-T of the (6-4) lesion during translesion replication. Thus these insertions yield the predominant 3′-T→C transition. However, in the case of the Dewar lesion, the hydrogen bonding of the G15 residue does not increase the thermal stability of the overall helix and does not restore the distorted backbone conformation of the DNA helix caused by forming Dewar lesion. Also, the G15 residue opposite the 3′ T of the Dewar lesion shows the poorer stacking

interactions with two bases of the Dewar product and with the adjacent A7 · T14 base pair than the corresponding A residue in DW/AA duplex. These structural features implicate that no thermal stability and no conformational benefits of G over A opposite the 3′ T of the Dewar lesion may facilitate the preferential incorporation of an A in accordance with the A rule during translesion replication and lead to the low frequent 3′ T→C mutation at this site.