

Abasic Sites Impact on DNA Structure and Interstrand Cross-Links Generation Modelling

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Abasic sites belong to the most common types of DNA damages. Formation of such lesions occurs spontaneously, significantly during Base Excision Repair¹. It has been shown that 10.000 abasic sites are generated per cell per day. These lesions are efficiently repaired by enzymes if they are isolated, but in presence of locally multiply damaged sites, repair is more difficult, nearly impossible². NMR studies indicate that closely spaced abasic sites in clusters lead to strong DNA distortions. Furthermore, it has been shown that abasic sites can react with an opposite purine, generating interstrand cross-links. The aldehyde group of the abasic site condenses with the exocyclic amino group of the purine, leading to a covalent adduct, bonding the two strands. These moieties are highly cytotoxic oxidatively-generated DNA lesions, very deleterious for cells since it blocks the strands separation during DNA replication, leading to apoptosis³. The feasibility of such lesions has been proved^{4,5}, with high yields (15-70%) reported for the formation of Ap-Adenine cross linking⁶. These findings suggest that the B-helix is flexible enough to allow the two reactants to approach and react, despite the mechanical constraints that it could induce.

We investigated the structural impact of abasic clusters in 23-bp oligonucleotides², and interstrand cross-links in 21-bp oligonucleotides⁶ (Figure 1) using molecular dynamics simulations. Structural analysis allowed us to probe the effect of such lesions on the double-helix and to rationalize experimental data. These investigations have been realized in collaboration with Nancy and Praha Universities. We plan to extend in a more systematic manner the modelling to other lesions for which structure can hardly be obtained by experimental means.

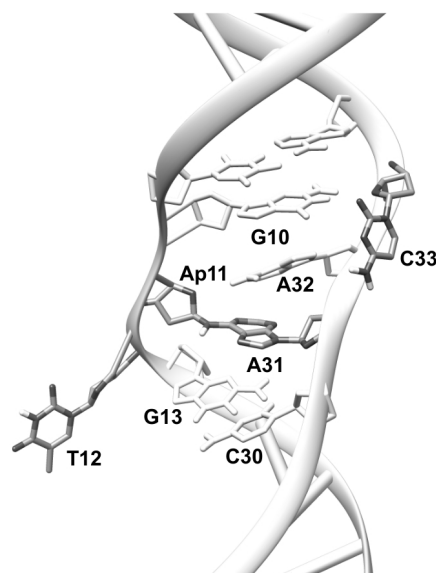


Figure 1. Cartoon representation of a 21-bp oligonucleotide containing Ap(11)-dA(32) cross-link obtained by modelling (water is omitted). Stable conformation presenting local rearrangement of the surrounding nucleic acids, including as T12 and C33 exclusion.

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