Applying a coarse-grained model to investigate structure and dynamics of oxidatively generated DNA lesions

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DNA in a cell is constantly subjected to oxidative stress which can lead to a formation of various complex DNA lesions. Important families of such lesions are intra- and interstrand cross-links (IaCLs and IeCLs) featuring two covalently bound nucleobases either within one strand or between the two DNA strands. These lesions are known to be highly mutagenic, thus playing an important role in carcinogenesis and aging.
IeCLs in particular can be formed from unrepaired abasic sites by oxidative processes. These sites constitue the most frequent DNA damage and have been extensively studied recently. However, the structural mechanism of IeCLs formation from abasic sites is only poorly understood. Detailed knowledge of structural and mechanical properties of DNA oligomers containing oxidized abasic sites is thus crucial. In case of IaCLs, no experimental structures are available, although the knowledge of their properties is important for interpreting the lack of repair of these lesions.
We employed a DNA coarse-grained model of rigid bases to asses structural and mechanical properties of oligomers containing either oxidized abasic sites or IaCLs. Parameters of the model were inferred from unrestrained explicit solvent molecular dynamics simulations.
Our results explain experimentaly proven high affinity of abasic site facing C base for the formation of IeCLs and suggest a mechanistic explanation of the phenomenon [1]. As for oxidative IaCLs, we observe that their structure significantly differs from photodimers and that the structure depends markedly on bases involved in the cross-link [2]. These differences may have specific implications for recognition processes.

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References

[1]Chandan, P., Drsata, T., Lankas, F. and Dumont, E. (2013) Structure, Dynamics, and Interactions of a C4'-Oxidized Abasic Site in DNA: A Concomitant Strand Scission Reverses Affinities.
[2]Dumont, E., Drsata, T., Guerra, C. F. and Lankas, F. (2015) Insights into the Structure of Intrastrand Cross-Link DNA Lesion-Containing Oligonucleotides: G[8-5m]T and G[8-5]C from Molecular Dynamics Simulations. Biochemistry, 54, 1259-1267.