HOW OXIDATIVE LESIONS AFFECT DNA SECONDARY STRUCTURE

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Guanine rich regions can adopt non-canonical four-stranded DNA structures called G-quadruplexes. Contiguous runs of guanines are especially susceptible to oxidation and contain the highest frequency of 8-oxo-7,8-dihydroguanine (^{oxo}G) - a major product of reactive oxygen species (ROS). We have analyzed the effect of ^{oxo}G on human telomeric (hTel) and promoter (bcl2) G-quadruplex structures. While substituting most G positions with ^{oxo}G proved detrimental, some positions within G-rich sequences were found to retain the G-quadruplex structure. Accommodation of ^{oxo}G at sites in *syn* or *anti* in non-substituted hTel G-quadruplex requires a minor structural rearrangement or a major conformation shift, respectively. Nevertheless, thermal stability of resulting G-quadruplex structures was typically reduced.[1] However, in an isolated case a reduction of structural polymorphism and a surprising boost in thermal stability of a bcl2 G-quadruplex with ^{oxo}G was also observed.[2] This was achieved by distinct hydrogen bonding properties of ^{oxo}G, which facilitate formation of an antiparallel basket-type G-quadruplex with a three G-quartet core and a G·^{oxo}G·C base triad. ^{oxo}G could act as an epigenetic modification, which alters DNA secondary structure and subsequently regulates gene expression by altering the binding of transcription factors to the DNA. This suggests a potential novel regulatory role of oxidative stress in gene transcription.

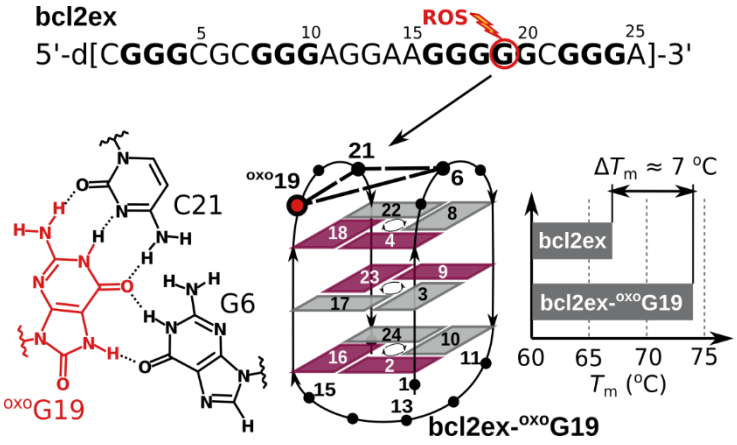

Figure 1. ^{oxo}G stabilizes the bcl2 G-quadruplex through extensive hydrogen bonding with loop nucleotides

Acknowledgements. This work was supported by the Slovenian Research Agency [J1-1704, P1-0242].

REFERENCES

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