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The effect of Mutations caused by oxidative DNA damage on the binding of anticancer drug mitoxantrone to the G-quadruplex structure

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Abstract

G-quadruplexes are unique DNA structures formed by sequences rich in guanine that play a role in regulating gene expression. 8- oxo-dG is the most prevalent oxidized form of the nucleotides that causes G > T transversion. This mutation is involved in the pathogenicity of ROS-related diseases. This research investigates the effect of guanine to thymine mutations on the interaction between the anticancer drug mitoxantrone and the four-stranded DNA structure, known as a G-quadruplex, in the promoter region of the c-Myc gene. Mitoxantrone is a topoisomerase II inhibitor that disrupts DNA replication and repair in cancer cells, thereby hindering cell proliferation. Utilizing absorption and fluorescence spectrometry along with gel electrophoresis, we investigated how G to T mutations on the tetrad planes influence on the binding of mitoxantrone to c-Myc G-quadruplex. The results of native PAGE indicated that the mutations change migration pattern and electrophoretic mobility of the G-quadruplex structure implying conformational change of the structure upon the mutatins. The percentage of hypochromicity and Stern-Volmer quenching constant of mitoxantrone changes upon the mutations. In addition, the mutations influence on the stability of the interaction in the presence of urea. In conclusion, our findings reveal that specific mutations in guanine caused by oxidative stress alter interaction between the anticancer drug and non-B DNA G-quadruplex structure. These results provide valuable insights for targeted drug

design against G-quadruplexes, with implications for enhancing therapeutic approaches in the oxidative stress condition of the cancer cells.

Key words: G-quadruplexes, c-Myc, Mitoxantrone, Absorption spectroscopy, Fluorescence spectroscopy, Gel electrophoresis

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