Influence of ligand binding on DNA G-quadruplex and duplex radio-induced denaturation

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The structure-function paradigm is of outstanding importance in biology, as can be noticed by considering proteins such as collagen, antibiotics such as vancomycin or DNA strands. Denaturation of these biomolecules due to loss of their structure (unfolding, conformational change…) can thus be very harmful for living organisms, and occurs under the action of external factors such as heating, change in pressure or chemical environment, but also ionizing radiation. Direct radiation effects on proteins and DNA strands such as fragmentation, cross-linking or release of small neutral molecules have been studied, but structural changes have scarcely been investigated, despite their importance in many fields, especially medicine. Indeed, techniques such as radio- or proton-therapy or tomography use ionizing radiation: X and gamma rays, but also ion beams. On the other hand, gas-phase experimental studies by means of mass spectrometry (MS) have brought a wealth of information on biomolecular systems, thanks notably to a perfect control of their stoichiometry. These last years, in collaboration with the group of T. Schlathölter from the University of Groningen (Netherlands), we have probed the response upon ionizing radiation (photons and ion beams) of collagen mimetic peptides,[1–4] vancomycin/receptor complexes involved in molecular recognition[5] but also DNA G-quadruplexes.[6] The latter are secondary DNA stable structures found in telomeres (*cf.* figure), the protective end-caps of chromosomes in most eukaryotic organisms. With aging, the length of telomeres reduces, but cancer cells use an enzyme called telomerase to keep this length constant. Therefore, telomerase inhibition is a promising strategy in cancer therapy. Since G-quadruplexes prevent telomerase to bind DNA, ligands that stabilize this structure might help in this way.

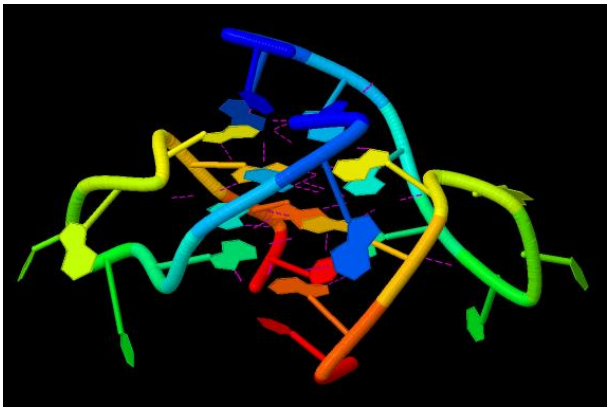

Figure 1: DNA G-quadruplex structure.

In this internship, the selected student will prepare and perform experiments consisting in irradiating DNA-ligand noncovalent complexes stored in an ion trap, and analyze the products by mass spectrometry. G-quadruplexes will be compared to duplexes, which are the usual DNA structures. He/she will also acquire and analyze data, write summaries, and give short talks to present the obtained results to other researchers. All these tasks require strong team-working abilities but also self-sufficiency.

References

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