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Telomeric G-quadruplexes: folding and molecular recognition

Guanine rich DNA sequences can fold into complex structures called G-quadruplexes in which four guanines form square planar structure stabilized with eight Hoogsteen hydrogen bonds, stacking interactions between the neighboring G-quartets and coordinated cations. They can be found in telomeres where they decrease the activity of the enzyme telomerase, which is responsible for maintaining the length of telomeres and is involved in around 85% of all cancers.1 Formation of stable G-quadruplexes in the region of the telomeric single-stranded overhangs has been found to inhibit telomerase activity. Therefore, telomeric G-quadruplexes are emerging as promising targets for anticancer agents able to inhibit the telomerase activity by binding to G-quadruplexes and thus stabilizing them.

Folding/unfolding pathways of the model telomeric human DNA, 5'-AGGGTTAGGGTTAGGGTTAGGG-3' (Tel22) in the presence of K+ ions were investigated by calorimetric (DSC, ITC) and spectroscopic (CD, UV-absorption) methods. Global thermodynamic analysis of experimental data obtained on monitoring the folding/unfolding of Tel22 induced by changes of temperature and K+ concentration showed that unfolding of Tel22 may be described as a monomolecular equilibrium three-state process that involves thermodynamically distinguishable folded, intermediate and unfolded state.2 Results confirm recent theoretical predictions of Tel22 folding pathways.3

Understanding the driving forces of human telomeric DNA folding into G-quadruplex structures sets the basis for studying ligand-Tel22 interactions. We have studied binding of netropsin, ethidium bromide, DP77, DP78 and Phen-DC3 to Tel22. In all cases, complex formation is enthalpy driven, accompanied with negative change in heat capacity. Binding constants are between 104 and 106.

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