STRUCTURE OF THE HUMAN TELOMERIC DNA

Attila Ambrus
Dep of Medical Biochemistry, Semmelweis University, Hungary

Human telomeric DNA consists of tandem repeats of the sequence d(TTAGGG) that fold into G-quadruplexes. The formation of such a DNA conformation in the telomere inhibits the activity of the telomerase enzyme, thus considered to be an attractive target for cancer therapeutic intervention. However, knowledge of the intact human telomeric G-quadruplex structure formed under physiological conditions is a prerequisite for structure-based rational drug design. Here we report the break-through finding of the folding topology of the human telomeric DNA in K^+ solution determined by NMR. Our results demonstrate a novel, unprecedented intramolecular G-quadruplex folding topology with hybrid-type mixed parallel/antiparallel G-strands. This telomeric G-quadruplex structure contains three G-tetrads with mixed G-arrangements, which are connected consecutively with a double-chain-reversal side loop and two lateral loops, each consisting of three nucleotides TTA. The folding presented here is different from those reported previously in Na^+ solution and in crystalline state. Our thorough analysis explains all the experimental data reported earlier on the human telomeric G-quadruplex and provides important insights for understanding the polymorphism and interconversion of various G-quadruplex structures. The folding topology of the human telomeric G-quadruplex determined here, first time in the physiological K^+ solution environment, is of particular pharmacological relevance as it can specifically be targeted now by G-quadruplex interactive small molecule drugs.