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Polymorphic G-quadruplex forming segment in promoter region of the c-MYC oncogene

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C-MYC is an important regulator of fundamental cellular processes such as regulation of cell cycle progression, normal cell growth and apoptosis. Overexpression of *c-MYC* was found in many types of human malignancies, including breast, cervix, colon, and small-cell lung cancers, glioblastomas, osteosarcomas, and myeloid leukemias. Down-regulation of *c-MYC* was proposed to be efficient strategy to combat listed types of cancer. The nuclease hypersensitive element III1 is responsible for ~90% of all transcriptional activity of the *c-MYC* gene. G-rich strand of the NHE III1 is structurally polymorphic and adopts multiple G-quadruplex structures. Targeting of the G-quadruplex(es) within NHE III1 using small molecule ligands was demonstrated to down regulate expression of the *c-MYC*. Whether the NHE III1 function is connected with the particular G-quadruplex conformation and its population in the polymorphic mixture and/or whether polymorphism itself is of functional importance is currently unknown. To address a role of structural polymorphism for NHE III1 function, we elaborated hybrid approach, based on combination of high-resolution methods of structural biology, concept of neutral evolution and *in vivo* functional assays. We show that sequence alterations occurring during ultra- short evolutionary times are functionally silent, while they exert dramatic impact on stereo- chemical behaviour of G-quadruplex conformational ensemble. Resolution of polymorphic mixtures of G-quadruplex structures using combination of high-resolution NMR spectroscopy and single particle FRET allows assessment of conservation of individual G-quadruplex conformations in polymorphic mixture through the evolution. The method is generally applicable for identification of functionally important conformation(s) in systems displaying inherent structural polymorphism.

Biography

Michaela Krafcikova has completed her Master's degree in the field of Molecular Biophysics at the Masaryk University, Czech Republic. At present, she is a first year PhD student of Biomolecular Chemistry (Masaryk University, Czech Republic). Her research focuses on role of G-quadruplex motifs in regulation of gene expression. She co-authored one paper (Slaninova et al. 2016).

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