Transcription-facilitating histone chaperons interact with genomic and synthetic G4 structures

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I. Pavlova[I,II], V. Tsvetkov[I,III,IV], E. Isaakova[I,II], V. Severov[I], M. Lagarkova[I,V], G. Pozmogova[I,V], A. Varizhuk[I,V,VI]

[I]Federal Research and Clinical Center of Physical-Chemical Medicine of Federal Medical Biological Agency, Moscow, Russia, [II]Moscow Institute of Physics and Technology, Doldoprudny, Russia, [III]Computational oncology group, I.M. Sechenov First Moscow State Medical University, Moscow, Russia, [IV]A.V. Topchiev Institute of Petrochemical Synthesis, Russian Academy of Sciences, Moscow, Russia, [V]Center for Precision Genome Editing and Genetic Technologies for Biomedicine, Federal Research and Clinical Center of Physical-Chemical Medicine of Federal Medical Biological Agency, Moscow, Russia, [VI]Engelhardt Institute of Molecular Biology, Moscow, Russia

The heterodimeric complex FACT (FAcilitates Chromatin Transcription) is a histone chaperone (HC) that promotes nucleosome reassembly to relieve the nucleosomal barrier for Pol II. In our recent human protein microarray (protoarray)-based analysis of the G-quadruplex (G4) interactome, FACT and its functional analog BRD3 efficiently bound several model G4 DNA structures [1]. Other structural and functional FACT-analogs, nucleolin and ATRX, were reported to interact with G4 DNA earlier [2,3]. So we assumed that affinity to G4 structures is a common feature of FACT-like HCs. First, we made a preliminary set of G4 motifs and verified their G4 folding in pseudointercellular and pseudoextracellular conditions by circular dichroism spectroscopy. Second, we checked HC-G4 binding in vitro by microscale thermophoresis, fluorescence assay, and polyacrylamide gel electrophoresis. As a result, we detected affinity in the low micromolar to nanomolar range. Then, we studied intercellular localization and toxicity of G4s on cancer cell lines to check if exogenous G4s can be used as anti-cancer agents. We also found out that genomic G4 motifs are often colocalized with occupancy sites of chosen HCs, so genomic G4s might be involved in transcription regulation too. We conducted molecular modeling experiments to discover whether HC-binding G4s could interfere with the HC function. To sum up, our findings encourage future investigations of genomic G4 contribution to nucleosome remodeling and transcription. This work was supported by RFBR [19-04-00050 A].

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