Natural ligands of tetraplex DNA structures as one of the important elements of gene regulation

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Over the past decade, many studies have confirmed that non-canonical DNA (ncNA) structures can play an important role in the regulation of critical cellular processes and can be promising targets for treating oncological and infectious diseases. An actively developing field of modern pharmacology is connected with the search for new synthetic drugs targeted to non-canonical DNA G-quadruplexes (G4s) and I-motifs (IMs) structures. Of particular fundamental interest is the potential gene-regulatory role of natural G4 / IM ligands — metabolites and components of nutrients. Although G4 stabilizing properties of a number of flavonoids and porphyrin derivatives are known today, this area has not been sufficiently studied. Here, we first characterized DNA structural selectivity of a set of metabolites of porphyrins and chlorins, abundantly present in the human body. Our approach is based on a set of common methods: spectrofluorometry, Förster resonance energy transfer (FRET) melting and fluorescent intercalator displacement (FID). The original panel of oligonucleotide targets included fragments of the human genome: G4 oligomers of various topologies, imperfect G4 and a set of IMs. Several natural ligands exhibited high affinity for the above targets, and specific interactions were of particular interest. For instance, we revealed a special selectivity of tripyromethane to the promoter site of oncogene cKit (Kd=0.7±0.2 mkM) and chlorine derivative Ce6 (Kd=3.6±0.2 mkM) to the telomeric G4 site 22AG. Collectively, the data obtained indicate the possibility of the participation of natural ligands in genomic regulation and can be useful for understanding the mechanisms of development of pathologies associated with impaired porphyrin metabolism (for example, with multiple sclerosis, lupus, etc.). This work was supported by RSF [20-15-00017].