DNA non-canonical interactions as one of the possible factors of genomic rearrangements

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The current view on chromatin plasticity suggests that protein factors orchestrate chromatin rearrangements, while DNA plays a more or less passive role. This paradigm may be a simplification: polymorphism of the DNA secondary structure and its impact on the higher-order structure are underestimated. We show that lengthy dsDNA harboring tetraplex motifs (G-quadruplexes, G4s, and i-motifs, IMs) can spontaneously form inter-duplex junctions. We visualized such complexes between model and genomic DNA fragments using high-resolution atomic force microscopy. Control duplexes lacking tetraplex motifs formed no junctions. We additionally confirmed the participation of G4s in DNA-DNA synapsis using tetraplex-DNA-specific antibodies and elucidated the topologies of the synaptic complexes using molecular modeling. The complexes are sensitive to microenvironment (pH, molecular crowding, monovalent cations, et cetera). They sustain pseudo-physiological conditions, however, their existence in vivo awaits bonafide verification. The general principle of their formation resembles presumed G4-driven enhancer-promoter interactions, but we show that both G4s and IMs contribute to the DNA association [1, 2]. We also provide in vitro evidence for G4/IM recognition by chromatin remodeling factors. For instance, we show that transcriptional repressor CTCF, which regulates the demarcation of topologically associated domains, is highly sensitive to IM folding. Secondary structures, rather than CpG methylation levels, may determine CTCF occupancy at IM-prone CpG islands. Collectively, our findings indicate that noncanonical (tetraplex) DNA folding may underlie engagement of chromatin remodelers, facilitate transient DNA-DNA contacts and contribute to shaping the long-standing chromatin organization and genomic rearrangements. This work was supported by RFBR [19-15-00024].

[1] A.D. Protopopova et al. PCCP, 2018, 20, 3543-3553. [2] A.M. Varizhuk et al. NAR 2018 (46) 8978-8992.