

structures. Recent findings [Dhakal et al. *Biophys J.* 2012; 102 (11):2575] suggest that in sequences containing four G/C-runs coexistence of G-quadruplexes (GQs) and I-motifs and in unlikely, presumably due to steric hindrance, and GQs or I-motifs are instead opposed by single-stranded loops. We assumed that in the case of microsatellites and other sequences with multiple (>4) G/C-runs, simultaneous formation of GQs and I-motifs might be possible provided that they are mutually shifted, which excludes steric hindrance (Figure 1). To verify our hypothesis and to study the impact of pH and salt concentration on conformational rearrangements in such G/C-rich sequences, we studied a series of DNA fragments from the human genome (chr 18, +66294092 to +66294035): the GQ-forming strand with 6 G-runs (G₃AT)₃G₃, its I-motif-forming complement and their truncated analogs containing only 4 G/C runs. We also synthesized elongated oligonucleotides with non-G/C rich flanks to model secondary structures in duplex media and their non-GQ/non-I-motif mutants.

The formation of individual GQs and I-motifs was demonstrated by physicochemical methods (UV-melting and circular dichroism spectroscopy). Noncanonical structures in duplex media were additionally studied by FRET and by monitoring fluorescence intensity of EtBr intercalated in duplex. Fluorescence of EtBr intercalated in GQs/I-motifs or ss-DNA (loops) is insignificant. Thus, decreased fluorescence in the microsatellites concerned in comparison with control B-DNA under GQ/I-motif-favoring conditions may be regarded as an evidence for the existence of non-B secondary structures (pH and salt-dependence of EtBr fluorescence intensity was taken into account).

Our preliminary results confirm the formation of non-B-DNA (presumably I-motif or mutually shifted I-motif and GQ) in native microsatellites. The equilibrium between duplex, I-motif and GQ is highly salt-dependent and may be shifted by the addition of various ligands. Assessment of the duplex:I-motif:GQ:loop ratios under different conditions and visualization of the 'shifted' structures by atomic force microscopy is currently underway.

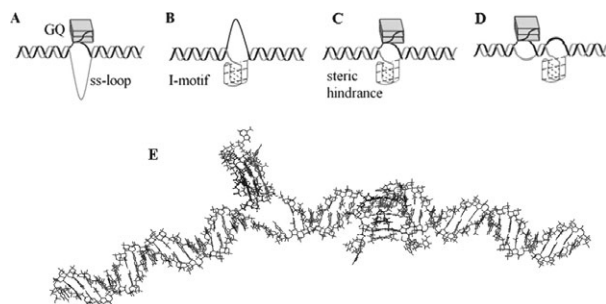


Fig. 1. GQs and I-motifs in duplex media. Possible variants of spatial organization.

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A, B – Sequences containing four G-runs/ four C-runs. GQs or I-motifs are opposed by single-stranded loops.

C – simultaneous existence of GQ and I-motif opposite each other – the unlikely variant.

D, E – mutually shifted GQ and I-motif (sequences contain >4 G/C-runs).

Keywords: G-quadruplex, I-motif, Secondary DNA structures.

WED-071

Sensitisation in the IFN- α/β ,IFN- γ crosstalk reveals mechanisms for enhanced information processing capacity of the STAT1,STAT2 signalling pathway

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Signaling pathways are the main cellular mechanism to transmit information about extracellular cues to the decision-making machinery of posttranslational protein modifications and gene expression processes. In the mammalian immune system processing information about extracellular cytokine concentration is of crucial importance for the tight control of the immune response and efficiency of the defence mechanisms. Malfunction of the signal transduction is tightly related to a variety of disorders ranging from impaired immunity to autoimmune diseases and cancer. Among the most intensely studied pathway is the JAK – STAT mechanism that controls cellular response to the plethora of cytokines, particularly to Interferons α/β and γ . Although interferons have been characterised as having antiproliferatory and apoptotic effect their mechanism of action is significantly more subtle and is a subject of intense investigations. In our work we have theoretically and experimentally examined the crosstalk between IFN- α/β and IFN- γ . The experimental measurements of the STAT1 and STAT2 activation upon stimulation with various combinatorial protocols provided novel insight about the sensitising role of IFN- α/β for subsequent IFN- γ detection. To clarify experimental data we constructed a mathematical model that is capable to explain the sensitisation mechanism, and together with the employed information theoretic methodology explains that prestimulation can enhance information processing capacity of the Jak1/Stat1. Our results provide a detailed mechanistic insight and general design principle that enables information processing in the immune system to be a dynamic process. We explain how adaptation leads to selectivity of information transmission, which is known to be a crucial mechanism for tight control of the immune response.

Keywords: Interferon, Jak/Stat, Stimulation.

WED-073

Stem cells: novel tool for treatment of human rare disorders. Computational modeling of adult stem cells

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Stem cells (SCs) could be considered as relatively new living cells with perspective characteristics and properties. They are a good tool for transplantation, in vitro and in vivo manipulations too. In cancer (leukemia) SCs have been used for surviving of the human organism as well. The aim of the work presented could be formulated as follows: to give some important points on experiments and theory of stem cells. Also to create a new computational model based on classical mathematics and mechanics theories for adult stem cells at different environments conditions. Author's FORTRAN programs have been designed and used for numerical experiments.

Keywords: None.