Impact of Cytosine Methylation on the bcl2Mid G-Quadruplex Structure: Structural and Thermodynamic Insights

A Talk by

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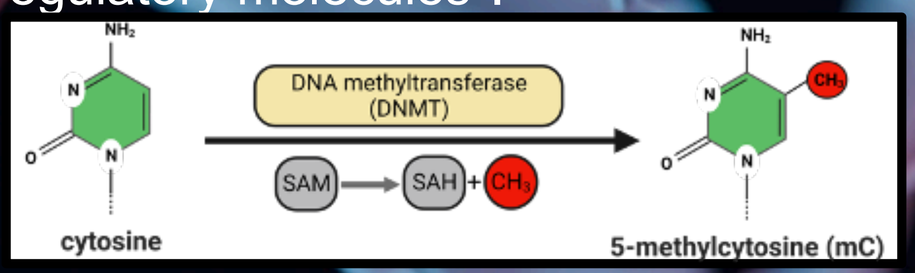
About the Speaker

Natasa Medved was born on 25th August 1986 in Ljubljana, Slovenia. She received her B. Sc.Degree in Biochemistry at the University in Ljubljana, Faculty of Chemistry and Chemical Technology in 2011 and worked in a medical biochemistry laboratory for 7 years. In 2018, she joined Slovenian NMR Centre as the lab manager, coordinating work in laboratory and leading oligonucleotide synthesis. In the same year, she began her Ph.D. studies at the University in Ljubljana, Faculty of Chemistry and Chemical Technology, focusing on the effects of epigenetic modifications on the G-quadruplex structure.

Talk Abstract

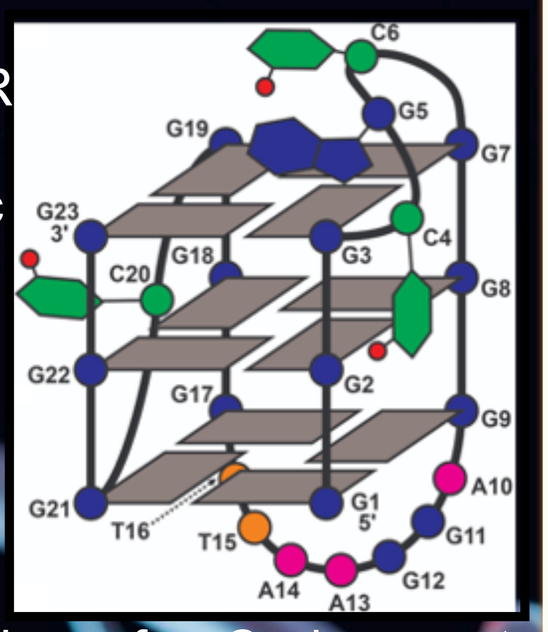
Cytosine methylation, a common epigenetic modification in mammalian DNA, occurs predominantly within CpG dinucleotides. CpG-rich regions, known as CpG islands (CGIs), are found in about 40% of mammalian genes, mainly in G/C-rich promoter and exon regions. CGIs are usually unmethylated in healthy cells, allowing gene transcription in the presence of transcription factors. Under certain conditions, however, methylation can largely suppress gene expression[1].

The enzyme DNA methyltransferase (DNMT) catalyzes the methylation of the cytosine residue, which leads to the formation of 5-methylcytidine (mC). This modified form of cytosine retains the ability to form Watson-Crick base pairs with guanine. However, despite structural compatibility, the presence of mC can disrupt the stacking and groove dimensions of DNA, which can affect the interactions of DNA-binding proteins and other regulatory molecules[2].



Recent studies have shed light on the intriguing role of G-quadruplexes, non-canonical secondary DNA structures formed by guanine-rich sequences, in modulating DNA methylation patterns and gene expression[3].These structures, which are characterized by their planar arrangement of four guanine residues connected by Hoogsteen-type hydrogen bonds, are stabilized by monovalent cations, mainly K^+ or Na^+ ions[4].

Our study investigated the influence of cytosine methylation on the structure and thermodynamic stability of the bcl2mid G-quadruplex, which is located on the G-rich strand of the P1 promoter of the BCL2 gene[5].



Our results, based on NMR and CD spectroscopy as well as differential dynamic calorimetry (DSC) measurements, show that the presence of mC does not hinder the formation of G-quadruplexes within the original oligonucleotide.

Surprisingly, the introduction of mC does not significantly alter the parent G-quadruplex topology but leads to local structural rearrangements and changes in thermodynamic stability. These results highlight the complex interplay between DNA methylation and G-quadruplex formation, with potential implications for gene regulation and epigenetic processes.

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Hosted By

Prof. Kavita Dorai, Dept. of Physical Sciences & Convener NMR Facility, IISER Mohali

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