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Mechanism of B-to-Z transition induced by A…A mismatch in a DNA duplex comprising of CAG trinucleotide repeat expansions

Thenmalarchelvi Rathinavelan
Indian Institute of Technology Hyderabad, India

Conformational polymorphism of DNA is a major causative factor behind several incurable trinucleotide repeat expansion disorders (TREDs) that arise from overexpansion of TREs located in coding/non-coding regions of specific genes. Hairpin DNA structures that are formed due to overexpansion of CAG repeat lead to Huntington's disorder and spinocerebellar ataxias. Hairpin structure formed during CAG repeat overexpansion contains periodic occurrence of A…A mismatches and hijacks the mismatch repair proteins (MSH2-MSH3) through tighter binding. Although DNA hairpin stem structure generally embraces B-form with canonical base pairs, it is poorly understood in the context of periodic non-canonical A…A mismatch in a CAG overexpansion. Molecular dynamics simulations on a DNA hairpin stem containing A…A mismatches as in a CAG repeat overexpansion show that A…A dictates local Z-form irrespective of starting glycosyl conformation, in sharp contrast to canonical DNA duplex. B-to-Z transition occurs through 'zipper mechanism' facilitated by base extrusion, backbone and/or base flipping. Root cause for such B-to-Z transition is due to the mechanistic effect that originates from the pronounced non-isostericity exhibited by A…A mismatch with flanking canonical base pairs. Based on these structural insights we envisage that such an unusual DNA structure of the CAG hairpin stem may have a role in disease pathogenesis. As this is the first study that delineates the influence of a single A...A mismatch in reversing DNA helicity, it would further have an impact on understanding DNA mismatch repair.

Biography

Thenmalarchelvi Rathinavelan has completed her PhD from Department of Crystallography and Biophysics, University of Madras. Subsequently, she did her Post-doctoral studies from Center for Bioinformatics/Department of Molecular Biosciences, The University of Kansas, USA. Currently, she is working as an Assistant Professor in IIT Hyderabad and has published more than 10 research papers in reputed journals.

tr@iith.ac.in

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