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Studies on the role of DNA dynamics in Neurodegeneration: New challenges and excitements

Jagannatha Rao KS
INDICASAT AIP, Republic of Panama

DNA is a dynamic and crucial molecule whose conformation kinetics plays a major role in biological function. Reports from our lab and elsewhere indicated the presence of non-BDNA forms of conformations in neurodegenerative diseases like Fragile X-syndrome, Huntington's chorea, Alzheimer's and others. Recently, our laboratory discovered the presence of Z-DNA in the hippocampal region of severely affected Alzheimer's disease (AD) brain samples and modified B-conformation in Parkinson disease. The alternate purine–pyrimidine bases are the potential sequences adopting Z-DNA, and these are present in the promoter regions of AD specific genes like amyloid precursor protein (APP), Presenilin and ApoE. We hypothesized that Z-DNA might be involved in the expression of these pathologically important genes. In the present paper, we have developed theoretical model on the possible mechanisms/hypothetical proposition of Z-DNA transition and its implications in AD. We developed a model where we try to understand that Z-DNA is formed in the promoter region of the APP, and Presenilin genes and this conformation may absorb the negative supercoils at that region. The decrease in the supercoil density alters the native supercoiling domain and positively regulates gene expression of like APP and Presenilin. We further try to understand that Z-DNA may be involved in the down regulation of genes involved in Aβ clearance defense mechanisms in AD. The proposed model tries to understand the AD behavioral pathology like emotions, eating behavior memory loss, and coordination failure.

e: Kjr5n2009@gmail.com