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G-quadruplex in parp1-mediated DNA damage response

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Each cell in the human body can receive tens of thousands of DNA lesions resulting in genomic instability and disease. The DNA damage response is a fundamental cellular system that protects cells from endogenous and exogenous insults to DNA. Though repair pathways are known, the mechanism of sensing, signaling, and repair are not completely defined. We have gathered evidence for a novel signaling mechanism functioning through G-Quadruplex (G4DNA) sequences. G4DNA is found in key regulatory regions of the cell such as promoters of proto-oncogenes and telomeres. Using a monoclonal antibody to folded G4DNA, our data suggest that the presence of G4DNA quadruplexes decrease in the nucleus with a concomitant increase in the cytoplasm during oxidative stress. Base excision repair (BER) is known to function on oxidized DNA bases such as 8-oxoG. Therefore, in order to determine why oxidative stress leads to the reduction of G4DNA quadruplexes in the nucleus, we are focusing on proteins involved in BER. Poly (ADP-ribose) polymerase 1 (PARP-1) is a DNA damage response protein that functions in BER and has been shown to bind G4DNA. The enzymatic activity of PARP-1, termed PARylation, is necessary for proper function of BER. Our preliminary data suggest that PARP-1enzymatic activity is stimulated by G4DNA only when the G4 structure contains one or more single-stranded DNA loop regions of >1 nucleotide. It has been shown by others that damaged guanines within G4DNA are extruded out of the quadruplex structure into long single-stranded DNA loops. We hypothesize that PARP-1 binds G4DNA and is enzymatically activated by the presence of a ssDNA loop extrusion that occurs when G4DNA is damaged during oxidative stress. We will measure binding between PARP-1 and various G4DNA substrates containing oxidized guanines and be varying single-stranded DNA loop lengths in order to test this hypothesis.

Biography

Andrea Edwards is a current graduate student at the University of Arkansas for Medical Sciences. She works under the advisement of Dr Kevin Raney in the Department of Biochemistry and Molecular Biology. Her current research is focused on providing further insight into the DNA damage response. Her area of interest includes G-Quadruplex sequences. These sequences occur in important regions of the genome and are also susceptible to oxidative damage. Her research goal is to determine the repair pathway involving these sequences. Mutation of these promoters within several proto-oncogenes has been associated with numerous cancers. Her goal is to provide information that could be used to develop better therapeutics targeted to cancer.

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