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Repair of DNA G-quadruplexes orchestrated by human FANCJ and REV1

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G-quadruplexes (or G4s) are stable structures formed by guanine-rich nucleic acids. G4-containing DNA regions are ubiquitous throughout the human genome, and these sequences are especially prone to oxidative damage. Accumulation of such DNA lesions is precursors for breast and ovarian cancers, Fanconi anemia, and other genetic diseases. FANCJ is a DNA helicase that unfolds G4s in human cells, and it coordinates with the REV1 polymerase and the *BRCA1* tumor suppressor to participate in separate DNA repair pathways. How these genomic caretakers recognize damaged DNA is still not well-understood. This work aims to define the substrate binding preferences of FANCJ, REV1, and *BRCA1*. Recombinant proteins were purified for biolayer interferometry (BLI) binding studies, and BLI results were validated by fluorescence spectroscopy measurements. We have recently identified an AKKQ amino acid motif within FANCJ that targets this helicase to G4 DNA structures. We now show that FANCJ also binds to 8-oxoguanine modified G4s with high affinity using this AKKQ motif. Subsequent G4-unfolding requires ssDNA binding and ATP hydrolysis. The unfolded G4 can quickly reform, and FANCJ undergoes repeated rounds of G4 processing while remaining bound to the DNA strand. We also show that FANCJ binds directly to the C-terminal domain of the REV1 translesion synthesis polymerase. These activities altogether would allow FANCJ to remove damaged G4s and then handoff the DNA substrate to REV1 in order to bypass a stalled replication fork.

Biography

Colin G Wu is a new Assistant Professor in the Department of Chemistry at Oakland University (Rochester, MI). He did his graduate work with Timothy Lohman at the Washington University School of Medicine (St. Louis, MO) and his postdoctoral studies with Maria Spies at the University of Iowa (Iowa City, IA). His research primarily focuses on the molecular mechanisms by which DNA repair enzymes function. Currently, his work involves understanding how FANCJ, REV1, and *BRCA1* assemble onto damaged DNA structures. His group uses a combination of biochemical/biophysical, single-molecule, and structural approaches to gain a detailed view of the macromolecular interactions involved in this DNA repair network.

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