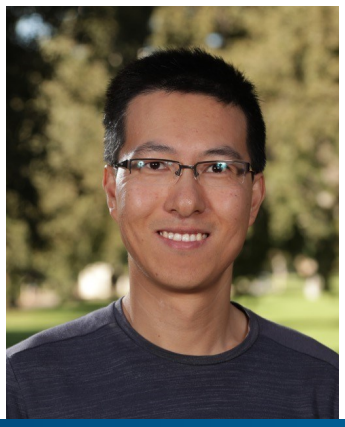
DICKERSON BIOCHEMISTRY SEMINAR SERIES



Exploiting Abasic Site Chemistry to Decipher Mitochondrial Genome Biology

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Human mitochondrial DNA (mtDNA) encodes 37 essential genes and plays a critical role in mitochondrial and cellular functions. Compared to nuclear DNA (nDNA), mtDNA is more susceptible to chemical modifications by endogenous and exogenous factors partly due to its proximity to the oxidative phosphorylation system and the lack of certain DNA repair pathways. Our research aims to understand the chemical and molecular mechanisms by which DNA modifications are processed in the mitochondrial genome and their implications in human diseases. In this seminar, I will discuss our recent efforts to probe the role of mitochondrial transcription factor A (TFAM) in damaged mtDNA degradation. We focus on a prevalent type of DNA modification, i.e., abasic (AP) sites, formed by the loss of nucleobases during natural depurination or depyrimidination and DNA repair. We used biochemical and cellular assays to demonstrate that TFAM accelerates DNA scission at AP sites. The reaction produces chemically reactive entities at the DNA terminus and leads to secondary products, such as TFAM-DNA cross-links and glutathionylated DNA single-strand breaks, which could serve as triggers for mtDNA degradation and the recruitment of additional proteins. We have also identified the cross-linking amino acids of TFAM using mass spectrometry. Together, our research demonstrates the involvement of TFAM in processing AP DNA damage in mitochondria. Last but not least, I will discuss how we exploit the chemistry of AP sites to develop specific chemical probes to label and enrich AP-DNA. We have successfully used the workflow to map AP sites and DNA alkylation modifications using next-generation sequencing in cultured human cells.

Friday, February 10 at 3:30pm

Mani L. Bhaumik Collaboratory, Dongwon Yoo Seminar & Conference Hall (Young Hall 4222)

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