SPECIAL SEMINAR

Monday, January 28th, 2019
3:30 pm - Chemistry #1315

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Illuminating Epigenetic Mechanisms in Cancer with Designer Chromatin

In the eukaryotic cell, the genome is packaged in a nucleoprotein complex known as chromatin. Histones comprise the protein component of chromatin and serve as a hot bed for posttranslational modifications (PTMs) that dynamically modulate local chromatin state to control DNA transcription, replication, and repair. Importantly, cancer cells depend on altered epigenetic landscapes to drive genomic instability and aberrant gene expression. In order to precisely target epigenetic misregulation in disease, it is critical to elucidate the mechanistic basis of how specific chromatin states are established and maintained. This talk will discuss how synthetic access to defined chromatin substrates enables the discovery of mechanisms by which histone PTMs modulate the genome. In the first part, a DNA-barcoded mononucleosome library was used to profile the activity of crucial DNA damage sensor enzymes (PARP1/2), uncovering new regulatory features in the DNA damage response. In the second part, designer chromatin substrates were used to investigate an oncogenic histone mutant, revealing details of how this mutation leads to deleterious epigenetic reprogramming. These efforts demonstrate how protein chemistry can be integrated with biochemical, biophysical, and genetic tools to facilitate analysis of the physicochemical principles underlying epigenetic dysregulation.

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