From mechanism to medicine: Decoding Chromatin and Cell Fate with Chemical Precision

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The David Lab investigates how chromatin organization and gene regulation are shaped by non-canonical chemical modifications and unconventional chromatin states, with chemical biology serving as both a conceptual framework and a primary experimental strategy. Rather than viewing chromatin regulation as exclusively enzyme-driven, we apply chemical principles to understand how intrinsic reactivity, metabolic byproducts, and altered structural environments directly modify chromatin and give rise to fundamental epigenetic behaviors. Central to our approach is deep expertise in peptide and protein chemistry, which we leverage to synthesize defined histone peptides, generate semi-synthetic proteins both *in vitro* and *in vivo*, and design peptidomimetic molecules as functional probes and therapeutic candidates. These capabilities also enable the development of new tools, including highly specific antibodies against chemically defined epitopes. Together, we build and apply a diverse toolkit of synthetic peptides, engineered chromatin substrates, small-molecule probes, and selective inhibitors to interrogate chromatin chemistry in controlled systems and in cells.

Using these approaches, we have identified a new family of non-enzymatic histone modifications that arise from endogenous metabolic byproducts and directly alter chromatin structure and function. We extend these chemical biology platforms to study epigenetic regulation in non-canonical chromatin contexts that emerge during genomic instability and infection, including micronuclei, extrachromosomal DNA, viral minichromosomes such as hepatitis B virus cccDNA, and chromatin-associated material on extracellular vesicles. Through chemical reconstitution and epigenomic profiling, we show that these atypical chromatin structures are governed by distinct epigenetic programs and can actively influence transcriptional regulation, inflammatory signaling, and cellular state.

In this talk, I will describe our recent advances, both chemical and functional, in uncovering how unique histone modifications shape chromatin organization and determine cell fate. I will also highlight how we develop and leverage peptide and protein chemistry technologies to precisely interrogate and manipulate these epigenetic mechanisms.

Selected Publications:

1. Zheng Q… David Y. Reversible histone glycation is associated with disease-related changes in chromatin architecture. ***Nat Commun***. 2019.
2. Agustinus A…, David Y†, Bakhoum SF†. Epigenetic dysregulation from chromosomal transit in micronuclei. ***Nature***. 2023.
3. Zheng Q…David Y†, Ian I†. Bidirectional histone monoaminylation dynamics direct neural rhythmicity. ***Nature***. 2025.
4. Prescott NA…David Y. A nucleosome switch primes Hepatitis B Virus infection. ***Cell***. 2025.
5. Akano I…David Y. The SWI/SNF-related protein SMARCA3 is a histone H3K23 ubiquitin ligase that regulates H3K9me3 in cancer. ***Mol Cell***. 2025.