New tricks for old dogs: novel chromatin targets of histone methyltransferase enzymes.

Histone lysine methylation represents one of the most prominently studied chromatin modifications where they impact transcription and epigenetic inheritance. While the enzymes that control the deposition and removal of lysine methylations on histone residues are evolutionarily ancient and widely conserved, their known substrates are almost exclusively restricted to these solitary lysine residues. This is true even though many of these enzymes have crucial roles in development and disease.

We are combining molecular genetic and LC-MS/biochemical approaches to systematically identify new and functionally relevant substrates for numerous conserved histone methyltransferase and demethylases present in yeast. Stemming from this work, we have identified the Nrd1-Nab3-Sen1 (NNS) transcriptional termination complex as a potential enzymatic target of Set1, a conserved histone H3 lysine-4 methyltransferase orthologous to human MLL, and Set3, which is activated by H3K4me and is itself homologous to MLL5. Specifically, Nab3-K363 is mono-methylated in a manner dependent on Set1 and Set3. Nab3-K363 resides within the Nab3 RNA recognition motif (RRM) and makes physical contact with nascently transcribed RNA. Our ongoing work is advancing the model that Nab3-K363 undergoes direct methylation by Set1 and/or Set3 and that this methylation impacts Nab3 RNA binding to regulate transcriptional termination in concert with other chromatin modifications. Having established this approach, we are interrogating numerous other chromatin-associated complexes that participate in the transcription cycle.