Histone Crotonylation: Enzymes and Function in Transcription and beyond

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Recent studies indicate that, in addition to acetylation, lysine residues in histones are subjected to various types of acylation including malonylation, propionylation, crotonylation and etc, raising the question as to the functions and enzymes for different types of histone acylation. As crotonylation occurs broadly in core histones and has been implicated in transcriptional regulation, we focus our attention on enzymes catalyzing dynamic histone crotonylation. We demonstrate that among the known histone acetyltransferases (HAT), only CBP/p300 and MOF possess histone crotonyltransferase (HCT) activity. We show that CBP and p300 are likely the major HCTs in mammalian cells, whereas MOF is an evolutionarily conserved HCT. By generating novel CBP/p300 mutants with deficient HAT but competent HCT activity, we demonstrated that CBP/p300 can stimulate transcriptional activation in the absence of HAT activity. We also present evidence that class I histone deacetylases (HDACs) rather than sirtuin family deacetylases (SIRTs) are the major histone decrotonylases (HDCRs) and that histone crotonylation is as dynamic as histone acetylation in mammalian cells. Notably, we have generated novel HDAC1 and HDAC3 mutants with impaired HDAC but sustained HDCR activity. Using these mutants we demonstrate that selective histone decrotonylation in mammalian cells correlates with a broad transcriptional repression. Together our studies provide compelling evidence that in transcriptional regulation histone crotonylation plays a broad and non-redundant function to acetylation. Furthermore, we will present evidence that crotonylation is a potential biomarker for cancer diagnosis.