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Chromatin recognition and regulation of the acetyltransferase CBP/p300

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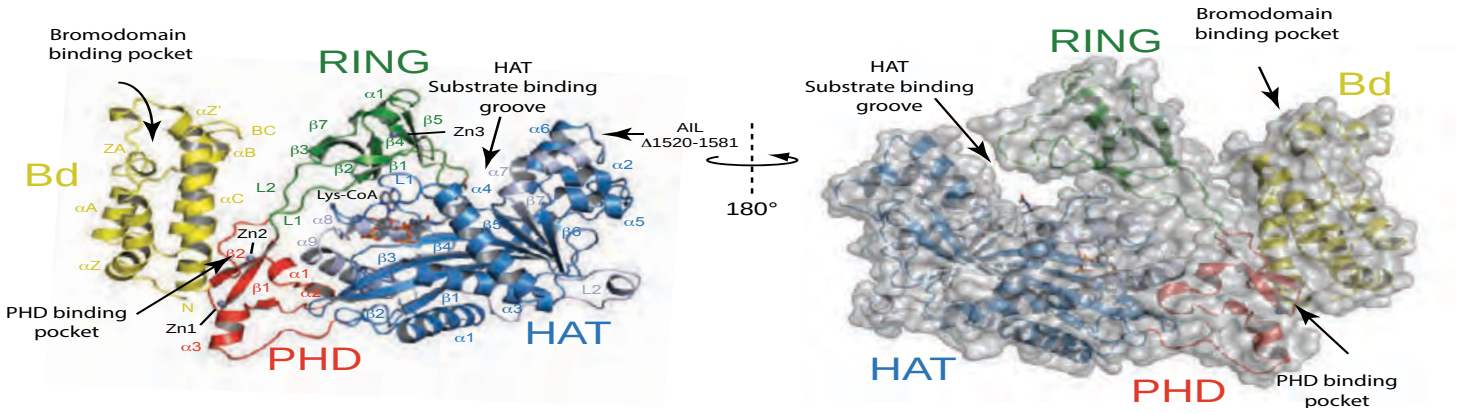
Gene regulation in higher eukaryotes requires recruitment of the transcriptional co-activators CBP/p300 that associate with transcriptional regulators and integrate a large number of signal transduction pathways. Recruitment of CBP/p300 results in acetylation and remodeling of inhibitory chromatin. Recently we have determined the 2.8Å crystal structure of the catalytic core of p300 containing its Bromodomain, the CH2 region and HAT domain in complex with the bi-substrate inhibitor, Lys-CoA. Unexpectedly the structure reveals that the CH2 region contains a discontinuous PHD domain which is interrupted by a RING domain. The Bromodomain, PHD, RING and HAT domains adopt an assembled configuration in which the RING domain is positioned over the HAT substrate binding pocket. Disease mutations that disrupt RING attachment lead to upregulation of HAT activity, revealing an auto-inhibitory role for this domain. Detailed investigation of chromatin substrate recognition showed that the Bromodomain preferentially interacts with histones containing combinations of acetylations rather than singly modified sequences, whereas the p300 PHD domain did not interact with canonical substrates. Our results demonstrate that the Bromodomain substrate specificity is compatible with HAT substrate acetylation patterns suggesting that positive feedback is likely an important component in establishment of active chromatin states. We here present progress in our understanding of the regulation of p300 activity, chromatin modification, readout and how disease-related mutations result in dysregulation of these activities.

[1] *M. Delvecchio, J. Gaucher, C. Aguilar-Gurrieri, E. Ortega. D. Panne, Nat Struct Mol Biol, 2013, 21, 1040-1047*



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