CENTER FOR RNA BIOMEDICINE

RNA Innovation Seminar

Monday, December 17, 2018 at 3:00pm
ABC Seminar rooms, Biomedical Research Science Building (BSRB), 109 Zina Pitcher

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"A non-enzymatic function associated with a putative histone demethylase regulates heterochromatin spreading and inheritance"

Abstract: Heterochromatin is characterized by histone hypoacetylation and an enrichment of methylation marks on histones which are associated with epigenetic silencing. In fission yeast, a single H3 methyltransferase Clr4 (Suv39h) directs all of the methylation of H3K9 i.e., H3K9me2/3 which enforces the establishment of transcriptionally silent regions in the genome referred to as heterochromatin. A putative histone demethylase, Epe1, is recruited to sites of heterochromatin via interaction with a chromo-domain containing protein Swi6, homolog of HP1. The loss of Epe1 has been associated with the propagation of silent epigenetic states in a DNA or RNA sequence independent manner. How Epe1 carries out its function as an anti-silencing factor remains unknown. Despite having sequence homology with known histone demethylases, Epe1 exhibits no detectable demethylase activity *in vitro*. Here, we demonstrate that mutations within the catalytic JmjC domain of Epe1 disrupt its interaction with Swi6. Using a combination of genetic and biochemical assays, we show that the interaction between Epe1 and Swi6 is direct, depends on the active conformation of the JmjC domain and is sensitive to mutations that affect co-factor binding. Surprisingly, in cells the interaction between Epe1 and Swi6 requires functional heterochromatin. We reconstituted this dependence *in vitro* and demonstrate that the presence of an H3K9 tri-methyl peptide enhances the interaction between the two proteins. We attribute this stimulatory effect of H3K9 methylation to an auto-inhibitory role for the C-terminal region of Epe1. Deleting this segment resulted in a dramatic increase in Swi6 binding and no further stimulation in the interaction between Epe1 and Swi6 upon addition of an H3K9me3 peptide. Finally, we demonstrate that this non-enzymatic role of Epe1 regulates the binding of a histone deacetylase. Our work demonstrates that Epe1 selectively binds and inhibits heterochromatin bound Swi6 molecules which in turn impedes downstream heterochromatin assembly.