MS109.O01

Molecular basis of the selective methylation of histone H3.1

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Histone proteins are critical components of the chromatin fiber. With the exception of histone H4, histone proteins exist as different variants with assigned specialized functions and are proposed to act as key elements for the selective deposition of histone post-translational modifications (PTMs). Among these variants, H3.3, which differs from H3.1 by only 5 residues, has been predominantly found in the proximity of genes that are highly expressed; however the functional consequences of that marking have remained enigmatic. Herein we report the crystal structure of the trithorax-related SET domain histone H3.1 K27 methyltransferase ATXR5 in complex with histone H3.1 and the product cofactor S-adenosylhomocysteine. Overall, the SET domain folds as an all β-strands structure preceded by the pre-SET domain which folds as three long α-helices. The histone H3 is maintained in an elongated conformation by residues located both in the SET and pre-SET domains of ATXR5. Interestingly, we found that a three residue loop folds back on top of the ATXR histone H3.1 binding cleft shielding the peptide from the solvent and maintaining P30 and A31 of H3.1 in a shallow hydrophobic pocket. Strikingly, substitution of A31 for a threonine, the corresponding residue in histone H3.3 in plant, severely impairs ATXR5 methyltransferase activity. Finally, biochemical and structural studies revealed that, with the exception of R26 mono-methylation, post-transcriptional modifications of residues neighboring K27 is detrimental to ATXR5 activity. Overall, our results suggest that the deposition of H3.3 serves to prevent K27 mono-methylation and heterochromatin formation during DNA replication.

Keywords: histone H3, heterochromatin