Cell Cycle 13:6, 879–880; March 15, 2014; © 2014 Landes Bioscience

Histone deacetylation: Establishing a meiotic histone code

Comment on: Balboula AZ, et al. Cell Cycle 2014; 13:600–11; PMID: 24317350; http://dx.doi.org/10.4161/cc.27410

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Histone posttranslational modifications are essential for the control of gene expression, chromatin structure, and genome integrity. Genome-wide histone modifications induce changes in large-scale chromatin structure leading to the formation of distinct chromosomal domains that are heritable through mitosis and essential for cell division. Transmission of epigenetic information during mitosis is required for the faithful inheritance of transcriptional programs and for maintenance of cell identity.[1] Importantly, genome integrity is also maintained through a series of mitotic histone modifications that coordinate higher-order chromosome structure and accurate chromosome segregation.[1]

Global histone deacetylation is an important mechanism that takes place during the transition of the interphase nucleus into mitosis and is essential to regulate proper chromosome condensation, coordinate chromosome–microtubule interaction and to ensure faithful chromosome segregation.[2] Histone deacetylation is also prominent during meiosis onset in the mammalian oocyte, where it constitutes an important developmental transition in preparation for meiotic chromosome segregation.[3,4] The functional significance of this mechanism for the establishment of accurate chromosome–microtubule interactions and for proper chromosome segregation during the 2 critical meiotic divisions in the mammalian female gamete has been well documented.[4,5] However, the specific chromatin remodeling enzymes involved as well as the mechanisms responsible for regulating this important developmental transition remain to be determined. Until now, several histone deacetylases have been involved in this process. Notably, current evidence reveals that this global chromatin-remodeling mechanism exhibits distinct strategies in the female germ line.[3]

Genome-wide histone deacetylation at multiple lysine residues of histones H3 and H4 has been implicated in the establishment of critical chromatin marks and recruitment of key regulatory proteins required for chromosome structure and function.[1] The experimental evidence obtained until now indicates that histone deacetylase 3 (HDAC3) is the principal enzyme inducing global deacetylation in somatic cells. Shortly after prophase, HDAC3 forms a complex with A-kinase-anchoring proteins, AKAP95 and HA95, to become associated with mitotic chromosomes, where it is required for global deacetylation of histone H3 and H4.[6] In contrast, HDAC2 seems to be the enzyme largely responsible for inducing global deacetylation of histone H4 in mouse oocytes, specifically at lysine 16 (H4K16Ac).[7] Loss of HDAC2 function induces defects in chromosome condensation and segregation in maturing oocytes, and mutant females exhibit subfertility.[7] However, the protein complexes required for the association of HDACs with the chromatin template during the G_2/M transition in mammalian oocytes remain to be determined. Now, Balboula et al.[8] show that the retinoblastoma binding protein (RBBP7) is a maternally recruited message translated during meiotic maturation that plays a role in regulation of histone deacetylation in the mouse oocyte.

RBBP7 is a component of several co-repressor protein complexes known to interact with histone deacetylases. The authors show that in mouse oocytes RBBP7 is localized to the meiotic spindle, and its protein levels increase between metaphase I and metaphase II followed by subsequent degradation at the zygote stage embryo. Functional ablation of RBBP7 using siRNA/morpholino knockdown in mouse oocytes inhibited global deacetylation of meiotic chromosomes and interfered with the centromeric localization of Aurora kinase C and survivin, 2 prominent members of the chromosome passenger complex (CPC), resulting in abnormal chromosome segregation.[8] Importantly, overexpression of Aurora kinase C, the catalytic subunit of the CPC, partially restored the rates of meiotic maturation and rescued the effects on chromosome alignment defects. Interestingly, knockdown of endogenous RBBP7 inhibited global deacetylation of H3K4Ac, H4K8Ac, H4K12Ac, and H4K16Ac, but not H3K9Ac, H3K14Ac, and H4K5Ac, suggesting that different acetylation marks are displaced from the chromosomes by dedicated HDACs. These results provide evidence indicating that interfering with global histone deacetylation during meiosis prevents CPC function. These findings contribute with novel observations that shed light onto the mechanisms of global histone deacetylation during meiosis and suggest that RBBP7 might be important to mediate the association of specific HDACs with the meiotic spindle.

Evidence has been provided on the persistence of specific histone acetylation marks that survive global deacetylation in mitotic but not meiotic chromosomes such as H4K12Ac.[3] The function of such histone modification remains to be determined. However, contrary to mitotic cells, where chromosomal epigenetic marks constitute important "bookmarks" to restore the transcriptional program of a cell, this program is erased and re-set to re-establish totipotency through genome reprogramming in the zygote. At the clinical level, the studies of Balboula et al.[8] shed light into the mechanisms by which oocytes from females of advanced reproductive age may exhibit defects in global histone deacetylation and a striking rise on the incidence of aneuploidy.

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