TESTICULAR OVER-EXPRESSION OF DEACETYLASE SIRT1 IN CB1-KNOCKOUT MOUSE INTERFERES WITH HISTONE DISPLACEMENT BY AFFECTING ACETYLATION OF HISTONE H4.

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Spermiogenesis represents the terminal differentiation phase of germ cells as it differentiates round spermatid in spermatozoa (SPZ). During this differentiation phase a massive chromatin remodeling drastically changes nuclear condensation status of germ cells. Chromatin remodeling involves i) histone displacement via H4tetraAc at K5,8,12,16 and ii) histone-to-protamine exchange. In mammals, histone displacement preserves a small percentage of histone so that SPZ contains protamines-bounded DNA and a small fraction of nucleo-histone chromatin.

Post translational modifications of histone tails (HPTMs) marks nucleo-histone chromatin. This chromatin contains condenses housekeeping, miRNA, developmental and paternally-expressed imprinted genes, suggesting that any interference with mechanism of histone displacement may disturb sperm histone content and HPTMs with potential inter/trans-generationally inheritable effects.

The cannabinoid receptor 1 (CB1) promotes histone displacement as CB1 knockout (CB1-/-) mice produce SPZ with abnormal histone content.

To understand the role of CB1 in this mechanism we analyzed gene expression of the deacetylase Sirt1 and H4tetraAc levels (at K5,8,12,16, in combination or isolated), in wild type (WT) and CB1-/- testis.

Results demonstrate that CB1 gene deletion interfered with histone displacement by upregulation of Sirt1 expression. Indeed, Sirt1 as well as H4K5Ac, -K8Ac and -K12Ac levels were more higher in testis from CB1-/- mice than WT. Viceversa, H4K16Ac and H4tetraAc levels were less high in testis from CB1-/- than WT. Testicular inhibition of Sirt1 promoted lower levels of H4K5Ac, -K8Ac and -K12Ac while H4K16Ac and H4tetraAc levels increased.

We concluded that CB1 deletion upregulated Sirt1 expression. This overexpression affected acetylation of histone H4 at K5, K8, K12 and K16 resulting to decrease H4tetraAc levels with negative effects on histone displacement and sperm histone content.