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Histone H2Ax is required for proper chromosome synapses and double strand breaks repair of mouse spermatocytes

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In male mouse, chromosome dynamics and recombination are tightly regulated by a pachynema checkpoint that arrest meiotic progression of recombination defective spermatocytes, which are than eliminated by stage IV of the epithelial cell cycle. In addition, male mouse meiocytes cell death is also activated by the failure of meiotic sex chromosome inactivation (MSCI). In the latter case, the apoptotic arrest is driven by the lack of silencing of XY-linked genes. In most of meiotic recombination mutants studied, so far, have been shown that in presence of a grossly aberrant synapses, also XY gene silencing fail. Thus both a defective chromosome dynamic and impaired MSCI contributes to spermatocytes elimination. Among several mutants H2Ax-/- spermatocytes are considered to be a model for apoptotic elimination exclusively driven by MSCI failure; such that no defects have been reported in chromosome dynamic and recombination. In this study we demonstrate that a fraction (~ 30%) of H2Ax-/- spermatocytes are defective in proper chromosome pairing, indicating that MSCI failure is not the only cause for their elimination by stage IV. In agreement with this finding, we find that the absence of H2Ax impair the proper localization, onto chromatin, of DNA repair factors, such as MDC1, BRCA1, MSH4 and MLH3. Interestingly, the defects in chromosome synapses and MLH3 foci assembly are ameliorated by Spo11 heterozygosis. Overall these results demonstrate that, in meiotic cells, H2Ax is require for the efficient processing of Spo11-induced double strand breaks.

Keywords: H2Ax, spermatogenesis, DNA repair

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