DNMT3L: A COORDINATOR OF EPIGENETIC MODIFICATIONS DURING SPERMATOGENESIS

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Spermatogenesis is a process with unique epigenetic requirements. The differentiation from diploid spermatogonia to haploid spermatozoa requires regulation of genomic imprint establishment, stage specific gene expression, meiotic division, and the histone-protamine transition. The methyltransferase regulator, Dnmt3L, is expressed during gametogenesis and is necessary for establishment of maternal methylation imprints in the oocyte. Targeted disruption of Dnmt3L does not appear to affect oogenesis, as mature oocytes are generated, however resultant heterozygous progeny die mid gestation due to biallelic expression of imprinted genes. Dnmt3L–/– males however show spermatogenic arrest. We found that this arrest occurs during prophase I of meiosis, with spermatocytes lost by both apoptosis and germ cell sloughing. A progressive degeneration ensues, resulting in a Sertoli cell phenotype. Electron microscopy of meiotic spermatocytes revealed that homologous chromosomes fail to align and form synaptonemal complexes. Furthermore, Dnmt3L–/– spermatocytes show abnormal methylation on paternally imprinted genes and abnormal global retention of histone acetylation, implicating Dnmt3L in histone deacetylase recruitment. Thus, during spermatogenesis, Dnmt3L is crucial for two distinct epigenetic modifications; imprint establishment and global histone deacetylation prior to homologous chromosome alignment. The latter defect is likely to affect the alignment of homologous chromosomes and trigger the pachytene checkpoint leading to spermatocyte death. Since Dnmt3L has no DNA methlytransferase or HDAC activity itself, we propose that Dnmt3L is essential for the coordination of epigenetic layers, at least during spermatogenesis.

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