CDK2 regulates the NRF1/Ehmt1 axis during meiotic prophase I

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Abstract

Meiosis generates four genetically distinct haploid gametes over the course of two reductional cell divisions. Meiotic divisions are characterized by the coordinated deposition and removal of various epigenetic marks. Here we propose that nuclear respiratory factor 1 (NRF1) regulates transcription of euchromatic histone methyltransferase 1 (EHMT1) to ensure normal patterns of H3K9 methylation during meiotic prophase I. We demonstrate that cyclin-dependent kinase (CDK2) can bind to the promoters of a number of genes in male germ cells including that of Ehmt1 through interaction with the NRF1 transcription factor. Our data indicate that CDK2-mediated phosphorylation of NRF1 can occur at two distinct serine residues and negatively regulates NRF1 DNA binding activity in vitro. Furthermore, induced deletion of Cdk2 in spermatocytes results in increased expression of many NRF1 target genes including Ehmt1. We hypothesize that the regulation of NRF1 transcriptional activity by CDK2 may allow the modulation of Ehmt1 expression, therefore controlling the dynamic methylation of H3K9 during meiotic prophase.

Figure

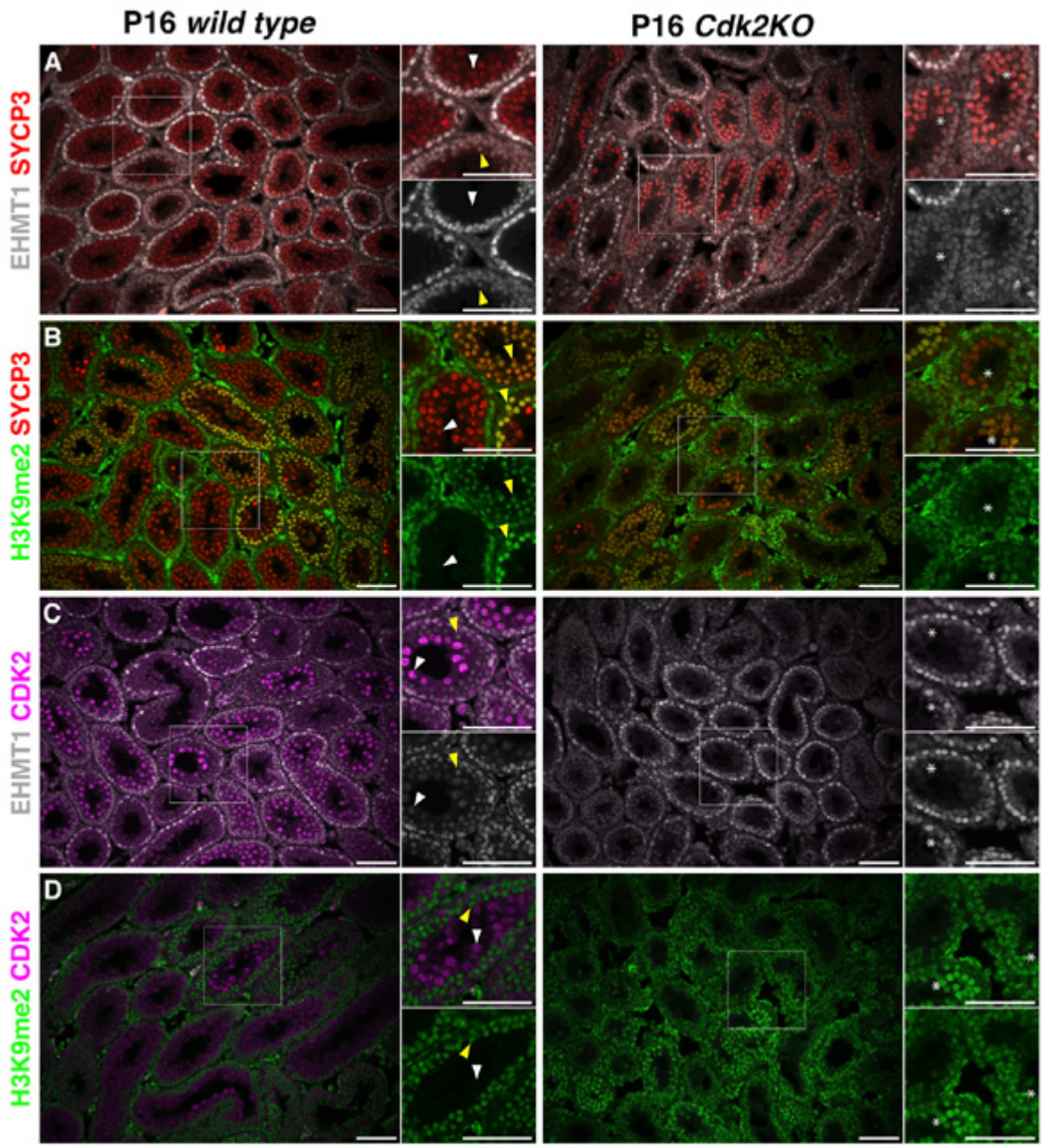

Figure Legend: Immunofluorescence analysis of P16 wild-type and Cdk2KO testis. Immunostaining was performed on P16 testis sections from wild-type (left) and Cdk2KO mice (right). Double immunostaining of EHMT1 (white) or H3K9me2 (green) with either SYCP3, a marker of spermatocytes for all stages of meiotic prophase I (red; A and B), or CDK2 (purple; C and D). For each image, areas of interest are highlighted (white boxes) and displayed as magnified images toward the upper right-hand side. Additional single channel images for either EHMT1 or H3K9me2 are also shown to the lower right-hand side. This is to indicatewhere costaining has occurred in the merged image. For wild-type images,

yellow arrowheads indicate early prophase I (preleptotene, leptotene, and zygotene) spermatocytes, and white arrowheads indicate pachytene stage spermatocytes. For Cdk2KO images, potential pachytene-arrest stage spermatocytes are indicated by white asterisks. At least 25 images of distinct areas of seminiferous tubules were analyzed for each genotype and for each costaining. Original images were individually pseudo-colored and combined as indicated using Adobe Photoshop CC 2018. Scale bars, 50 μm.