H3K4me3-dependent epigenetic memory regulates transcriptional reactivation in the oocyte

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Topic: Basic Science, Reproductive (epi)genetics

Keywords: Meiosis; Histone methylation, Oocyte, Transcription

Study question: How does the oocyte regulate its transcriptional activity in light of its prolonged meiotic arrest? (max: 50 words)

Summary answer: A histone methylation-mediated epigenetic memory programed by the demethylase KDM5 is required for the correct temporal reactivation of the oocyte's transcriptional activity. (max: 50 words)

What is known already: During oogenesis oocytes transit from stages of transcriptional activity to those of transcriptional quiescence, and such transitions are believed to be essential for proper gamete formation. Although the temporal regulation of these transitions has been well documented across diverse organisms, the molecular mechanisms underlying these processes remain largely unknown (max: 75 words)

Study design, size, duration: Basic research using the Drosophila melanogaster (fruit fly) model organism. The Drosophila ortholog of the human KDM5 gene family (hereafter referred to as dKDM5) was down-regulated specifically in the female germline by in vivo RNAi (knockdown efficiency: 97%). Outputs were compared to that of a mock RNAi. (max: 50 words).

Participants/materials, setting, methods:
Transcriptional activity in the oocyte was temporally measured by an ex vivo ovary incorporation assay (Click-iT assay). Oocyte chromatin structure was analyzed and quantified by confocal microscopy after staining for DNA and H3K4me3. dKDM5 localization was analyzed by substituting the endogenous gene by a HA-tagged genomic construct. (max: 50 words)

Main results and the role of chance:
Germline-specific dKDM5 knockdown results in severely reduced female fertility. Oocytes display precocious transcriptional reactivation and an equally precocious chromatin remodeling, leading to the premature acquisition of an open chromatin configuration. Both effects are a possible consequence of the significant up-regulation of H3K4me3 levels in the ovary, particularly in the meiotically-arrested oocyte. Increased H3K4me3 levels seem to solely impact the transcriptional status of the oocyte, as no evidence for either the activation of the DNA damage checkpoint or meiotic maturation defects were recorded. dKDM5 is evicted from the oocyte's chromatin by early oogenesis, indicating that the transcription defects recorded approximately 24 hours later are the possible

consequence of a H3K4me3-based epigenetic memory mechanism. (max: 125 words)

Limitations, reasons for caution: The functional consequences of the reported transcriptional deregulation need to be fully elucidated. (max: 50 words)

Wider implications of the findings: Our results provide novel insight into the epigenetic mechanisms employed by the oocyte to regulate its transcriptional activity during the prolonged meiotic arrest. Given the significant evolutionary conservation of both dKDM5 and H3K4me3, it is likely that the in pre-ovulatory oocytes of our species the transition from a transcriptionally active to an inactive state is under equivalent epigenetic control. The deregulation of this process can therefore be an underlying cause of infertility in patients with low oocyte quality. (max: 75 words)