



Lead Author Q&A – Qianshu Zhu

Dysregulated epigenetic memory in early embryos offers new clues to the inheritance of polycystic ovary syndrome (PCOS)

1. Were you surprised by any of the findings from this study?

Yes, while previous studies have confirmed that PCOS is associated with genetic and epigenetic factors such as DNA methylation, there has been little research into the heritability of histone modifications. Although it was not entirely unexpected that H3K27me3 might be involved, given its known role in metabolic disorders, the identification of H3K27me3 as a potential heritable epigenetic factor in PCOS was still a noteworthy finding.

2. Were the embryos analysed at the same developmental stages?

Yes, we conducted a comparative analysis across multiple stages of early human embryonic development. The developmental stages were carefully matched between the PCOS and control (normal) groups.

3. Based on your data, how much of the epigenetic dysregulation appears to be inherited from the oocyte?

According to our results, approximately 50% of the H3K27me3 abnormalities observed at the Zygotic Genome Activation (ZGA) stage seem to be inherited directly from the oocyte. The remaining abnormalities may be attributed to dysregulated expression of methyltransferase and demethylase genes.

4. Could you provide more details on which specific genes were most significantly affected by the dysregulated epigenetic marks in PCOS embryos?

The epigenetic dysregulation observed in PCOS embryos affected a wide range of genes. These include ZGA-related genes, genes encoding epigenetic modifiers, and genes involved in metabolic pathways, indicating a broad impact on early embryonic development.



5. Could you provide any insight into the mechanisms by which PRC2 inhibitors “rescue” abnormal gene expression?

We used two PRC2 inhibitors (EED226 and Valemetostat) to investigate this. Both independently demonstrated that inhibition of PRC2 led to a reduction in aberrant H3K27me3 levels in PCOS embryos. This in turn helped restore normal gene expression patterns, suggesting a potential therapeutic angle for correcting epigenetic imbalances.

6. How might these insights influence future fertility treatments or embryo screening approaches?

We believe that patterns of H3K27me3 could serve as a potential biomarker in assisted reproductive technologies (ART), offering a new avenue for assessing and potentially improving embryo quality during IVF procedures.

7. What are the next steps for this research?

Our next step is to conduct functional validation experiments in mouse models. Specifically, we plan to knock down *Kdm6a/b* to see whether the F1 and F2 offspring exhibit PCOS-like features. We will also analyse H3K27me3 landscapes and gene expression profiles to further explore the mechanistic role of this epigenetic mark in PCOS inheritance.