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Commentary

Analytical approach for specific populations at single-cell resolution: insights for ND-42 mediated mitochondrial derivative function during spermatid elongation

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In the *Drosophila* testis, mitochondria are essential organelles that undergo dynamic changes in size and shape to help produce mature spermatids [1]. During spermatogenesis, mitochondria initially localize in the cytoplasm of spermatogonia and spermatocytes, and form the Nebenkern near the nucleus of early stage of round spermatids after migration, aggregation and fusion. During the individualization stage, there are two mitochondrial derivatives that elongate along the entire spermatid tails, which are closely related to the axoneme [2, 3]. Although several studies have been performed to demonstrate the function of mitochondria during spermatogenesis, while the regulatory mechanism of mitochondria during elongation still remains largely unknown. Further studies related to mitochondria are necessary to identify key factors involving in the maintenance, expansion, and structural composition of mitochondrial derivatives during spermatid elongation.

Single-cell RNA sequencing (scRNA-seq) can accurately analyze the heterogeneity of cell populations, providing valuable insights into the differential expression levels of individual cell transcripts in certain cell populations [4]. Previous studies have shown that the 42 kDa subunit of NADH dehydrogenase (ubiquinone) (ND-42) is a subunit of the complex I protein in the mitochondrial electron transport chain [5, 6]. In this study [7], Yu et al., confirm that loss-of-function of ND-42 leads to mitochondrial disorders during spermatid elongation in the *Drosophila* testis. The authors systematically investigate ND-42-mediated mitochondrial function via scRNA-seq, which proposes a novel regulatory mechanism for spermatid mitochondrial maintenance.

The analysis of the scRNA-seq data reveals the referred genes and pathways, that are activated or repressed by loss-of-function of ND-42, are essential for spermatid elongation process. In addition, to further explore the molecular mechanism of mitochondrial dysfunction during spermatid elongation, the relevance between ND-42 and mitochondria-encoding genes was analyzed. The results show that ND-42 deletion leads to defective mitochondrial derivatives by affecting mitochondrial membrane potential and mitochondrial-encoding genes in elongated spermatids.

The authors, for the first time, show that ND-42 is essential for male fertility and spermatid elongation in the *Drosophila* testis, and reveal a more comprehensive understanding of the transcriptional landscape at single-cell resolution in the *Drosophila* testis. This study provides a new theoretical basis for the clinical diagnosis and treatment of male infertility.

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