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Research Highlight

Fat dad, fat kids: sperm small RNAs in control!

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An individual's diet appears to have a profound impact on the health of his/her offspring as recent studies indicate that offspring can inherit metabolic disorders from their fathers [1]. However, it remains unclear what factors in the sperm are responsible for the intergenerational inheritance of paternally acquired traits.

A recent study by Chen et al. [2] starts to shed lights on this question by demonstrating that a subset of small RNAs in the sperm, called tsRNAs, might mediate the transmission of the metabolic disorder from fathers to their offspring. By injecting the sperm head from the male mice on high fat diet (HFD) into normal mouse oocytes, they observed that the offspring displayed impaired glucose tolerance and insulin resistance. To identify the sperm-borne factors responsible for the induction of metabolic disorders in offspring, the authors injected total RNAs purified from HFD sperm into normal zygotes. Interestingly, the offspring showed impaired glucose tolerance, similarly to the sperm head injection, suggesting that sperm RNAs are involved in the transmission of the trait. To further pinpoint which subset of RNAs can cause the glucose intolerance in offspring, the authors performed sequencing analyses on small RNAs in the HFD sperm and identified tsRNAs were among those significantly altered. Injection of tsRNAs of HFD mouse sperm into normal zygotes was sufficient to induce glucose intolerance in offspring, suggesting sperm tsRNAs might be the factor mediating the intergenerational inheritance of the metabolic disorders in this particular case (Fig. 1a). However, synthesized tsRNAs undergo rapid degradation and injection of these synthetic tsRNAs failed to induce the phenotype. Using a recently developed LC–MS/MS-based technique, the authors discovered that the sperm tsRNAs contained higher levels of m^5C and m^2G in the HFD feed mice [3] (Fig. 1b). This is resonating with another recent report showing that RNA-mediated epigenetic heredity requires the cytosine methyltransferase *Dnmt2* [4]. Interestingly, it has been reported that adult sperm methylome can be perturbed by adverse prenatal environments, thus affects intergeneration metabolism [5]. These findings suggest that specific modifications in sperm DNA/RNAs might be essential for their stability and for mediating the transmission of the paternally acquired traits. To explain why tsRNAs from the HFD mouse sperm can cause metabolic disorders, the authors examined the transcriptomic changes in the offspring. Inspiringly, the dysregulated genes were enriched with metabolic genes and these genes appeared to be targeted by the altered tsRNAs. A similar observation of diet-induced changes in sperm tsRNAs and the effect of altered tsRNAs on embryonic gene expression has also been reported by an independent study, using low-protein diet [6]. It remains unclear, however, whether the effects result from the post-transcriptional regulation of metabolic genes by tsRNAs, or the changes in metabolic gene expression is due to other epigenetic changes in those genes induced by tsRNAs.

Many types of small RNAs have been identified in sperm, including miRNAs, endo-siRNAs, tsRNAs, etc. [7, 8]. In addition to tsRNAs [2, 9], altered miRNA expression in mice subjected to trauma or stress appears to be able to induce behavioral and metabolic changes in offspring [10,

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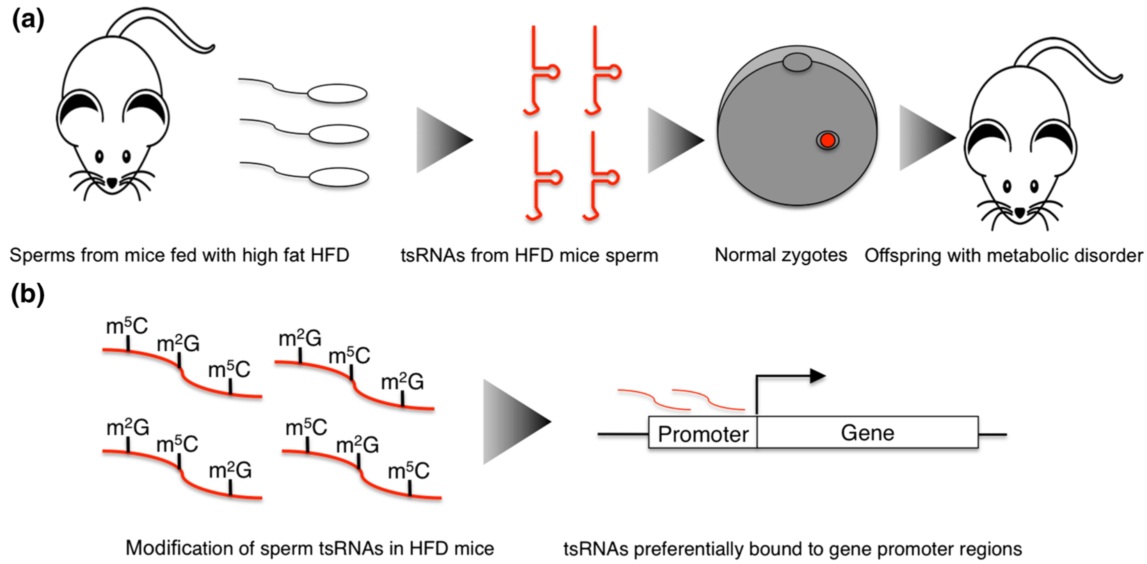

Fig. 1 (Color online) Sperm tsRNAs are important for paternally inherited metabolic disorders. **a** Injection of tsRNAs from sperms of mice fed with high fat diet (HFD) into normal zygotes results in offspring metabolic disorder. **b** HFD mouse sperm tsRNAs showed increased methylation of cytosine and guanine nucleotides, which appear to bind preferentially to gene promoter regions

11]. The sperm-borne miRNAs seem to act at post-transcriptional levels by affecting maternal and zygotic gene expression, leading to the specific phenotypes observed [2, 7, 9–11].

Taken together, these findings all point to a critical function of sperm-borne small RNAs in the inheritance of paternally acquired traits. However, many questions remain, e.g., can the sperm small RNA-induced phenotype be transgenerational? Can healthy diet correct the aberrant sperm tsRNA profiles induced by HFD diet? What are the primary effectors of sperm-borne miRNAs and tsRNAs? Revelation of the underlying mechanism will help us gain critical insights into the contribution of environmental exposure or dietary habit of the father to the overall health of his children and even potentially grandchildren.

Conflict of interest The authors declare that they have no conflict of interest.

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