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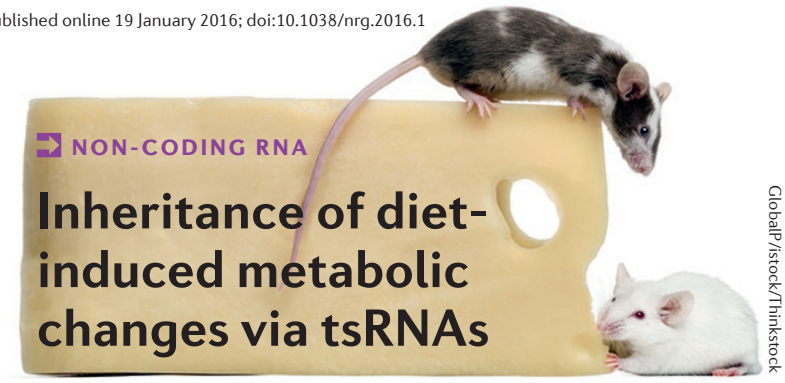

NON-CODING RNA

Inheritance of diet-induced metabolic changes via tsRNAs

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Metabolic changes associated with a high-fat diet can be passed from father to offspring, but the mechanisms that underlie this process are unclear. Now, Chen *et al.* show that mice fed a high-fat diet exhibit changes in sperm tRNA-derived small RNAs (tsRNAs) that contribute to the intergenerational inheritance of a metabolic disorder.

The authors fed mice either a high-fat diet (HFD) or a normal diet (ND) and subsequently injected sperm heads from both groups into normal mouse oocytes, which were then transferred to females. Resulting ND or HFD offspring were fed a normal diet, and no significant difference in weight was observed between groups. However, by 7 weeks, the offspring of mice fed a HFD displayed impaired glucose tolerance and insulin resistance.

As altered sperm microRNA profiles have been associated with paternal diet, the team explored a role for sperm RNA in the observed phenotypes by injecting total RNA purified from sperm into normal zygotes. Again, offspring were of similar weights, and the HFD offspring displayed impaired glucose tolerance; however, insulin sensitivity was similar between offspring from the HFD and ND groups, suggesting that sperm RNA is sufficient for the transmission of glucose tolerance but not insulin resistance.

To identify the RNAs involved, the authors profiled the small non-coding RNAs of the sperm from paternal mice and discovered that a larger fraction of tsRNAs than microRNAs exhibited differences between HFD and ND sperm. Sperm RNAs were then separated according to size, and three different RNA fractions from each paternal group were injected into normal zygotes. Only injection of sperm RNAs of 30–40 nt in length (predominantly tsRNAs) recapitulated the metabolic effects induced by total RNA injection. Notably, injection with synthetic RNAs had no effect on offspring metabolism. Reasoning that sperm tsRNAs might have modifications essential for the transmission of glucose intolerance, the authors analysed sperm RNA modification profiles and discovered an increase in N^2-methylguanosines and 5-methylcytidines (m^5C) in the tsRNAs of HFD sperm compared to ND sperm. Interestingly, one of these modifications (m^5C) has previously been linked to RNA-mediated intergenerational inheritance.

To investigate the causes of glucose intolerance in the offspring of HFD mice, the researchers conducted a genome-wide analysis of gene expression and DNA methylation in pancreatic islets from both groups of offspring. This revealed a DNA methylation-independent enrichment of differentially expressed genes in metabolic pathways, providing a possible explanation for the metabolic disorder in the offspring of HFD mice. Further experiments using early embryos revealed transcriptional changes in embryonic metabolic pathway genes after injection of HFD sperm tsRNAs.

Based on these results, the authors propose that tsRNAs are a paternal epigenetic factor that mediates the intergenerational inheritance of diet-induced metabolic disorder, and that early embryonic transcriptional changes lead to downstream reprogramming of gene expression in the islets of HFD offspring via a transcriptional cascade effect.

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ORIGINAL ARTICLE Chen, Q. *et al.* Sperm tsRNAs contribute to intergenerational inheritance of an acquired metabolic disorder. *Science* http://www.dx.doi.org/10.1126/science.aad7977 (2015)