

ACHIEVEMENTS

Sperm RNA Links Paternal Obesity to Offspring's Metabolism

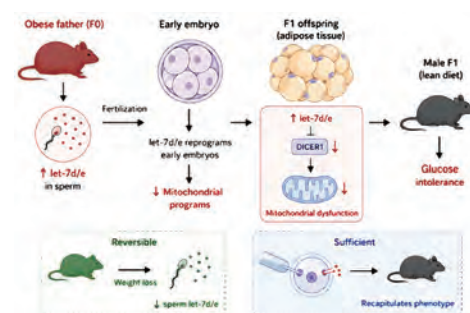
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NTU research team led by Assistant Professor Chien Huang.

A father's weight before conception can subtly influence his children's metabolic health, according to a new study led by researchers at National Taiwan University (NTU) and the University of Southern Denmark (SDU). The study report, published in *Nature Communications*, identifies a tiny sperm-borne microRNA, *let-7*, as the molecular messenger that carries this signal from father to child.

The team, co-led by Assistant Professor Chien Huang (Department of Animal Science and Technology, NTU) and Prof. Jan-Wilhelm Kornfeld (SDU), fed male mice a high-fat diet before allowing a subgroup to lose weight on a low-fat diet. Both the obese fathers and their male offspring developed poor glucose tolerance and impaired mitochondrial gene activity in white adipose tissue, even though the offspring themselves had never consumed a high-fat diet. Remarkably, when the fathers lost weight, most of these metabolic changes were reversed in both generations.



Graphical abstract. Obesity in male mice (F0) increases levels of the microRNAs *let-7d/e* in sperm. During fertilization, *let-7* reprograms early embryonic development by suppressing mitochondrial gene programs. In the adipose tissue of F1 offspring, elevated *let-7* silences *DICER1*, leading to mitochondrial dysfunction and glucose intolerance in male offspring despite a lean diet. The effect is reversible (weight loss in F0 lowers sperm *let-7* levels) and sufficient (microinjection of *let-7* into normal zygotes reproduces the phenotype).

Digging deeper into the underlying mechanism, the researchers found elevated levels of the microRNAs *let-7d* and *let-7e* in the adipose tissue and sperm of obese male mice. Injecting these microRNAs into normal one-cell embryos reproduced the same metabolic abnormalities in the resulting offspring. Single-cell RNA sequencing of early embryos further revealed that *let-7* suppresses mitochondrial genes from the earliest stages of development. In adipose tissue, *let-7* acts by silencing DICER1, an enzyme responsible for processing other microRNAs, thereby impairing mitochondrial function and cellular energy production.



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Nature Communications.

To determine whether the same mechanism operates in humans, the team analyzed sperm samples from 15 men with obesity who were enrolled in a lifestyle-based weight-loss program at Zealand University Hospital in Denmark. Levels of the sperm-borne microRNAs *HSA-LET-7D* and *HSA-LET-7E* declined in parallel with body weight, suggesting that the mechanism is conserved between mice and humans and, importantly, is reversible.

"A father's metabolic health is not just his own concern. It is written into his sperm and delivered to the next generation—yet it is also reversible," asserted Assistant Professor Chien Huang. "Losing weight before conception may give the next generation a healthier start."

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