Oocyte Enzyme Reprograms Sperm-derived DNA for Healthy Offspring

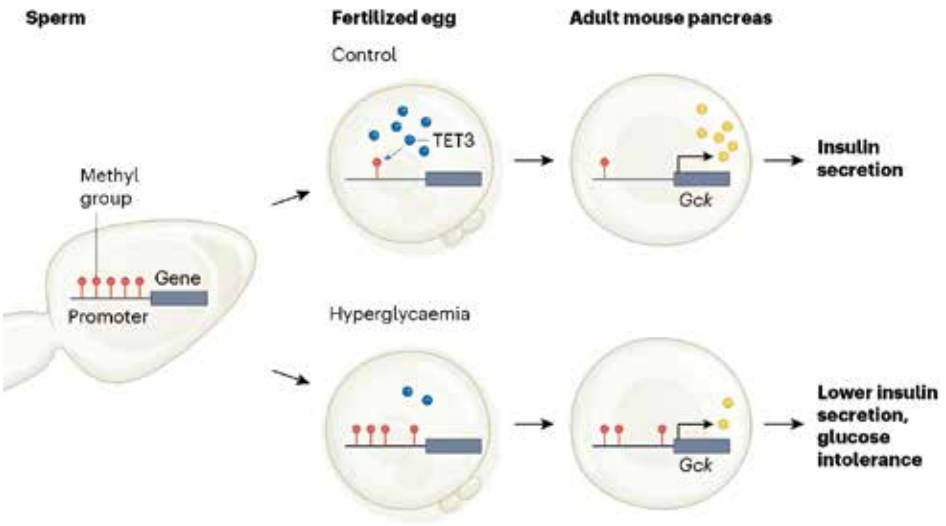
By YAN Fusheng (Staff Reporter)

Evidence has shown that the health status of a pregnant woman can affect her children's health over a long time and even to adulthood. Lousy diet habits, such as overeating before conception or during pregnancy that causes hyperglycaemia (high blood sugar), can make it more likely that a person's children will gain excessive weight or develop type 2 diabetes in adulthood. However, the mechanisms that confer this 'memory' of diet-induced metabolic disease have mostly remained elusive.

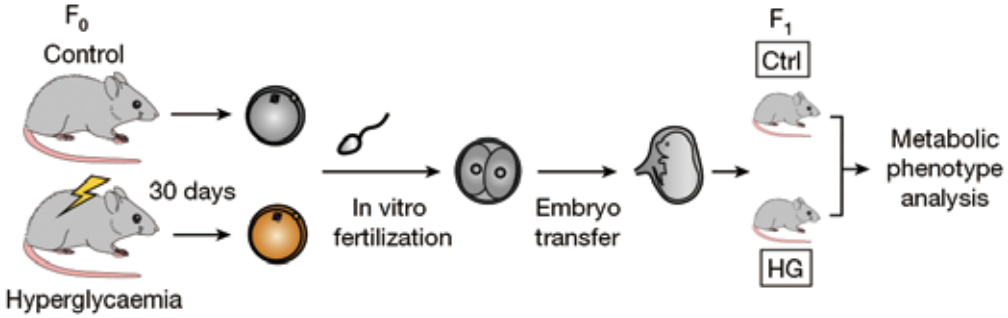
On May 26, a *Nature* study shows that pregestational hyperglycaemia leaves the offspring more vulnerable to glucose intolerance in adulthood. The study also reveals the molecular mechanisms of how the offspring inherit the memory of high blood sugar from their mothers.

The study, entitled "Maternal inheritance of glucose intolerance via oocyte TET3 insufficiency", was conducted by a joint team led by XU Guoliang from the CAS Shanghai Institute of Biochemistry and Cell Biology (SIBCB), Center for Excellence in Molecular Cell Science, and HUANG Hefeng from Fudan University.

The researchers first set out to create a nongenetic hyperglycaemia model by treating female mice with a toxin that damages insulin-producing beta cells in the pancreas. Next, they fertilized the eggs from these mice *in vitro* using sperm from healthy males and implanted them into healthy surrogate mothers. They found that the mice produced from hyperglycemic eggs are less able to metabolize glucose than are progeny generated from control eggs.



Insufficiency of the enzyme TET3 in eggs from mice with pregestational high blood sugar (known as hyperglycaemia) causes glucose intolerance in offspring due to reduced removal of methyl groups on sperm-derived DNA. (Image by Kawamura and Peters/*Science*)



Generation of mouse offspring from hyperglycaemic and control eggs by *in vitro* fertilization and embryo transfer into healthy surrogate mothers. (Image credit: *Science*)

Researchers then compared the mRNA profiles in mature eggs from hyperglycaemic mice and controls to examine the molecular mechanism. As a result, they uncovered that levels of one transcript called *Tet3* in hyperglycaemic eggs were half those in controls. Notably, they found that the *Tet3* level was also abnormally low in eggs from women with diabetes.

TET3 enzyme, the protein product of the *Tet3* mRNA, oxidizes methylated bases in DNA, leading to DNA demethylation and enabling the gene's transcription. In fertilized embryos, TET3 plays a crucial role in helping remove methyl marks on the paternal DNA throughout development.

They found that the methylation of paternal DNA is markedly higher in the hyperglycaemic eggs than in those derived from controls. Then, they set out to evaluate the long-term effects of reduced maternal TET3 activity on offspring by quantifying DNA methylation levels in embryonic pancreatic islets that contain many beta cells.

They found changes in the promoters of several genes involved in insulin secretion, including in a promoter that drives pancreatic expression of *Gck*, a gene critical for glucose metabolism.

The researchers also reported two to three times higher levels of methylation at the *Gck* promoter in early-stage embryos from a woman who had diabetes than those of two women free of diabetes, suggesting that a similar mechanism is functioning in humans.

By injecting exogenous *Tet3* mRNA into HG eggs, they reversed the maternal effects on offspring, resulting in a less methylated *Gck* promoter in the sperm-derived DNA.

"These data do not support the notion that epigenome alterations in mature oocytes upon exposure to maternal hyperglycaemia make a critical contribution to the susceptibility of the offspring," said the authors in the article. "Instead, they suggest that *Tet3* transcript levels are vulnerable during oocyte growth and maturation, and that the reduction in oocyte TET3 renders the offspring more susceptible to metabolic disease."

Hence, the researcher revealed a critical window in oocyte growth and maturation that is vulnerable to metabolic perturbation by high glucose.

"Our findings call for new guidance on pre-conception care for early prevention, regular screening and glucose control for diabetes among women of reproductive age to protect against disease in the subsequent generation."

References

Chen, B., Du, Y. R., Zhu, H., et al. (2022). Maternal inheritance of glucose intolerance via oocyte TET3 insufficiency. *Nature, 605*(7911), 761-766. doi:10.1038/s41586-022-04756-4

Kawamura, Y. K., & Peters, A. (2022). Maternal enzyme reprograms paternal DNA for healthy offspring. *Nature, 605*(7911), 621-622. doi:10.1038/d41586-022-01237-6