News & views

Epigenetics

High blood sugar inherited through eggs

Yumiko K. Kawamura & Antoine H. F. M. Peters

It emerges that high blood sugar deregulates the enzyme TET3 in the eggs of female mice, preventing it from properly modifying sperm-derived DNA when eggs are fertilized. This leads to metabolic defects in adult progeny. **See p.761**

Eating too much or too little before conception or during pregnancy can make it more likely that a person's children will gain excessive weight or develop type 2 diabetes in adulthood[1]. The mechanisms that confer this 'memory' of diet-induced metabolic disease have mostly remained elusive[2]. On page 761, Chen *et al.*[3] reveal a mechanism through which high blood sugar – a sign of some metabolic disorders – is transmitted from female mice to their offspring through their eggs.

Chen *et al.* set out to investigate how high blood sugar (known as hyperglycaemia) in female mice affects the animals' pups. The authors treated female mice with a toxin that damages insulin-producing beta cells in the pancreas – an approach known to induce chronic hyperglycaemia. Next, they fertilized the eggs from these mice *in vitro* using sperm from healthy males, and implanted them into healthy surrogate mothers. This enabled the researchers to focus on the effect of hyperglycaemia on the eggs themselves, excluding more-general effects caused by hyperglycaemia in pregnancy.

The mice produced from hyperglycaemic eggs had normal body weights when they reached adulthood, but were less able to metabolize glucose than were progeny generated from control eggs. This glucose intolerance (a sign of prediabetes and diabetes) was more pronounced in male than female progeny, increased with age in both sexes, and became worse if the animals were fed a high-fat diet. Chen *et al.* showed that glucose intolerance was due to reduced glucose-stimulated insulin secretion by pancreatic beta cells.

To investigate the mechanisms underlying these observations, the authors compared levels of messenger RNA in mature eggs from hyperglycaemic mice and controls. The comparison indicated that hundreds of genes were differentially expressed. Notably, levels of one transcript – *Tet3* – in hyperglycaemic eggs were half those in controls. *Tet3* expression was also abnormally low in eggs obtained from another mouse model of hyperglycaemia and obesity, and in eggs from women who had diabetes.

In DNA, the presence of methyl groups at promoter sequences (which normally drive gene expression) is typically associated with gene repression. The TET3 enzyme oxidizes methylated bases in DNA, leading to DNA demethylation and so allowing gene transcription to occur[4,5]. In fertilized embryos, TET3-mediated demethylation acts mainly on paternal DNA[5–8], preventing the maintenance of sperm-borne DNA methylation throughout development and enabling gene expression later in life. Chen and colleagues found that oxidation of methylated DNA was markedly lower in the paternal genome of fertilized eggs derived from the hyperglycaemic mice than in those derived from controls (Fig. 1).

The authors evaluated the long-term effects of reduced maternal TET3 activity on offspring by quantifying DNA methylation levels in embryonic pancreatic islets, which contain many beta cells. They focused on promoter sequences that had maintained extra methylation in the paternal genome of progeny produced from hyperglycaemic eggs, compared with controls. They found changes in the promoters of several genes involved in insulin secretion, including in a promoter that drives pancreatic expression of *Gck*. This gene encodes glucokinase – a key enzyme in glucose-stimulated insulin secretion.

The researchers went on to show increased DNA methylation of the paternal-derived

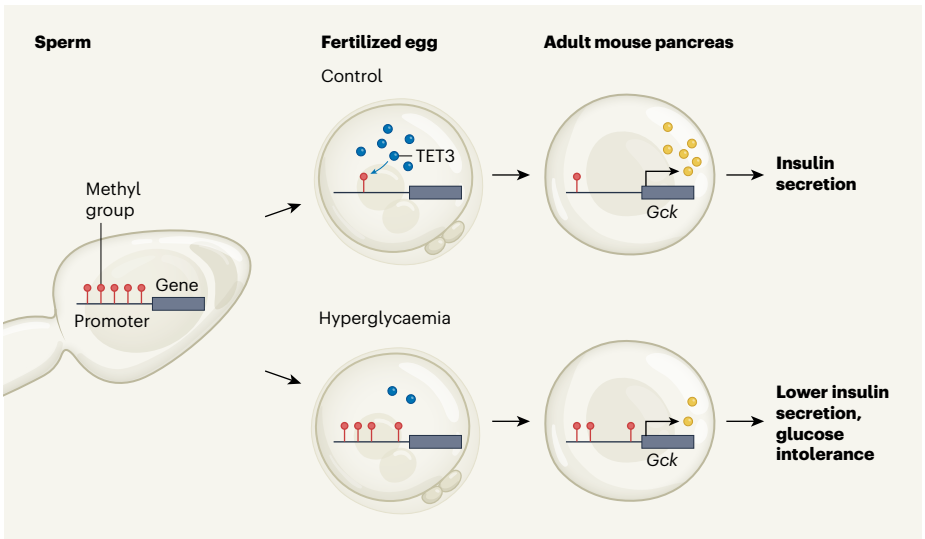

Figure 1 | The enzyme TET3 mediates inheritance of metabolic disorder. The DNA of sperm is tagged with many methyl groups – methylation in the promoter sequences that normally drive transcription leads to gene repression. Chen *et al.*[3] show in mice that demethylation of this paternal DNA, which occurs after fertilization, is altered if blood sugar levels were high in mothers (a condition called hyperglycaemia) as their eggs matured. In fertilized eggs from healthy (control) mothers, the enzyme TET3 mediates demethylation of promoters. When the progeny become adults, normal transcription of metabolic genes such as *Gck* in the pancreas leads to normal insulin secretion. By contrast, if eggs are derived from hyperglycaemic mothers, TET3 levels are lower in fertilized eggs, and less demethylation occurs. In adulthood, expression of *Gck* is abnormally low (although some demethylation does still occur during development), leading to lower levels of insulin secretion and so to glucose intolerance – a sign of prediabetes.

pancreatic *Gck* promoter at various stages of development, as well as postnatally. This hypermethylation was associated with reduced *Gck* expression in pancreatic islets. Administration of the glucokinase activator dorzagliatin, an antidiabetic compound being tested in phase III clinical trials[9], enhanced glucose tolerance and increased insulin secretion from pancreatic islets. Together, these data identify the paternally derived *Gck* gene as an important target of maternal TET3 activity. The authors also reported two to three times more methylation at the *GCK* promoter in early-stage embryos from a woman who had diabetes than in equivalent embryos from two women who did not, suggesting that a similar mechanism is at work in humans.

Interestingly, *GCK* is part of a group of human genes that, when mutated, drive a disorder called maturity-onset diabetes of the young 2 (MODY2) (see go.nature.com/3owzrjm). Clinical data indicate that mutation of just one of the two copies of *GCK* is enough to cause disease — a phenomenon known as haploinsufficiency. Taking this knowledge together with Chen and colleagues' findings, we propose that hypermethylation of paternal-genome-derived DNA at the *GCK* promoter might have the same effect as *GCK* mutations, causing pancreatic *GCK* haploinsufficiency and MODY2 traits in progeny. This idea requires further investigation in clinical studies. In addition, more research is needed to identify the transcription factor(s) that would normally regulate expression of *GCK* but whose activity is impeded by hypermethylation.

Next, Chen *et al.* asked whether reduced *Tet3* expression was the only contributor to *Gck* hypermethylation and glucose intolerance in progeny from hyperglycaemic eggs. In support of this idea, genetically engineered eggs in which *Tet3* expression was abnormally low mimicked the effect of maternal hyperglycaemia, and deleting *Tet3* had even more-pronounced effects. Furthermore, injecting *Tet3* mRNA into embryos suppressed the effects of hyperglycaemia, whereas supplying catalytically inactive TET3 exacerbated them.

Together, these data suggest that sperm-borne DNA methylation — even from male mice that have healthy diets — can promote metabolic distress in progeny, and that TET3 activity in early embryos negates this risk. Such a function for TET3 might have evolved to accommodate the fact that DNA methylation levels are overall twice as high in the genome of sperm as in that of eggs[10]. We cannot, however, exclude the possibility that TET3 is also involved in demethylation of metabolic genes located on the maternal genome.

Finally, the authors provide evidence that eggs are very susceptible to hyperglycaemia when they are maturing. In line with this idea, exposure to high levels of glucose led to a drastic reduction in *Tet3* mRNA levels in mouse and human eggs that were undergoing maturation *in vitro*. Because no gene transcription occurs as eggs are maturing, this decrease is likely to reflect destabilization of *Tet3* mRNA that was transcribed before maturation. We note that genes controlling mRNA stability (such as *Ybx1*, *Ybx2* and *Zfp36*) are downregulated in hyperglycaemic eggs compared with controls (See Supplementary Table 1), possibly because of transcriptional misregulation during egg growth. It will be exciting to explore the mechanisms by which glucose signalling controls *Tet3* transcription and mRNA stability.

Obesity in reproducing couples often affects both partners, and it is known[2] that a high-fat diet primes eggs and sperm to transmit metabolic disorders to offspring in an additive manner. Chen and colleagues have identified a mechanism that can account for transmission from female mice, and a separate mechanism that involves small non-coding RNAs associated with sperm has been described for the inheritance of paternal metabolic disease in rodents[11–13]. Going forwards, it will be important to determine whether these two mechanisms are relevant to humans and, if so, how they intersect.

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Biogeochemistry

Ocean acidification leads to silicon sequestration

David A. Hutchins

The seas are acidifying as a result of carbon dioxide emissions. It now emerges that this will alter the solubility of the shells of marine organisms called diatoms — and thereby change the distribution of nutrients and plankton in the ocean. **See p.696**

The ecologically dominant phytoplankton in much of the ocean are a group of unicellular organisms known as diatoms. On page 696, Taucher *et al.*[1] present a study that uses a combination of experimental, observational and modelling approaches to examine how the diatom-driven effects of ocean acidification — a consequence of rising carbon dioxide concentrations in seawater — will affect biogeochemical cycles. The separate lines of evidence suggest that ocean acidification will have far-reaching effects on the export of elements to the deep ocean.

Diatoms are highly efficient at converting dissolved CO_2 into organic carbon through photosynthesis, whereupon this organic carbon becomes incorporated into particles that sink rapidly to the deep ocean. Diatoms therefore serve as primary engines of a 'biological pump' that exports carbon to the deep ocean for sequestration[2]. Each diatom cell is enclosed in a shell of silica (SiO_2, where Si is silicon), and the solubility of the silicon in this biomineral is pH-sensitive — it becomes less soluble as seawater acidity rises[3,4]. Although these features of diatoms are familiar to marine scientists, their combined implications for future biogeochemical cycles in the context of ocean acidification had not been explored.

Enter Taucher and colleagues. They carried out a series of five experiments in various parts of the ocean in which natural phytoplankton communities were grown in large enclosures (with volumes of 35–75 cubic metres) known as mesocosms, which simulated future ocean acidification. When the authors measured the elemental composition of the diatom-derived debris at the bottom of the mesocosms, they observed much higher ratios of silicon to nitrogen than the ratios of particles suspended near the surface. This suggested that, at low seawater pH, diatom silica shells were dissolving much more slowly than nitrogen-containing compounds in the same sinking material. In other words, silicon was being exported from the surface to deeper waters preferentially to