

RESEARCH HIGHLIGHT

The effects of acquired paternal obesity on the next generation

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It is well established that the health of mothers can influence the health of their offspring. This can occur as a result of the transfer of viruses or toxins *via* the placenta or the milk, a compromised nutrient supply to the embryo or abnormal behavioural interactions between mother and offspring.¹ However, examples of paternal health affecting the next generation are rare. A recent paper published in *Nature* by Ng *et al.*,² shows that an acquired disease in male rats can lead to abnormalities in the next generation. Similar transgenerational effects down the male line have been reported in rats following the administration of particular drugs.³ However, in the study by Ng and colleagues the trigger was the 'over-administration' of a major component of our natural diet, and the disease itself is common throughout the world, making the findings particularly interesting.

Male rats were fed a high fat diet (HFD) that, as expected, led to increased body weight and adiposity, impaired glucose sensitivity and insulin sensitivity. These obese males, and lean males that had been fed a control diet, were then mated with females that had only had the control diet. The offspring (F1) of the two groups were subjected to a variety of metric, metabolic and histological tests. The female offspring of HFD fathers, when compared to those of control fathers, displayed impaired insulin secretion and glucose tolerance, and significant changes to the pancreatic islets of Langerhans. Furthermore, microarray analyses revealed extensive gene expression changes in the pancreatic islets of females with HFD fathers.

Care was taken to house the males with the females for a limited period of time. In fact they spent only 8 days together. Removal of

the fathers before the offspring were born greatly reduces the possibility of paternal behaviour being the cause of the offspring's pancreas abnormalities. Therefore, the mechanism of inheritance can be narrowed down to a change in sperm or seminal plasma factors. While this reasoning significantly reduces the possible molecular causes of the phenotype, there are still several possibilities (see Figure 1).

The DNA methylation patterns in mature spermatozoa are as unique as any other terminally differentiated tissue. These patterns are erased shortly after fertilisation in a genome-wide epigenetic reprogramming event.^{4–6} This reduces the likelihood of any abnormal DNA methylation being able to direct abnormal expression patterns in the next generation. However, certain regions are protected or are resistant to post-fertilisation demethylation events. These include genomic/parental imprints^{7,8} and the mouse intracisternal A-type particle retrotransposons.⁹ Ng and colleagues discovered that the gene with the greatest change in expression in the pancreatic islets of females with HFD fathers, *Ill3ra2*, has an associated DNA methylation change at its promoter. This does implicate epigenetics in the offspring phenotype but characterisation of the DNA methylation status of this region in the sperm of the obese rats and in the offspring at the preimplantation stage would be required for it to be considered the causative inherited factor.

Recent discoveries into the chromatin and RNA of spermatozoa provide other possible mechanisms for the paternal effect. While the majority of DNA in sperm is packed in protamines, a small fraction, between 2 and 15% depending on the species, is bound by nucleohistones. The nucleohistones retain transcription-regulating modifications such as acetylation of lysine residues, and these epigenetic marks are believed to prime genes for

expression in early embryonic development.^{10,11} A perturbation of these marks in the sperm of obese males could therefore impact offspring development. Secondly, despite the fact that the amount of RNA contributed to the zygote by the sperm is dwarfed by that from the oocyte, there is growing evidence that sperm-borne mRNA and microRNA can influence offspring phenotypes even into adulthood.^{12,13}

Obesity is thought to increase DNA damage in sperm through a variety of mechanisms such as increasing reactive oxygen species levels, by affecting normal spermatogenesis through increased testes temperature or altered hormone levels, or by increasing levels of fat-soluble toxins.^{14,15} Indeed, sperm from mice fed a HFD have been reported to have an increase in reactive oxygen species levels and DNA damage.¹⁶ Unlike epigenetic marks, DNA mutations are permanent and could be responsible for the offspring's pancreatic abnormalities. However, the sperm genome would presumably be mutated at random, and it is hard to reconcile this with such a high incidence of one particular abnormality in the offspring.

Finally, changes to pancreas function and morphology similar to those seen by Ng and colleagues have also been seen in the offspring of obese mothers.¹⁷ This may be a clue that points to the paternal obesity mechanism imitating the changes in embryo demand/maternal supply of nutrition that are seen with obese mothers. Genetic or epigenetic changes in sperm that go on to alter embryonic nutrient demand, or seminal plasma factors¹⁸ that alter gestational nutrient exchange could therefore be responsible.

The lesser contribution of males than females to prenatal development makes study of transgenerational disease easier to dissect when it is down the male line. However, there are still several potential

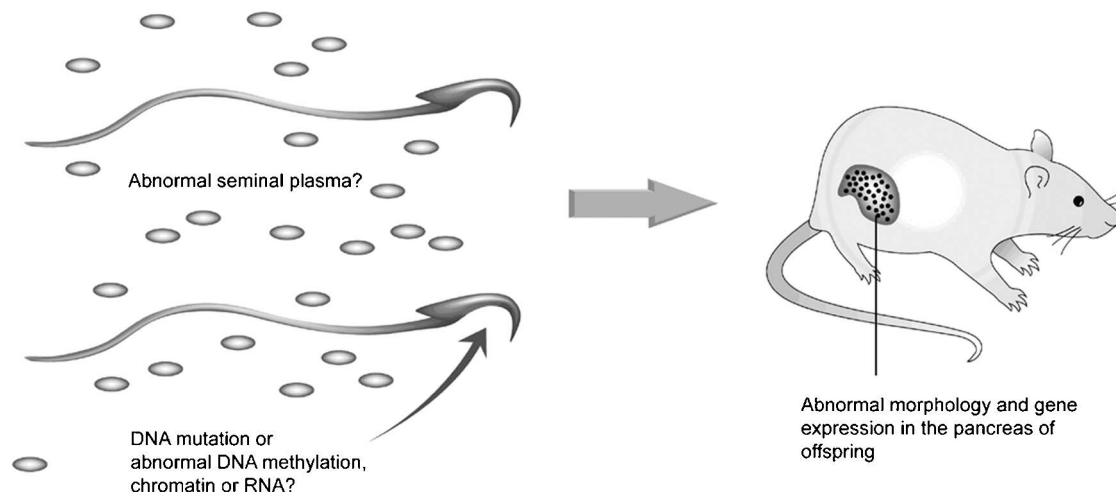


Figure 1 Changes in obese male semen that could alter offspring phenotype.

routes for disease transmission and much to be done to determine which of the changes is responsible.

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