Two studies show father's diet can impact on offspring

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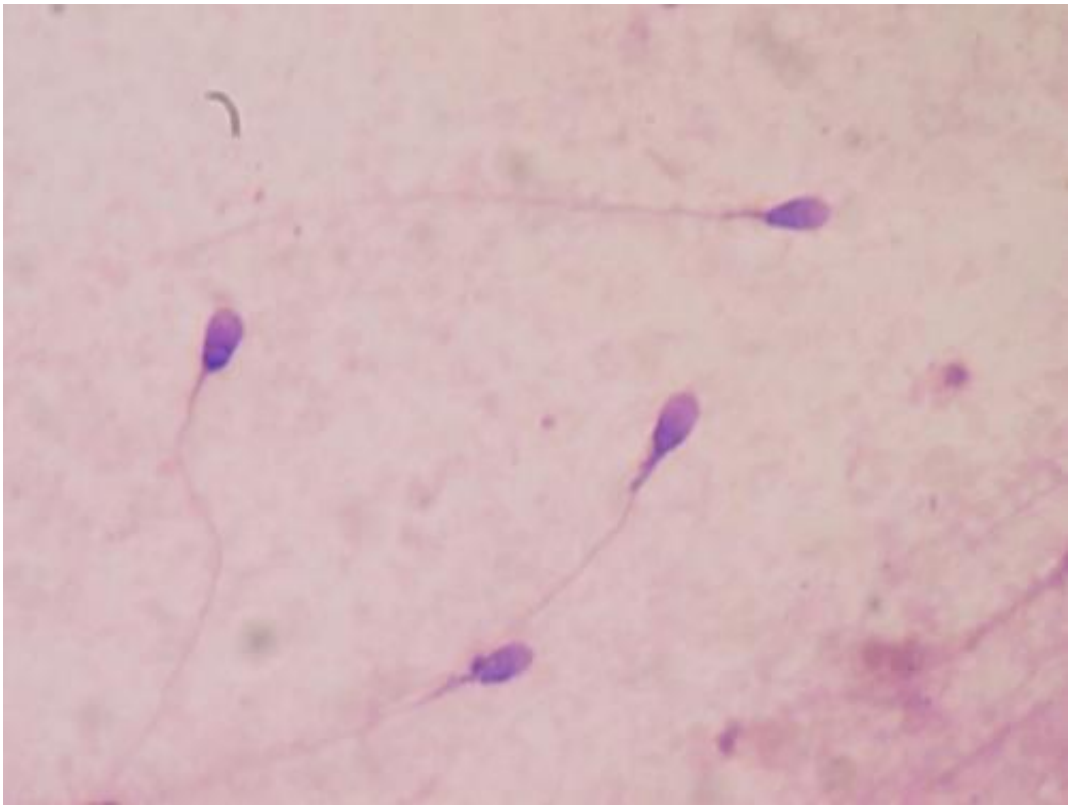

Human sperm stained for semen quality testing in the clinical laboratory. Credit: Bobjgalindo/Wikipedia

(MedicalXpress)—Two teams of researchers conducting independent experiments have found evidence that indicates that what a male mouse eats prior to mating with a female mouse can have an impact on the offspring that result. The first group, from several institutions in China,

ran experiments testing the impact of male mice eating a high fat diet, on offspring, while the second team, with members from the U.S. and Canada, tested the impact of a low-protein diet by male mice prior to siring offspring. Both teams describe their experiments and results in papers published in the journal *Science*.

For many years it has been assumed that the only impact male mammals can have on their offspring, due purely to mating, is from the DNA they carry in their sperm. In recent years, however, some study results have suggested that they can have another impact due to what are known as transfer RNAs (tRNAs). These two new studies add more evidence, suggesting that tRNA fragments can carry information that adversely impacts offspring.

In the first study, the team fed one group of mice a high fat diet, while another group was fed a normal diet. Sperm was harvested from both groups and used to impregnate female mice. Offspring had their weight monitored along with their level of glucose intolerance and insulin resistance. The team repots that the offspring of the males fed the high fat diets did not gain more weight than those from the control group, but they did develop an impaired resistance to insulin and glucose intolerance—precursors to diabetes. To ensure that the change was due to tRNA fragments, the team ran the same experiment again, but the second time around they purified the RNA before injection into the eggs. The resulting offspring developed intolerance to glucose but did not develop insulin resistance.

In the second study, the researchers conducted the same type of experiment but had the male study group eat a low-protein diet. The team reports they found no differences between the offspring except for changes to a group of genes that are responsible for the development of stem cells.

Though not studied yet, it appears likely that the same results would occur with humans, which suggests that couples looking to have children ought to be aware of or modify the diets of both potential parents.

More information: 1. U. Sharma et al. Biogenesis and function of tRNA fragments during sperm maturation and fertilization in mammals, *Science* (2015). DOI: 10.1126/science.aad6780

ABSTRACT
Several recent studies link parental environments to phenotypes in subsequent generations. Here, we investigate the mechanism by which paternal diet affects offspring metabolism. Protein restriction in mice affects small RNA levels in mature sperm, with decreased let-7 levels and increased levels of 5′ fragments of glycine tRNAs. tRNA fragments are scarce in testicular sperm, but are gained as sperm mature in the epididymis. Epididymosomes—vesicles that fuse with sperm during epididymal transit—carry RNA payloads matching those of mature sperm, and deliver RNAs to immature sperm in vitro. Functionally, tRNA-Gly-GCC fragments repress genes associated with the endogenous retroelement MERVL, both in ES cells and embryos. Our results shed light on small RNA biogenesis and its dietary regulation during post-testicular sperm maturation and link tRNA fragments to regulation of endogenous retroelements active in the preimplantation embryo.

2. Q. Chen et al. Sperm tsRNAs contribute to intergenerational inheritance of an acquired metabolic disorder, *Science* (2015). DOI: 10.1126/science.aad7977

ABSTRACT
Increasing evidence indicates that offspring metabolic disorders can result from the father's diet, but the mechanism remains unclear. Here, in a paternal high-fat diet (HFD) mouse model, we show that a subset of sperm tRNA-derived small RNAs (tsRNAs), mainly from 5′ tRNA

halves and ranging in size from 30 to 34 nucleotides, exhibit changes in expression profiles and RNA modifications. Injection of sperm tsRNA fractions from HFD male into normal zygotes generated metabolic disorders in the F1 offspring and altered gene expression of metabolic pathways in early embryos and islets of F1 offspring, which was unrelated to DNA methylation at CpG-enriched regions. Hence, sperm tsRNAs represent a type of paternal epigenetic factor that may mediate intergenerational inheritance of diet-induced metabolic disorder.