Non-genetic transmission of obesity – it's in your epigenes

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Abstract

Obesity and its related metabolic co-morbidities can be inherited across generations through non-genetic mechanisms. In a recent report, Huypens *et al.,* using an *in vitro* fertilization approach, provide evidence that exposure to high-fat diet modifies egg and sperm epigenetic information, rendering the progeny more prone to obesity.

Keywords: Epigenetic inheritance, obesity, in vitro feritilization

The prevalence of obesity worldwide has reached pandemic proportions. This is believed to be the result of complex interactions between an individual's genetic make-up and environmental cues. The Developmental Origins of Health and Disease (DOHaD) concept has highlighted how the fetal and early-postnatal environment such as the nutritional milieu is particularly important in shaping long-term health (1). Indeed, human studies have provided strong evidence that maternal obesity during pregnancy is a risk factor for obesity in the offspring (2). Research on animal models of dietary manipulation during pregnancy and lactation (under- and over-nutrition) has further showed that obesity can be transmitted across multiple generations via either the maternal (3) or the paternal line (4) through epigenetic mechanisms.

Here, using a well-established mouse model where probands were fed a high-fat diet (HFD, 60% kcals from fat), Huypens *et al.* (5) report that only 6 weeks of HFD feeding of the parents was associated with increased body weight gain and metabolic disturbances in the adult F1 generation. In order to assess the contribution of epigenetic changes to the gametes in the transmission of obesity to the next generation, the authors performed *in vitro* fertilization (IVF). IVF reduces confounding variables related to the gestational and early post-natal environment (lactation). Sperm and oocytes isolated from mice fed a high-fat or control or low fat diet were *in vitro* fertilized, and blastomeres from all combinations of parental gametes were transferred into healthy lean foster dams.

Offspring born from gametes derived from mothers and/or fathers fed a HFD were fed a HFD for 6 weeks (from 9 to 15 weeks of age), and developed different degrees of obesity. Sex-differences were also observed. Female offspring born from maternal and paternal HFD gametes gained more weight than their male counterparts. Interestingly, this risk was reduced if only maternal eggs were exposed to HFD prior to fertilization, suggesting that the effects of maternal and paternal diet on F1 females body weight and adiposity were additive. Conversely, no combinatorial effect was observed on male

body weight when offspring were generated from HFD gametes. Male mice born to HFD-exposed maternal gametes where heavier than controls, and had the highest risk of developing obesity. Unfortunately no data is provided on the offspring prior to the HFD challenge, therefore it is unclear if effects are only observed following the additional challenge of post-natal HFD feeding.

Having established the effects of parental nutrition on offspring growth and body composition, Huypens *et al.* (5) characterized the animals' metabolic profile. Females from obese parental gametes showed a pronounced delay in blood glucose clearance rate during a glucose tolerance test, which was associated with hyperinsulinemia, obesity and increased fat mass. Interestingly, males born from gametes of HFD fed parents developed severe insulin resistance before any change in body weight and body composition. The insulin resistant state was acquired by the progeny mainly via the maternal line. Indeed, mice born to HFD gametes were as insulin resistant as mice born to HFD mothers only. This is perhaps not surprising since HFD mothers were obese and insulin resistant, and it is well established that offspring of obese and/or diabetic mothers have an elevated risk of developing type-2 diabetes (6). It is worth noting that the effects observed might have been exacerbated by the postnatal HFD challenge. This situation resembles the tendency of offspring from obese mothers to consume high caloric food, and to be more prone to develop obesity and insulin resistance, than offspring from lean mums (7).

The molecular mechanisms underlying this modality of transmission have not been investigated by the authors, but are non-genetic, as the study was carried out in isogenic mice. It can be speculated that the epigenetic state of unknown elements contained in the egg and sperm is modifiable upon pre-conceptional HFD feeding, and that these are resistant to the normal reprogramming waves that occur during embryo development, and are therefore heritable. Although modulation of DNA methylation and histone modification status are good candidates (8), there is also compelling evidence that small non-coding RNAs (snRNA) such as microRNAs, piRNAs and tRNAs play a crucial

role in the inter-generational inheritance of the metabolic phenotype. An altered piRNA profile was recently observed in sperm of obese mice (9) and humans (10). Most importantly, injection of specific microRNAs into naive zygotes was able to recapitulate a diet-induced obesity metabolic phenotype (9) or effects of paternal stress (11) in mouse F1 offspring. Another class of snRNA called tRNAs, have recently been implicated in the epigenetic transmission of metabolic phenotype in mice, and their abundance is known to be altered in the sperm of obese humans, compared to lean individuals (10).

Collectively, Huypens *et al.* (5) data support the existence of non-genetic transmission of metabolic diseases via paternal gametes. A suboptimal maternal and paternal *milieu* before conception increases the risk of metabolic disturbances in the next generation through non-genetic mechanisms, adding a new level of complexity to the trans-generational inheritance of complex traits. Characterizing the epigenetic drivers underlying this phenomenon will broaden our understanding of the burden of obesity in the world, and will help us develop therapeutic strategies to arrest the vicious cycle of transmission of metabolic diseases.

Acknowledgments

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Figure legend:

Figure 1. Parental gametes mediate the transmission of obesity to the F1.

Gametes isolated from probands either fed a control or high fat diet, were used for *in vitro* fertilization. Blastomeres obtained from different combinations of gametes were implanted in lean surrogate dams to generate the F1, which developed obesity and insulin resistance in adult age through the inheritance of unknown epigenetic triggers mainly via the maternal line.