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Can a maternal obesogenic diet influence offspring oocyte lipid droplets and mitochondria?

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Consumption of an obesogenic (OB) diet is linked with infertility. Hyperlipidemia alters the ovarian follicle microenvironment and induces lipotoxicity in the oocytes, mainly characterized by mitochondrial (MT) dysfunction and lipid accumulation. Increased reactive oxygen species (ROS) production by the defective MT leads to oxidative stress and reduced oocyte quality. Since MT are exclusively maternally inherited, transmission of aberrant MT from the oocyte to the embryo may alter MT functions in the offspring germline. In addition, the obesogenic maternal uterine and lactation environment can also impact the developing offspring oogonia, which may lead to defective oocyte MT in newborns. Therefore, we hypothesized that oocyte lipid content and MT are not only affected by an OB diet but also by the mother's obesogenic background.

To test this hypothesis, female Swiss mice were fed a control (C, 10% fat, 7% sugar) or OB diet (60%fat, 20% sugar) for 7 weeks (w), then mated with the same males. Female offspring from each litter were equally weaned on a C or OB diet in a 2x2 factorial design, resulting in 4 treatment groups: C»C, C»OB, OB»C and OB»OB. Per treatment group, at least 5 oocytes per offspring (at least 7 females) from 7-8 C mothers or 6-8 OB mothers were collected at 10w of age after hormonal stimulation (10IU PMSG and 10IU hCG i.p.). Oocytes were stained and imaged (LeicaSP8 Confocal microscope) to quantify lipid droplet (LD) content (BODIPY, $x10^3$ μm^3), MT inner membrane potential (MMP) (JC1) and ROS (CellRox Deep Red) ($x10^3$ pixel intensity). Data were analyzed in SPSS using two-way ANOVA, and shown as mean±SEM. In addition, active MT distribution patterns were categorized as peri-cortical, diffuse or aggregated, analyzed using generalized linear models and presented as mean%±SEM.

No interactions between maternal and offspring diets were observed. However, LD content was affected by offspring diet (*P*=0.000), irrespective of the maternal diet, as it was significantly increased both in C»OB compared to C»C (7.2±0.3 vs 5.7±0.3) and in OB»OB vs OB»C (6.8±0.3 vs 5.5±0.3). Similarly, MMP was significantly increased only by offspring diet (*P*=0.025), both in C»OB vs C»C (55.7±2.9 vs 46.9±2.3) and in OB»OB vs OB»C (56.3±2.7 vs 52.9±3.0). Comparably, ROS accumulation was only affected by offspring diet (*P*=0.007), and was also higher in C»OB vs C»C (31.9±2.6 vs 24.2±2.0) and in OB»OB vs OB»C (30.6±3 vs 25.3±2.4). MT distribution was not affected by offspring diet. In contrast, maternal diet significantly increased the proportion of MT aggregation (*P*=0,016), irrespective of the offspring diet, as it was increased in OB»C vs C»C (6.3%±4.7 vs 0%±0.0) and in OB»OB vs C»OB (7.8%±4.1 vs 0%±0.0). This category exhibited high ROS accumulation and very low MT MMP.

In conclusion, while we could confirm the increase in LD content, MMP and ROS in oocytes upon direct exposure to an OB diet, it appears that oocyte MT in offspring born to obese mothers have more MT aggregation with an increased ROS accumulation and a low MMP. This study stresses the importance of a heathy dietary intake for both mother and offspring to guarantee oocyte quality.

Keywords: intergenerational effects, oocyte quality, obesogenic diet