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OBESITY

Link between maternal obesity and offspring is STELLA

> alteration of methylation in zygotes is due to maternal obesity

Maternal obesity is linked to poor pregnancy outcomes such as congenital abnormalities and neonatal conditions, the effects of which can be far reaching, as well as miscarriage. Offspring of women with obesity often have disrupted growth patterns and an increased risk of developing metabolic disease later in life; however, the mechanisms responsible for these outcomes are poorly understood. New research by Qiang Wang and colleagues in obese mice found that developmental pluripotency-associated protein 3 (DPPA3; also known as STELLA) insufficiency in mature oocytes might be the link between maternal metabolic syndrome and its effects on embryonic development.

DPPA3 is a maternal factor vital for early embryogenesis; soon after fertilization, DDPA3 is involved in global epigenetic remodelling and has a role in the epigenetic mechanisms of embryonic programming. Using proteomic analysis, the researchers found oocytes from mice fed a high-fat diet (HFD) had considerably reduced DPPA3 protein expression compared with oocytes from mice fed a normal diet.

During global epigenetic remodelling after fertilization, the paternal genome is completely demethylated and 5-methylcytosine (5mC) is oxidized to 5-hydroxymethylcytosine (5hmC) after zygote formation. The demethylation of the maternal genome is delayed and these events establish an epigenetic asymmetry between paternal and maternal pronuclei of the zygote. DPPA3 is the demethylation-protecting factor preventing 5mC in the maternal pronucleus from premature oxidation to 5hmC. Immunofluorescence staining of late-stage zygotes (pronuclear 4) with antibodies specific for 5mC and 5hmC showed a considerable reduction in 5mC staining and an increase in 5hmC staining in the maternal pronucleus of zygotes from mice fed a HFD. "The establishment of pronuclear epigenetic asymmetry in zygotes from mice fed a HFD is severely disrupted, inducing maternal 5hmC accumulation and DNA lesions," explains Wang.

Bisulphite sequencing analysis of late-stage zygotes from mice fed a HFD showed that there was global hypomethylation of the genome, including promoter regions, introns, exons, untranslated regions, and CpG islands. The researchers found that hypomethylation was enriched in DNA transposons, which might activate their expression and transposition to result in the DNA damage that was observed in zygotes from HFD-fed mice. These results indicate that the alteration of methylation in zygotes is due to maternal obesity.

Conversely, overexpression of DPPA3 suppressed the premature oxidation of 5mC to 5hmC after fertilization in the maternal genome and had little effect on the paternal genome. "Overexpressing DPPA3 in HFD oocytes not only restores the epigenetic remodelling in zygotes, but also partly ameliorates the maternal obesity-associated embryonic defects," explains Wang. This amelioration was demonstrated by bisulphite sequencing analysis showing full methylation restoration of three of five genes that are methylated in zygotes from mice fed a normal diet, but they were hypomethylated in untreated zygotes from HFD-fed mice.

"In the future, we aim to investigate whether this epigenetic mechanism also contributes to the transgenerational effects of environmental exposures on the offspring," concludes Wang. "Prevention of the transmission of these deficits will be the key goal of future efforts."

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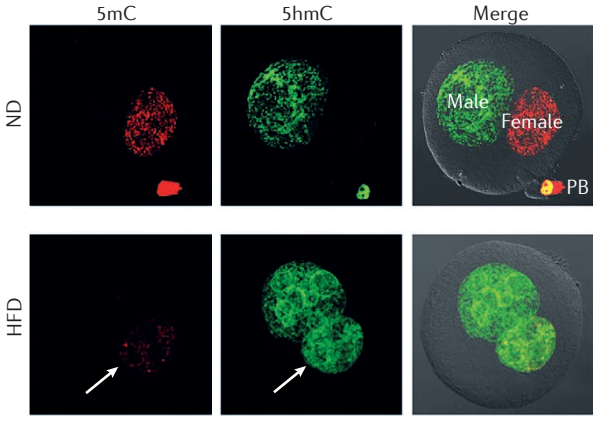

Late-stage (pronclear 4) zygote from normal diet (ND) and high-fat diet (HFD) mice co-stained with anti-5mC (red) and anti-5hmC (green) antibodies. 'Male' and 'female' indicate the paternal and maternal pronuclei, respectively. Arrows indicate loss of 5mC and gain of 5hmC in the maternal pronuclei of HFD zygotes. PB, polar body. Reproduced with permission from Han, L. et al. *Nat. Genet.* https://doi.org/10.1038/s41588-018-0055-6 (2018), Macmillan Publishers Limited.

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