HORIZON 2020

Maternal Obesity and Epigenetic Reprogramming: from Gametogenesis to Early Embryonic Development

Reporting

Project Information

MOBER

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Project website

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Periodic Reporting for period 1 - MOBER (Maternal Obesity and Epigenetic Reprogramming: from Gametogenesis to Early Embryonic Development)

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Summary of the context and overall objectives of the project

Food choice and eating habits have dramatically changed over the last fifty years. Nowadays our society faces not only a notorious excess of caloric intake, but also a decrease in physical activity. Consequently, the escalating global epidemic of overweight and obesity is taking over many parts of the world. Obesity leads to long-term health problems.

Remarkably, the impact of obesity on reproduction is understudied. Reproductive function gains relevance because gametes transfer not only genetic material, but potential alterations in epigenetic marks might be propagated to subsequent generations. Thus, the present research proposal investigated how maternal obesity promotes epigenetic changes in the oocyte and early embryo development. The objectives were to understand: (i) the extent to which the oocyte is vulnerable to maternal obesity; (ii) if changes established in the oocyte are able to interfere with the early embryo development. Different mouse strains reflecting variable susceptibility to obesity were subjected to diet-induced obesity protocols, representative of our social dietary habits.

Work performed from the beginning of the project to the end of the period covered by the report and main results achieved so far

The oocyte epigenome has the potential to control initial reprogramming events in the early embryo; furthermore, the oocyte methylome controls multiple differentiation-related and physiological processes in the trophoblast, thereby determining the functional properties of the placenta. Therefore, following the analysis of the oocyte epigenome, the impact of our dietary protocols were followed up at the embryonic level, assessing the methylome and transcriptome of the E 3.5 blastocyst.

Objective 1: Characterisation of the impact of obesity on the oocyte methylome and transcriptome
Objective 2: Assessment of the effect of obesity-induced epimutations on embryo development

Objective 1:Characterisation of the impact of obesity on the oocyte methylome and transcriptome
Changes in the oocyte methylome and transcriptome were characterised in both B6 and 129 female mice. Eight-week old animals were fed HFD or CD, for 16 wk. These time-points are representative of short- versus long-term diet induced obesity (DIO)..

The oocyte was studied after ovulation (MII oocyte), at this stage the oocyte methylome is fully established. The animal protocol and collections for the programme were performed at the Institute of Animal Reproduction and Food Research (IARFR), as well as library generation for RNA and DNA. The material was subsequently shipped to Babraham Institute (BI) for sequencing analysis.

The DESeq2 analysis identified 1569 differentially expressed genes (DEGs) in oocytes (FDR<0.01) from obese or non-obese mothers. Interestingly, transcripts affecting early development, such as Dppa3 and Plac1, were significantly increased in HFD oocytes. Unbiased CpG methylation analysis of the oocytes revealed 450 differently methylated regions (DMRs), with an absolute cut-off of 20% ($p<0.05$): 61% of these DMRs overlapped genes and lost methylation ($p<0.05$).

Objective 2: Assessment of the effect of obesity-induced epimutations on embryo development

The transcriptome analysis of whole blastocysts revealed 218 DEGs (FDR<0.05) with several genes known to be involved in maintenance of methylation.
Whole genome methylome analysis in blastocysts revealed 205 DMRs (p<0.05) with 10% of blastocyst DMRs coinciding with those in the oocyte, suggesting potential longer-term consequences of methylation changes induced in oocytes.

In conclusion, in the present study I demonstrate that the oocyte epigenome senses metabolic performance of the mother, and subsequently this impacts embryo developmental programming.

Progress beyond the state of the art and expected potential impact (including the socio-economic impact and the wider societal implications of the project so far)

Generally, the beneficiaries of our work include academia; industry, including biotechnology; policymakers; medical research charities; scientific journals; research councils; international funding agencies; the students within the Group; and the general public. Due to the collaborative nature of the programme, direct outcomes are expected in both countries UK and Poland. Clinical scientists in a number of fields from animal to human health, including clinical and cancer epigenetics, obstetrics and gynaecology, child health and reproductive health and infertility, will also benefit. Indeed, the programme made possible various collaborations within the research circle in Cambridge, and in Europe. I am now working closely with Dr Miguel Constancia, from the Institute of Metabolic Sciences, University of Cambridge, on methods for studying adipocyte biology. Additionally, I have also established a collaborative effort with the research group of Dr Joris Vrien, Leuven University, Belgium, to further study the impact of obesity in uterine function and infertility in women.

The data generated are being now submitted to journals listed in the Journal Citation Reports. The programme also provided an opportunity for students from the laboratory in Poland (Institute of Animal Reproduction and Food Research), to come to Babraham and access state of the art methods on sequencing and imaging methods.

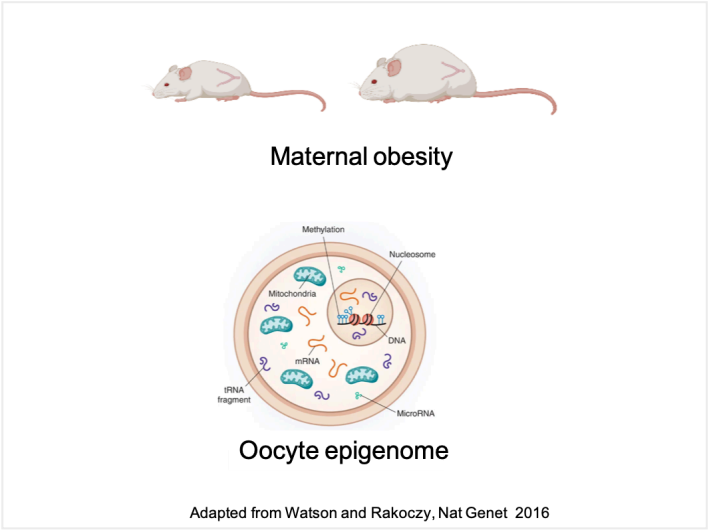
Other beneficiaries were the Babraham Impact team (Knowledge Exchange and Commercialisation), with whom I have discussed potential opportunities to commercialise the data, and contacts were made with the Centre for Science and Policy (CSAP), University of Cambridge.

Results dessimination:
Proceedings in International Conferences
Talks by Galvão A
1) Galvão A, et al. Effects of maternal obesity on oocyte methylome are reflected on blastocyst epigenome, “Mechanisms and Evolution of Intergenerational Change”, 24-26th September 2019. ppS45.

2) Galvão A, et al. How Maternal Obesity Affects the Oocyte Epigenome and Preimplantation Embryos, “3rd Danube Conference on Epigenetics”, 9th – 12th October 2018, Budapest Hungary. Pp 38.
3) Galvão A, et al. Maternal Obesity Modulates the Oocyte Methylome and Transcriptome , “Society for Study of Reproduction and Fertility”, 10th – 13th July 2018, New Orleans, USA. Flash talk. Pp143.

Posters
1) Walewska E, Witek K, Kelsey G, Galvão A, Obesity Alters Leptin Signalling in Mouse Uterus: Putative Link to Epigenetic Regulation during Decidualisation. Centre for Trophoblast Research Annual Conference, 8th-9th July 2019 Saint John’s College Cambridge, UK
2) Galvão A, et al. Maternal obesity affects the epigenome of oocytes and preimplantation embryos. “Advances at the interface between metabolism and epigenetics”, 16th-17th January 2019, Robinson College, Cambridge, UK.
3) Wołodko K, Walewska E, Adamowski M, Galvao A, Leptin Signalling Characterisation in the Ovary of Diet-Induced Obese and Pharmacologically Hyperleptinemic Mouse, “Society for Study of Reproduction and Fertility”, 10th – 13th July 2018, New Orleans, USA. Flash talk. Pp: 52.
4) Adamowski M , Wołodko K, Galvao A, Ovarian-specific Regulation of Inflammasome in Obese Mice; “Society for Study of Reproduction and Fertility”, 10th – 13th July 2018, New Orleans, USA. Pp: 136.
5) Galvão A,et a . Maternal obesity affects the oocyte epigenome in mice. “Epigenomics of Common Diseases”, 14th-17th November 2017, Welcome Genome Campus, Hinxton, Cambridge, UK. Pp:P15.

Public engagement
16th-17th March 2019 “Cambridge Science Festival”, Race against the aging clock, Cambridge, UK
2nd-8th July 2018 “Royal Society Summer Science Exhibition”, Race against the aging clock, London, UK



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