Maternal exposure to dietary heme iron elicits sex-related gut microbiota reshape associated with gut barrier and glucose metabolism defects in mice offspring

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Abstract VKS

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BACKGROUND:

The heme iron provided by meat products has been positively associated with an increased risk of cancers and diabetes (1,2). Heme-induced colorectal cancer promotion is explained at least in part by its ability to induce luminal peroxidation of dietary polyunsaturated fatty acids, thus leading to the formation of cytotoxic and genotoxic luminal reactive aldehydes in the colon (3). Gut microbiota involvement in this process has been recently shown in adult male rats fed for 21 days with heme-enriched diet (4). Interestingly, *Escherichia coli* strongly covariated with luminal heme-induced reactive aldehydes produced at adulthood.

As *E.coli* is a well-known maternally transmitted bacteria belonging to the first colonizers after birth, our aim was to explore whether a disruption of maternal gut homeostasis induced by heme-enriched diet during the perinatal period may influence (i) neoformation of lipid peroxydation-derived reactive aldehydes (LPRA), (ii) gut ecosystem and (iii) glucose metabolism in offspring.

METHODS:

Female C3H/HeN mice were fed AIN76 diets supplemented with ferric citrate (control) or heme iron during gestation and lactation. Diets were balanced for protein, fat and iron (0.036%). From weaning to 9 weeks of age, offspring was fed the control diet. At weaning, microbiota composition of mother and offspring (16S rDNA gene sequencing, Illumina, Miseq) and LPRA formation in fecal waters and urine (TBARS and DH-NMA respectively) were studied. These analysis were repeated once offspring reached adulthood and continued with an oral glucose tolerance test and *ex-vivo* jejunal permeability assessment (Ussing chambers).

RESULTs:

At the weaning stage, the maternal heme intake affected the fecal bacterial community of both mothers and offsprings. In mothers fed the heme-enriched diet, greater richness associated with lower eveness was observed. These α diversity indexes were lower in all offsprings at this stage due to microbiota immaturity but were not affected by the maternal diet. $\boldsymbol{\beta}$-diversity was significantly different between groups according to the generation, gender and maternal iron form intake, althought mother to offspring transfert of some heme-altered taxa were noted. This imprinting in reponse to heme-enriched maternal diet persisted in offspring microbiota at adulthood and was

associated with more marked sex-related alterations. Indeed only males developed an impaired phenotype characterized by (i) significant higher levels of LPRA, while luminal concentrations of heme iron remained comparable to those of control offspring, (ii) jejunal paracellular permeability increase and (iii) altered blood glucose regulation following the oral glucose challenge associated with a lower insulin concentration in blood.

CONCLUSION:

This work highlights how maternal exposure to dietary heme iron can markedly trigger gut homeostasis disruption through lipid peroxidation in male offspring, and how the contribution of the maternal environment during the perinatal period influences offspring propensity to develop metabolism disorders. Whether maternal transmitted gut microbiota is sufficient to promote intestinal barrier defects and glucose intolerance in a sex-dependent manner remains to be determined.

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