



# Maternal diets trigger sex-specific divergent trajectories of gene expression and epigenetic systems in mouse placenta

Anne Gabory, Laure L. Ferry, I. Fajardy, Luc Jouneau, Jean David Gothie Gothié, A. Vigé, Cecile Fleur, S. Mayeur, C. Gallou-Kabani, M. S. Gross, et al.

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Biliary atresia is the leading cause of liver transplantation in children. Despite initial description of biliary atresia over a century ago, very little is known about its onset. Recently, a possible effect of environment was raised through the assessment of decreased DNA methylation in the disrupted development of bile ducts.<sup>1</sup> To check the hypothesis of the influence of environment on biliary atresia, we took the opportunity of a 30-year cohort of all biliary atresia cases in French Polynesia that displays the highest incidence worldwide. On the basis of a whole population-based study that combines both simplified two-season climatic condition and a population cluster, we collected birth months of the cohort and of the total population over 30 years. Radar plotting of the data clearly evidenced an unexpected shift of patient's births towards the dry season. Comparison of birth distribution between dry and wet season in patients with biliary atresia *v.* the total population indicates a highly significant difference ( $P = 0.007$ ,  $\chi^2$ -test). Our observation reveals for the first time a significant seasonality of biliary atresia in a geographic isolate with monocentric recruitment. Furthermore, we believe that the seasonal dynamics we encounter fit nicely with a model resulting from an infection, likely influenced by genetic background, for which the mouse models of biliary atresia may be regarded as paradigms. Finally, we also discuss why seasonality still remains debated at the time of study,<sup>2,3</sup> and how our methodology should help solving old controversial debate and cast lights on the most recent results.<sup>4</sup>

**Key words:** critical periods, developmental programming, exposures, fetal programming, newborn/neonate

**Statement of interest:** The authors declare no conflict of interest.

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#### SEXUAL DIMORPHISM

A. Gabory and U. Simeoni

Communications in this session showed striking sex differences in the programming effects of metabolic disorders in

the offspring of various animal species. Males and females show a clear differential sensitivity to both maternal obesogenic diet and exposure to endocrine disrupting pollutants, expressed as both metabolic and epigenetic markers.

#### ORAL N°62

**Maternal diets trigger sex-specific divergent trajectories of gene expression and epigenetic systems in mouse placenta**

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There is mounting evidence that placenta can be considered as a programming agent of adult health and diseases.<sup>1</sup> Placental weight and shape at term are correlated with the development of metabolic diseases in adulthood in humans. Maternal obesity and malnutrition predispose the offspring to develop metabolic syndrome, a vicious cycle leading to transmission to subsequent generation(s), with differences in response and susceptibility according to the sex of the individual. Adaptations in placental phenotype in response to maternal diet and body composition alter fetal nutrient provision. This implies important epigenetic changes.<sup>2</sup> However, the epigenetics of placental development in DOHaD studies is still poorly documented, particularly concerning overnutrition. We used histology, microarray analysis and epigenetic techniques to investigate the effects of a high-fat diet (HFD) on mouse development. We showed for the first time that not only the gene sets but also their biological functions affected by the HFD differed markedly between the two sexes. Remarkably, genes of the epigenetic machinery and global DNA methylation levels showed sexual dimorphism. Imprinted gene expression was altered, with locus-specific changes in DNA methylation. Thus, these findings<sup>3,4</sup> demonstrate a striking sexual dimorphism of programming trajectories in response to the same environmental challenge. Explaining the sex-specific causal variables and how males *v.* females respond and adapt to environmental perturbations should help physicians and patients anticipate disease susceptibility.

**Key words:** epigenetics, nutrition, placenta, sexual dimorphism

**Statement of interest:** Authors report no conflict of interest.

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#### ORAL N°5

##### Gender differences in the aggravation of metabolic disorders induced by food contaminants in offspring of obese mice

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Several data indicate that endocrine-disrupting compounds are involved in the epidemic incidence of obesity and type 2 diabetes. In this study, we aimed at defining whether a mixture of low-dosed pollutants may aggravate metabolic disorders induced by obesity in mice lifelong fed a high-fat high-sucrose diet (HFSD). The mixture consisted in two persistent (Dioxin, PCB153) and two non-persistent (DHEP, BPA) pollutants, to which humans are largely exposed through diet on a daily basis. In brief, female mice were fed HFSD with or without pollutants, each added at their tolerable daily intake (TDI) in the mixture, and the progeny was given the same diet than its dam from weaning. Metabolic parameters were monitored in 12-week-old F1 mice that were either exposed (HFS-TDI group) or not exposed (HFS-0 group) to the pollutant mixture. F1 mice were obese with no difference in body weight and food intake between groups of the same sex. Glucose tolerance tests demonstrated that upon HFSD, female mice remained less glucose intolerant than male mice. However, pollutants aggravated this metabolic disorder in females but not in males, thus leading HFS-TDI females to the same glucose intolerance than HFS-0 and HFS-TDI males. To better understand the basis of these gender differences, we studied by RT-qPCR the expression of candidate genes related to lipogenesis in liver, and to inflammation in sub-cutaneous adipose tissue (scAT). Interestingly, effects were pollutant- and gender-dependent. Particularly, the hepatic expression of PPAR-encoding gene was enhanced in HFS-TDI males, and that of SREBP1c-encoding gene was decreased in HFS-TDI females, as compared with the respective HFS-0 group. In scAT, pollutants increased IL6 gene expression in females

and MCP1 in males, as compared with the respective HFS-0 group. In conclusion, a mixture of low-dosed pollutants altered the metabolic profile of obese mice. Effects were gender specific with males being more sensitive to the diet and females more sensitive to pollutants.

**Key words:** endocrine disrupter, food contaminants, maternal exposure, metabolic disorders, nutrition, obesity

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#### ORAL N°25

##### Maternal methionine-restricted diet, epigenetics and offspring development: the case of force-fed ducks for 'foie gras' production

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The current studies on DOHaD in human and animal models<sup>1,2</sup> have stimulated studies at INRA in the field of fatty liver (foie gras) production, focusing on early nutrition and epigenetics. Foie gras production results from the storage of lipids (mainly triglycerides) synthesized from the starch of the feed during a 2-week force-feeding. It exploits the hybrid mule duck<sup>3</sup> (common duck female × Muscovy drake). The early nutritional modulation studied was methionine restriction in order to target DNA-methylation, as experimented in the sheep.<sup>4</sup> It was applied to the mule duck's dam. Three levels of methionine contents were designed: 4.2 g/kg (control, C), 2.6 g/kg (maximum restriction,  $R_m$ ) and an intermediate level ( $R_i$ ). The dams were fed the experimental diets from the age of 10 weeks until the conception of mule ducks offspring of both sexes, at 31–32 weeks of age. The mule ducks were force-fed from the age of 12 weeks and slaughtered. The traits studied were body weight at 4, 8, 12 and 14 weeks of age, carcass weight at slaughter, fatty liver weight, pectoral muscle (magret) weight and subcutaneous fatness of the magret, an indicator of the overall subcutaneous fatness. They were analysed by analysis of variance with the fixed effects of the sex, of the maternal diet and their interaction. The effect of the diet was significant for 12-week body weight ( $R_m = R_i > C$ ,  $P = 0.06$ ) and for magret fatness ( $R_m > R_i > C$ ,  $P = 0.09$ ). The most striking results concerned fatty liver, exhibiting a significant sex by diet interaction ( $P < 0.01$ ); the ranking of the diets was  $R_m > R_i = C$  in males and  $C > R_i = R_m$  in females. The 20% increase in fatty liver weight in male mule ducks in the