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## **Locus-specific epigenetic changes associated with peripheral leptin resistance in increased resistance to a high-fat diet in mice born to obese mothers fed a control diet during gestation**

Linda Attig, J.P. Jais, A. Vigé, Aurore Beauger, M.S. Gross, C. Gallou-Kabani, J.D. Gothié, Anne Gabory, Luc Jouneau, Claudine Junien

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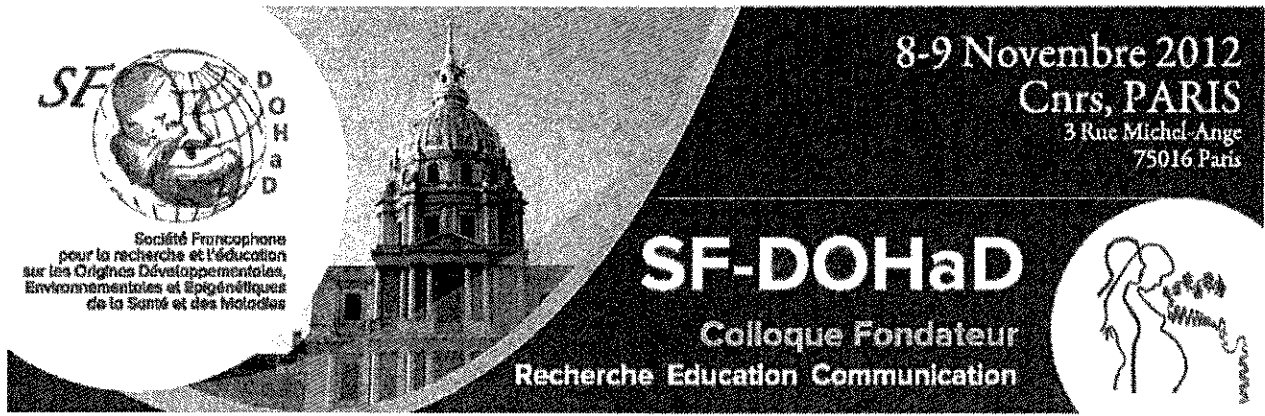
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## ORAL N°41

**Adoption prevents metabolic alterations in male rats with intrauterine growth restriction resulting from maternal undernutrition**

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Epidemiological and experimental data show that intrauterine growth restriction (IUGR) sensitizes the development of adult chronic diseases such as obesity, diabetes and/or hypertension.<sup>1-3</sup> It was also reported that growth alterations during the early postnatal period (i.e. lactation) can exert long-term effects on programming/deprogramming of metabolic diseases.<sup>4</sup> Using an experimental model of maternal perinatal undernutrition of 50% (FR50 model) in rats that induces intrauterine and extrauterine growth retardation in the offspring, we have shown that FR50 male animals exhibit reduced body weight, alterations in carbohydrate metabolism and mild hypertension at the age of 6 months. In neonates, adoption of IUGR newborns from mothers fed *ad libitum* allows normalizing their body weight as soon as postnatal day (PND) 4, and restoring PND10 and PND21 plasma leptin concentration to levels comparable to those observed in control newborns, suggesting that mother regimen during lactation dictates leptin plasma levels in pups. Interestingly, adoption also prevents the development of hypertension and alterations in glycaemic control observed in response to an oral glucose tolerance test. Finally, undernutrition during lactation decreases milk leptin concentration. In our experimental model, adoption allows an early catch-up growth and restoration of plasma leptin levels during lactation, and is associated with long-term prevention of metabolic alterations programmed perinatally in adult male rats. This work opens new perspectives for identifying compounds that may enter in the composition of infant formula, in an attempt to precociously 'deprogram' diseases in adults.

**Key words:** Barker hypothesis, breastfeeding, developmental programming, early development and adult disease

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

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## ORAL N°59

**Locus-specific epigenetic changes associated with peripheral leptin resistance in increased resistance to a high-fat diet in mice born to obese mothers fed a control diet during gestation**

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Epigenetic mechanisms are evoked to explain interindividual and across-generation variations in the proneness or resistance to develop diet-induced obesity (DIO) of inbred C57BL/6J mice even under the same high-fat diet.<sup>1,2</sup> Feeding obese and diabetic mothers a control diet during the periconceptional/gestation/lactation period led to a pronounced sex-specific shift from proneness to resistance to DIO in the offspring.<sup>3</sup> In this study, Affymetrix microarrays highlighted the prominent role of leptin-leptin receptor cytokine pathways and a cross-talk between muscle and liver. The top-ranking genes were the leptin (*Lep*) gene upregulated in muscle, and the leptin receptor (*Lepr*) and suppressor of cytokine signaling 2 (*Socs2*) genes drastically downregulated in liver only. Weight-gain proneness as opposed to resistance was associated in muscle with an inflammatory process related to altered levels of adipokines, and in liver with an altered lipid processing and increased lipid droplets formation, suggesting a strong connection of *Lepr* and *Socs2* to fat metabolism. Locus-specific epigenetic analyses by bisulfite-pyrosequencing and CHIP PCR of *Lep*, *Lepr* and *Socs2* revealed a role for specific CpG methylation and histone acetylation and methylation marks in the tissue-specific regulation of these genes with specific profiles associated with the obesity-prone phenotype, whereas resistant mice epigenetic landscapes evoked a strong tendency toward 'normality'. Emphasizing the hitherto unsuspected role of *Lepr* gene expression in peripheral leptin resistance<sup>4</sup> and its liver specificity, this work is the first to describe epigenetic changes in *Lepr* associated with its downregulation as potentially useful markers in the follow-up of leptin resistance treatment in obese patients.

**Key words:** DNA methylation, epigenetics, histone post-translational modifications, leptin resistance, leptin signaling, metabolic adaptation

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

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