The cellularity of offspring’s adipose tissue is programmed by maternal nutritional manipulations

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Epidemiological studies initially demonstrated that maternal undernutrition leads to low birth weight with increased risk of adult-onset obesity. Maternal obesity and diabetes associated with high birth weight, excessive nutrition in neonates, and rapid catch-up growth also predispose offspring to fat accumulation. As stated by the Developmental Origin of Health and Disease concept, nutrient supply perturbations in the fetus or neonate result in long-term programming of individual body weight set-point. Adipose tissue is a key fuel storage unit mainly involved in the maintenance of energy homeostasis. Studies in numerous animal models have demonstrated that the adipose tissue is the focus of developmental programming events in a gender- and depot-specific manner. This review summarizes the impact of maternal nutritional manipulations on cellularity (i.e., cell number, size, and type) of adipose tissue in programmed offspring. In rodents, adipose tissue development is particularly active during the perinatal period, especially during the last week of gestation and during early postnatal life. In contrast to rodents, this process essentially takes place before birth in bigger mammals. Despite these different developmental time windows, altricial and precocial species share several mechanisms of adipose tissue programming. Maternal nutritional manipulations result in increased adipogenesis and modified fat distribution and composition. Inflammation changes such as infiltration of macrophages and increased inflammatory markers are also observed. Overall, it may predispose offspring to fat accumulation and obesity. Inappropriate hormone levels, modified tissue sensitivity, and epigenetic mechanisms are key factors involved in the programming of adipose tissue’s cellularity during the perinatal period.

Introduction

It is now well accepted that adult-onset metabolic disorders may derive from events taking place during fetal and postnatal development. In particular, epidemiological studies demonstrated that intrauterine growth retardation (IUGR) and low birth weight are associated with higher adiposity in adulthood. Maternal obesity and diabetes associated with high birth weight, excessive nutrition in neonates and rapid catch-up growth also increase the risk of adult-onset obesity. These observations have participated in establishing the Developmental Origin of Health and Disease (DOHaD) hypothesis. This concept states that an adverse environment in utero or during infancy, including dysnutrition, can program or imprint the development of several tissues, including the adipose tissue. It then may permanently determine physiological responses and ultimately produce energy balance dysfunction and diseases later in life. Numerous studies in animals have confirmed that perinatal nutritional manipulations can program adipose tissue in offspring.

Three types of adipose tissue have been described, mostly composed of mature adipocytes (specialized fat-storing cells) and a stromal vascular fraction (preadipocytes, fibroblasts, endothelial cells, and immune cells). First, the white adipose tissue (WAT) is a specialized tissue that stores energy as triglycerides (TG) via lipogenic pathways. During period of negative energy balance, stored TG are hydrolyzed by lipolytic pathways, driven by the noradrenergic innervations (Fig. 1). The sympathetic system may also control fat cell number via inhibition of adipocyte proliferation. WAT expansion involves adipogenesis, a two-step process by which preadipocytes are first recruited from precursor cells and then differentiated into adipocytes. Adipogenesis is driven by the expression of adipogenic and lipogenic transcription factors including peroxisome proliferator-activated receptor-γ (PPARγ), CCAAT/enhancer binding protein (C/EBPα, β, γ), the sterol regulatory element-binding protein 1c (SREBP1c), as well as the expression of specific lipid-metabolizing enzymes such as fatty acid synthase (FAS). WAT expansion also relies on lipogenesis (i.e., conversion of fatty acids into TG) in pre-existing adipocyte (Fig. 1). Second, the brown adipose tissue (BAT) is specialized in the production of heat. Brown adipocytes are characterized by high expression of uncoupling protein 1 (UCP1), a BAT-specific marker, fatty-acid-activated transcription factor PPARα and PPARγ coactivator 1-α (PGC1-α). BAT also differs from WAT by its cell origin, using its own developmental transcription factor pathway. Third, brite adipocytes (brown-in-white) have been detected within some WAT depots. While brite
Adipocytes possess most of the characteristics of brown adipocytes, they have a distinct origin from brown adipocytes. In particular, activation of the WAT sympathetic system via the β3-adrenoreceptor resulted in browning of white adipocytes (i.e., enhanced brite adipocytes) in rodents.5

As soon as 1962, it has been showed that rat epididymal fat pads exhibited a continual rise in DNA content from birth to 14 wk of age, suggesting modified WAT cellularity during this period. Once attained, the adipocyte number could not be changed. Thus, the timing of adipose tissue development determines the window of vulnerability to potential environmental insults, and this window markedly differs between species. In rodents, adipose tissue adipogenesis is particularly active during the perinatal period. In rats, these processes occur primarily during the last week of gestation, accelerate during early postnatal life (i.e., the lactation) until pups are completely weaned. Adolescence phase also constitutes a critical programming window for the development of adipose tissue.7 In contrast to rodent, adipogenesis essentially takes place before birth in bigger mammals such as sheep or primates.8 Despite this difference, altricial and precocial species share several mechanisms of offspring programming. This review summarizes the impact of maternal nutritional manipulations on cellularity (i.e., cell number, size, and type) of adipose tissue in programmed offspring.

Malgrown Offspring Display Altered Adipogenesis and Fat Accumulation

Intrauterine growth-restricted offspring

Two models of maternal undernutrition have been mainly described: maternal low-protein diet (8% instead of 20% protein) and global maternal food restriction ranging from 20% to 70% of control intake. Although both protocols usually produce IUGR, they result in different outcomes on the adult offspring’s adipocyte size and number.

Rat offspring of low-protein diet (LP) fed-dams during gestation and lactation have persistent smaller adipocytes.9

Although exposure to a maternal low-protein diet did not affect the capacity of in vitro preadipocyte cultures to divide or store fat in perinatal period (fetuses, neonates, and weaning), adult
offspring from LP dams exhibited increased rate of cultured preadipocyte proliferation.10 Consistent with these findings, the mRNA expression levels of C/EBPα and PPARγ were increased in the WAT of adult rat offspring from LP dams.11 Adult rats from LP dams also exhibited increased adipose tissue expression of miRNA-483-3p, known to regulate early and late stages of in vitro differentiation and the capacity of adipocytes to store lipids. Thus, this may contribute to the inhibition of adipocyte hypertrophy (i.e., lipid storage) that would affect other tissues by promoting ectopic TG storage.9

In contrast to maternal LP procedure, low birth-weight rat offspring from 50% food-restricted dams (FR50) during gestation from day 10 to term12 or from 70% food-restricted dams (FR70) throughout the gestation13 showed persistent hypertrophic adipocytes. As soon as postnatal day 1, IUGR offspring from FR50 dams exhibited enhanced PPARγ and its upstream regulatory transcriptional factors (C/EBPα, C/EBPβ, and C/EBPδ). Accordingly, at both postnatal day 1, primary cell cultures from IUGR neonates displayed increased preadipocyte proliferation and adipocyte TG accumulation.14 Increased adipocyte size was observed in offspring of FR50 dams as soon as weaning.12 Prior to the onset of overt obesity, the increased expression of adipogenic factors was accompanied with elevated expression of lipogenic factors (SREBP1c, FAS, and leptin) in weanling pups12 and adult offspring13 from FR dams.

Other animal models of IUGR have been developed. In particular, uterine artery ligation (mimicking uteroplacental insufficiency) in the pregnant dams leads to a gender- and depot-specific marked adiposity in adult rat offspring. As reported in offspring of undernourished rat dams, PPARγ mRNA expression levels were enhanced in WAT of juvenile offspring prior to the onset of overt obesity.15

The energy supply mismatch between overfeeding-induced postnatal catch-up growth and fetal nutrient restriction results in offspring with exacerbated fat accumulation. In agreement with these findings, cultured preadipocytes from overfed (i.e., reared in small litter increasing milk intake) juvenile rats from LP dams showed enhanced proliferation and differentiation.16 Overfed adult offspring from undernourished rat dams displayed marked adiposity with a global increase in adipogenic and lipogenic genes (SREBP1c, C/EBPα, PPARγ, FAS, and leptin) in a depot-specific manner.13 In addition, adult mice from LP dams cross-fostered to control lactating dams presented modified daily transcriptional profile of lipogenic and clock genes in WAT, suggesting an association between the disruption of the circadian clock and the programming of adiposity.17

In sheep, which have a similar profile of adipose tissue cell development as humans, a programmed effect on adipocyte development is implicated because of increased PPARγ levels. Indeed, PPARγ mRNA expression levels were lower within reduced fat depots in low birth-weight lamb. After a period of accelerated postnatal growth, adult offspring from undernourished dams during gestation presented overt obesity with increased PPARγ mRNA expression levels in WAT.8 Data obtained from altricial and precocial species suggest that undernourished offspring, especially when fed an obesogenic diet later in life, are vulnerable to adipogenesis and fat accumulation.

Maternal overfeeding

Models of maternal overnutrition and obesity rely on feeding the dams a high-fat (HF) or cafeteria (fat and sugar) diet before (preconceptional period) and/or during gestation and/or lactation. Offspring of obese animals are consistently prone to increased adiposity (i.e., hypertrophic adipocytes) in adulthood in a gender-dependent manner. Overnutrition during lactation and/or postweaning periods always worsens adipogenesis programming.18

A rat model of maternal obesity based on intragastric feeding of HF diet demonstrated that maternal obesity at conception programs increased adiposity in offspring despite normal birth weight. Indeed, a greater percentage of large adipocytes associated with elevated PPARγ were observed in adulthood suggesting enhanced adipogenesis.19 In agreement with these findings, fetuses from obese mice fed a cafeteria diet before mating and throughout gestation exhibited larger adipocytes.20 A sheep model of maternal overfeeding during late gestation was also associated with higher WAT mass in the fetus with enhanced PPARγ mRNA expression levels sensitizing to postnatal adiposity.8

In a rat model of maternal obesity induced by HF diet before mating and during pregnancy, newborns had similar body weights than pups born from control diet-fed mothers.21 Maternal HF diet during lactation had a significant impact on adiposity of the offspring resulting in accelerated catch-up growth and early obesity, apparent at the end of the lactation period.22 In rodent models, offspring of obese dams consistently shows fat expansion suggesting enhanced adipogenesis which may be attributed, at least in part, to upregulated PPARγ18 associated with downregulated PPARγ corepressors (SIRT1, SMRT, NcoR [nuclear receptor corepressor]).22 In agreement with these findings, overweight adult offspring from obese mice fed a cafeteria diet before mating and throughout gestation displayed marked adiposity in a gender-dependent manner. The adipocyte hypertrophy, more pronounced in female, was accompanied by reduced lipolytic adrenorenceptors and elevated PPARγ mRNA expression levels.18

In adulthood, obese rat offspring of cafeteria-diet-fed dams during gestation and lactation presented an increase in adipose tissue TG content with elevated lipogenic enzyme activities (lipoprotein lipase [LPL]). They also had abnormalities in fatty acid composition.23 Interestingly, a study showed that a mouse model of maternal gestational diabetes leads to overweight in adult offspring associated with larger adipocytes.24 These findings indicate that perinatal exposure to a diabetic milieu characterized by increased glucose and/or insulin levels can program developmental processes such as adipogenesis (Fig. 1).

Altered feeding in the neonatal period

Because adipogenesis mostly takes place after birth in rodents, models based on postnatal dietary manipulations (i.e., postnatal over- [small litters] or undernutrition [large litters] of the nursing
Perinatal Malnutrition Programs Modifications in Adipose Tissue Noradrenergic Innervation in Offspring

Several studies have shown that maternal nutrient restriction impairs sympathetic activity in WAT offspring. Weanling rats from FR50 dams during the last week of gestation and lactation exhibited elevated circulating norepinephrine level that could participate, via chronic β-adrenergic stimulation, to the remodeling of WAT into a thermogenically active BAT. Indeed, a marked increase in UCP1, PGC1α, and PPARα mRNA expression levels, markers of brown adipocytes and/or adaptive thermogenesis were observed in fat pads of offspring. These observations suggest a delay in the maturation of offspring WAT, favoring the acquisition of brite adipocytes in WAT and increased thermogenesis. Adult rat offspring from FR20 dams during the first 12 d of pregnancy exhibited a gender-dependent reduction of noradrenergic innervation to WAT and BAT as well as modified adrenoreceptor subtypes ratio. These modifications are associated with greater adiposity, enhanced adipocyte hyperplasia and hypertrophy. In addition, adult rats reared in small litters exhibited reduced BAT mass and thermogenesis (i.e., lower UCP1 mRNA expression levels), modified lipolytic adrenoreceptor subtypes ratio and impaired sympathetic outflow activity that might affect lipolysis.

Offspring of Malnourished Dams Exhibit Increased Circulating and Adipose Tissue Pro-Inflammatory Mediators Levels

Perinatal nutritional manipulations influence the circulating levels of several adipocytokines (i.e., tumor necrosis factor-α [TNF-α] and interleukin-6 [IL-6]) in obesity-prone offspring. Chronic inflammation of adipose tissue is viewed as a hallmark of obesity and metabolic syndrome. In particular, inflammation has detrimental effects on insulin secretion, insulin sensitivity, and lipid metabolism. It may reflect either a modification of the cell composition (i.e., immune cell infiltration), and/or an increase in pro-inflammatory markers mRNA gene expression in the WAT. Consistent with this notion, adipose tissue of perinatally undernourished adult sheep exhibited upregulation of key pro-inflammatory genes accompanied by a recruitment of macrophage within WAT. Interestingly, uteroplacental insufficiency resulting in IUGR is also associated with enhanced inflammatory mediators in WAT prior to the onset of overt obesity. In addition, fetuses of obese mice fed a cafeteria diet before mating and throughout gestation exhibited an increase in several pro-inflammatory markers in WAT, suggesting macrophage infiltration. Similarly, enlarged adipocytes of rat offspring reared in small litters displayed a postnatal induction of pro-inflammatory cytokines (i.e., TNF-α and IL-6) mRNA expression levels that were exacerbated under HF diet.

Programming mechanisms

Different opposite paradigms (undernutrition vs. overfeeding) have been used to study the long-term effects of nutritional manipulations in the perinatal period, and both protocol result in similar outcomes on the adult offspring’s adipose tissue. Thus, the perturbation of circulating factor levels as well as adipose tissue local factor levels, other than nutrients, induced by nutrition during neonate development may account for long-lasting adipose tissue cellularity perturbations.

Circulating and local factors

Several studies support the notion that inappropriate neonatal leptin levels lead to fat expansion by programming the hypothalamus adipose-axis. First, leptin displays marked in vivo and in vitro neurotrophic effects. Second, perinatal leptin manipulations have long-term detrimental effects resulting in an increase in adiposity in adulthood. Third, leptin directly activates adipogenesis by promoting differentiation of preadipocytes whereas it shows antilipogenic effects on mature adipocytes (Fig. 1). Increased insulin levels might also be a key factor of fat accumulation. Similarly, insulin exhibited in vivo and in vitro programming effects on the hypothalamus adipose-axis. In particular, insulin directly activates adipogenesis and lipogenesis whereas it inhibits lipolysis in mature adipocytes (Fig. 1).

On the one hand, persistent modified GC circulating levels might contribute to the susceptibility of obesity in adulthood. In line with these findings, maternal nutritional manipulations coincide with elevated perinatal circulating GC levels. Thus, it may lead to long-lasting disturbed HPA axis feedback with permanent hypercorticosteronemia. Chronic GC exposure activates adipogenesis primarily by regulating key adipogenic transcription factors (i.e., C/EBPα, PPARγ) (Fig. 1). It may also induce the expression of pro-inflammatory genes, favoring macrophage infiltration and providing the environmental conditions for inflammation.
On the other hand, the predisposition of increased adiposity may be due to local adipose tissue GC metabolism (i.e., modified GR, MR, 11β-HSD11, 11β-HSD2 expression levels), rather than systemic GC status (Fig. 1). Indeed, perinatal nutritional manipulations program the local adipose tissue GC sensitivity in a sex-specific manner. A primate model of maternal nutrient reduction in which offspring develop increased adiposity in adulthood was associated with elevated mRNA expression levels of glucocorticoid receptor (GR) and 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1), enzyme that amplifies local GC actions by converting inactive GC metabolites to active GC in fetal adipose tissue in a sex-specific manner.36

Low birth weight lamb with reduced fat deposition from undernourished dams during gestation, exhibits changes in potential GC sensitivity directly related to the increase in postnatal WAT mass. Indeed, adipose tissue GR and 11β-HSD1 mRNA expression levels displayed a progressive postnatal increase that parallels active catch-up growth and fat expansion. In contrast, 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) that degrades active GC to inactive metabolites was reduced.37

Similarly, hypertrophied WAT of overfed offspring reared in small litters displayed a postnatal induction of WAT GR and 11β-HSD1 mRNA expression levels. Postweaning HF diet exacerbated this profile. Interestingly, adult rat offspring from diabetic dams also showed an increase in 11β-HSD1 mRNA expression levels prior to the onset of overt obesity.29 As reported during postnatal catch-up growth in undernourished lamb,37 these observations emphasize the pivotal role of the GC WAT environment during the perinatal period on the subsequent development of obesity.

Finally, the ratio between adipose tissue 11β-HSD1 and 11β-HSD2 expression were modified in adult rat offspring from FR70 dams throughout the gestation and, thus, the local tissue ratios between active and inactive GC. In response to HF diet, the depot-specific upregulation of 11β-HSD2 mRNA, while 11β-HSD1 expression remains stable, might limit corticosterone metabolism.44 In mice, it has been shown that both male and female offspring may respond differently to altered GC status during pregnancy.45 Data from the Dutch Famine Study reveal that starvation during pregnancy can also have transgenerational consequences wherein second generation offspring have increased neonatal adiposity.46

**Epigenetic and Transgenerational Mechanisms**

Nutritional manipulations during the perinatal period are now considered as transient environmental challenges that can permanently imprint the offspring genome to exert their metabolic effect in adulthood. Indeed, maternal (and/or paternal) perinatal food manipulations may cause epigenetic modifications such as gene promoter region methylation (i.e., the CpG sites), chromatin histone acetylation/methylation and changes in miRNA expression levels in offspring.38 These nutritionally-induced epigenetic modifications may persistently affect transcriptional levels of key genes involved in adipogenesis39 (especially GR, C/EBPα, and PPARγ) and/or in inflammation40 to program long-term WAT cellularity. To our knowledge, only few studies have reported epigenetic modulations associated with programmed adipose tissue induced by maternal nutritional manipulations.9,19,41,42 However, these findings suggest a close link between maternal nutritional manipulations and programmed adipose tissue’s cellularity via epigenetics mechanisms.

Jousse et al.41 showed that adult mice from LP dams presented hypomethylation of the leptin promoter in WAT with lower leptin contents. Ferland-McCollough et al.9 showed that rat offspring from LP mothers exhibited an increase in miRNA-483-3p expression levels in WAT with a decrease in GDF3 (a member of the BMP/TGF-β family) protein content, a factor that impairs late stages of adipocyte differentiation. Masuyama et al.42 reported that exposure to a HF diet in utero causes an increase in leptin and adiponectin mRNA expression levels associated with epigenetic modifications in WAT of mouse offspring. In particular, lower acetylation and higher methylation levels of histone H3 at lysine 9 of the promoter of adiponectin were evidenced whereas higher methylation of histone 4 at lysine 20 in the leptin promoter was observed in obesity-prone offspring. Borengasser et al.19 showed that obesity-prone weanling rat from obese dams induced by intragastric feeding of HF diet presented greater ex vivo adipocyte differentiation associated with increased mRNA expression levels of key adipogenic and lipogenic transcription factors (PPARγ, C/EBPβ) and specific alterations in DNA methylation of CpG sites.

Nutritional manipulations in the perinatal period can predispose to obesity and imprint adipose tissue’s cellularity in offspring in a gender-dependent manner. For example, the consumption of HF diet during pregnancy appears to directly influence placental methylation and placental gene expression patterns only in female mice offspring.43 Thus, sex-specific differences in term of epigenetic modifications are associated with developmentally programmed phenotypes in animal models. Finally, although underlying mechanisms remain unclear, it appears that the transmission of epigenetic alterations might extend beyond the malnourished first generation resulting in the transgenerational inheritance of obesity. Thus, acute programming of somatic tissues can result in long-term health outcomes in the first generation. In addition, germ cells, which contribute genetic and epigenetic information to the second generation, undergo reprogramming during embryonic development.44 In mice, it has been shown that both male and female offspring showed increased body weight and adiposity over generations under multigenerational HF diet feeding. In particular, DNA hypomethylation on promoters on several inflammatory genes result in epigenetically increased expression across generations, which may contribute to persistent inflammation in adipose tissue.45 Data from the Dutch Famine Study reveal that starvation during pregnancy can also have transgenerational consequences wherein second generation offspring have increased neonatal adiposity.46

**Conclusion**

The periods of gestation and lactation appear to be particularly sensitive time windows for the developmental programming...
of adiposity. During these periods, plasma levels of circulating factors as well as adipose tissue hormone sensitivity show perturbations in offspring of malnourished dams resulting in long-last-
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References

1. Ravelli AC, van Der Meulen JH, Osmond C, Barker DJ, Bleker OP. Obesity at the age of 50 in men and women exposed to famine prenatally. Am J Clin Nutr 1999; 70:811-6; PMID:10539740

2. Barker DJ. The developmental origins of chronic adult disease. Acta Paediatr Suppl 2004; 93:26-33; PMID:15702667; http://dx.doi.org/10.1111/j.1651-2277.2004.tb00236.x

3. Lukaszewska MA, Eberle D, Vieu D, Breton C. Nutri-
tional manipulations in the perinatal period program adi-
pose tissue and its regulation of cell number. Am J Physiol Endocrinol Metab 2013; 305:E1195-207; PMID:24045869; http://dx.doi.org/10.1152/ajpendo.00231.2013

4. Bowser RR, Fuestuccia WT, Song CK, Shi H, Migliorini EB. Adipose protein-restricted rats. Am J Physiol Endocrinol Metab 2004; 286:E1167-75; PMID:15142857; http://dx.doi.org/10.1152/ajpendo.00558.2003

5. Seale P, Kajimura S, Spiegelman BM. Transcriptional control of brown adipocyte development and physi-
ological function—of mice and men. Genes Dev 2009; 23:788-97; PMID:19339685; http://dx.doi.org/10.1101/gad.177792.109

6. Vosselman MJ, van Marken Lichtenbelt WD, Schrau-
ming of adipose tissue miR-483-3p and GDF-3 expres-
sion by maternal diet in type 2 diabetes. Cell Metabol 2011; 23:2760-3; PMID:18833213; http://dx.doi.org/10.1016/j.cmet.2011.08.017

7. de Oliveira JC, Lisboa PC, de Moura EG, Barella LF, Miranda RA, Malta A, Franco CC, Ribeiro TA, Torre-
zan R, Gravena C, et al. Poor pubertal protein nutrition disturbs glucose-induced insulin secretion process in pancreatic islets and programs rats in adulthood to increase fat accumulation. J Endocrinol 2013; 216:195-206; PMID:23151360; http://dx.doi.org/10.1530/JOE-12-0408

8. Muhlhauser B, Smith SR. Early-life origins of meta-
bolic dysfunction: role of the adipocyte. Trends Endo-
crinol Metab 2009; 20:51-7; PMID:19054606; http://dx.doi.org/10.1016/j.tem.2008.10.006

9. Ferland-McCollough D, Fernandez-Twinn DS, Cannell IG, David H, Warner M, Vaug AA, Bork-Jensen J, Bunts C, Gant TW, Wille AE, et al. Program-
meg of adipose tissue miR-483-3p and GDF-3 expression by maternal diet in type 2 diabetes. Cell Death Differ 2012; 19:1003-12; PMID:22223106; http://dx.doi.org/10.1038/cdd.2011.183

10. Bieswal F, Hay SM, McKinnon C, Reusen B, Caignet M, Rees WD, Remacle CA. Prenatal protein restriction does not affect the differentiation and proliferation of rat adipocytes. J Nutr 2004; 134:1493-9; PMID:15173417

11. Guan H, Arany E, van Berk JP, Channon-Reig A, Thysen S, Hill DJ, Yang K. Adipose tissue gene expression profiling reveals distinct molecular pathways that define visceral adiposity in offspring of maternal protein-restricted rats. Am J Physiol Endocrinol Metab 2005; 288:E663-73; PMID:15562247; http://dx.doi.org/10.1152/ajpendo.00461.2004

12. Desai M, Guang Han, Ferrelli M, Kallichanda N, Lane RH. Programmed upregulation of adipogenic transcrip-
tion factors in intrauterine growth-restricted offspring. Reprod Sci 2007; 14:96; PMID:19078816; http://dx.doi.org/10.1177/1933719108315897

13. Lukaszewska MA, Mayerse S, Fajardy I, Delahaye F, Dutriez-Casteloot I, Montel V, Dickes-Coopman A, Laborie C, Lesage J, Vieu D, et al. Maternal prenatal undernutrition alters adipose tissue gene expression in adult male rat offspring after high-fat diet. Am J Physiol Endocrinol Metab 2011; 301:E548-59; PMID:21712534; http://dx.doi.org/10.1152/ajpendo.00011.2011

14. Yee JK, Lee WN, Ross MG, Lane RH, Han G, Vega J, Desai M. Peroxisome proliferator-activated receptor gamma modulation and lipogenic response in adip-
ocytes of small-for-gestational age offspring. Nutr Metab (Lond) 2012; 9:62; PMID:22726273; http://dx.doi.org/10.1186/1743-7075-9-62

15. Joss-Moore LA, Wang Y, Campbell MS, Moore B, Yu X, Callaway CW, McKeigan RA, Desai M, Moyer-
Mulerier LJ, Lane RH. Uteroplacental insufficiency increases visceral adiposity and visceral adipose PPAR-gamma2 expression in male rat offspring prior to the onset of obesity. Early Hum Dev 2010; 86:179-85; PMID:20227220; http://dx.doi.org/10.1016/j.earlhumdev.2010.02.006

16. Bol VY, Reusen BM, Remacle CA. Postnatal catch-up growth after fetal protein restriction programs prolifera-
tion of rat preadipocytes. Obesity (Silver Spring) 2008; 16:2760-3; PMID:18833213; http://dx.doi.org/10.1038/oby.2008.41

17. Sutton GM, Centanni AV, Butler AA. Protein malnu-
tsion programs the organization of hypothalamic feeding cir-
cuits and impairs leptin sensitivity in offspring. Endocrinology 2011; 152:4171-9; PMID:21862611; http://dx.doi.org/10.1210/en.2011-1279

18. Boulla-Cioaca S, Achard V, Tassiotto V, Dutour A, Grino M. Postnatal programming of gluconiccidic morbidum in rats modulates high-fat diet-induced reg-
ulation of visceral adipose tissue glucocorticoid expres-
sion and sensitivity and adiponectin and proinflammatory adipokines gene expression in adult-
hype. Diabetes 2008; 57:669-77; PMID:18057089; http://dx.doi.org/10.2337/db07-1316

19. Borengasser SJ, Zhong Y, Kang P, Lindsey F, Ronis MJ, Calais. Disclosure of Potential Conflicts of Interest

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intercascal brown fat. J Lipid Res 2007; 48:41-51; PMID:17041251; http://dx.doi.org/10.1194/jlr.M600287-JLR200

31. Sharkey D, Symonds ME, Budge H. Adipose tissue inflammation: developmental ontology and consequences of gestational nutrient restriction in offspring. Endocrinology 2009; 150:3913-20; PMID:19423760; http://dx.doi.org/10.1210/en.2008-1784

32. Breton C. The hypothalamus-adipose axis is a key target of developmental programming by maternal nutritional manipulation. J Endocrinol 2013; 216:R19-31; PMID:23108716; http://dx.doi.org/10.1530/JOE-12-0157

33. Bouret SG, Draper SJ, Simerly RB. Trophic action of leptin on hypothalamic neurons that regulate feeding. Science 2004; 304:108-10; PMID:15064420; http://dx.doi.org/10.1126/science.1095004

34. Huan JN, Li J, Han Y, Chen K, Wu N, Zhao AZ. Adipocyte-selective reduction of the leptin receptors induced by antisense RNA leads to increased adiposity, dyslipidemia, and insulin resistance. J Biol Chem 2003; 278:45638-50; PMID:12925533; http://dx.doi.org/10.1074/jbc.M304165200

35. Poulos SP, Hausman DB, Hausman GJ. The development and endocrine functions of adipose tissue. Mol Cell Endocrinol 2010; 323:20-34; PMID:20025936; http://dx.doi.org/10.1016/j.mce.2009.12.011

36. Guo C, Li C, Myant I, Nathanielsz PW, Sun K. Sexually dimorphic effects of maternal nutrient reduction on expression of genes regulating cortisol metabolism in fetal baboon adipose and liver tissues. Diabetes 2013; 62:1175-85; PMID:23238295; http://dx.doi.org/10.2337/db12-0561

37. Gnanalingham MG, Mostyn A, Symonds ME, Stephenson T. Ontogeny and nutritional programming of adiposity in sheep: potential role of glucocorticoid action and uncoupling protein-2. Am J Physiol Regul Integr Comp Physiol 2005; 289:R1407-15; PMID:16802557; http://dx.doi.org/10.1152/ajpregu.00375.2005

38. Lillycrop KA, Burdge GC. Epigenetic mechanisms linking early nutrition to long term health. Best Pract Res Clin Endocrinol Metab 2012; 26:667-76; PMID:22980048; http://dx.doi.org/10.1016/j.beem.2012.03.009

39. Masi MM, Párrizas M. Epigenetic regulation of adipogenesis. Curr Opin Clin Nutr Metab Care 2012; 15:342-9; PMID:22617562; http://dx.doi.org/10.1097/MCO.0b013e3283546fba

40. Toubal A, Treuter E, Clement K, Venetelof N. Genomic and epigenomic regulation of adipose tissue inflammation in obesity. Trends Endocrinol Metabol 2013; 24:625-34; PMID:24169451; http://dx.doi.org/10.1016/j.tem.2013.09.006

41. Jousse C, Parry L, Lambert-Langlais S, Maurin AC, Averous J, Bruhat A, Carraro V, Tost J, Letteron P, et al. Perinatal undernutrition affects the methylation and expression of the leptin gene in adults: implication for the understanding of metabolic syndromes. FASEB J 2011; 25:3271-8; PMID:21670064; http://dx.doi.org/10.1096/fj.11-181792

42. Masuyama H, Hiramatsu Y. Effects of a high-fat diet exposure in utero on the metabolic syndrome-like phenomenon in mouse offspring through epigenetic changes in adipokine gene expression. Endocrinology 2012; 153:2823-30; PMID:22434078; http://dx.doi.org/10.1210/en.2011-2161

43. Gallou-Kabani C, Gabory A, Tost J, Karimi M, Mayeur S, Lesage J, Boudadi E, Groux MS, Taurelle J, Vigi A, et al. Sex- and diet-specific changes of imprinted gene expression and DNA methylation in mouse placenta under a high-fat diet. PLoS One 2010; 5:e14398; PMID:21200436; http://dx.doi.org/10.1371/journal.pone.0014398

44. Dunn GA, Morgan CP, Bale TL. Sex-specificity in transgenerational epigenetic programming. Horm Behav 2011; 59:290-5; PMID:20483359; http://dx.doi.org/10.1016/j.yhbeh.2010.05.004

45. Ding Y, Li J, Liu S, Zhang L, Xiao H, Li J, Chen H, Petersen RB, Huan K, Zheng L. DNA hypomethylation of inflammation-associated genes in adipose tissue of female mice after multigenerational high fat diet feeding. Int J Obes (Lond) 2014; 38:198-204; PMID:24376364; http://dx.doi.org/10.1038/ijo.2013.98

46. Painter RC, Osmond C, Gluckman P, Hanson M, Phillips DI, Roseboom TJ. Transgenerational effects of prenatal exposure to the Dutch famine on neonatal adiposity and health in later life. BJOG 2008; 115:1243-9; PMID:18715409; http://dx.doi.org/10.1111/j.1471-0528.2008.01822.x