Proceedings of the Nutrition Society (2012), **71**, 276–283 doi:10.1017/S0029665112000055
 First published online 6 March 2012

The 5th International Immunonutrition Workshop was held at Puerto Vallarta, Mexico on 6–8 April 2011

5th International Immunonutrition Workshop

Opening Lecture
Interplay of early-life nutritional programming on obesity, inflammation and epigenetic outcomes

J. Alfredo Martínez*, Paúl Cordero, Javier Campión and Fermín I. Milagro
Department of Nutrition, Food Science, Physiology and Toxicology, University of Navarra, Pamplona, Spain

The huge health burden accompanying obesity is not only attributable to inadequate dietary and sedentary lifestyle habits, since a predisposing genetic make-up and other putative determinants concerning easier weight gain and fat deposition have been reported. Thus, several investigations aiming to understand energy metabolism and body composition maintenance have been performed considering the participation of perinatal nutritional programming and epigenetic processes as well as inflammation phenomena. The Developmental Origins of Health and Disease hypothesis and inheritance-oriented investigations concerning gene–nutrient interactions on energy homoeostasis and metabolic functions have suggested that inflammation could be not only a comorbidity of obesity but also a cause. There are several examples about the role of nutritional interventions in pregnancy and lactation, such as energetic deprivation, protein restriction and excess fat, which determine a cluster of disorders affecting energy efficiency in the offspring as well as different metabolic pathways, which are mediated by epigenetics encompassing the chromatin information encrypted by DNA methylation patterns, histone covalent modifications and non-coding RNA or microRNA. Epigenetic mechanisms may be boosted or impaired by dietary and environmental factors in the mother, intergenerationally or transiently transmitted, and could be involved in the obesity and inflammation susceptibility in the offspring. The aims currently pursued are the early identification of epigenetic biomarkers concerned in individual's disease susceptibility and the description of protocols for tailored dietary treatments/advice to counterbalance adverse epigenomic events. These approaches will allow diagnosis and prognosis implementation and facilitate therapeutic strategies in a personalised 'epigenomically modelled' manner to combat obesity and inflammation.

Obesity: Inflammation: Epigenetics: Perinatal nutrition: Developmental Origins of Health and Disease

The vast health problems associated with fat deposition resulting in obesity are not only laziness or gluttony trouble associated with inadequate sedentary lifestyles and unbalanced dietary habits, since in addition to a more susceptible genetic make-up to easier weight gain and fat deposition a number of recognised scientific evidences have theorised about the roles of other putative determinants[1]. Thus, there are proofs that some other possible contributing factors to the obesity epidemic are micro-organisms (infectobesity/microbioma), increased maternal age in mothers, assortative mating plus greater reproductive rates among couples with higher adiposity, sleep debits, hormonal and neurological disorders, undue weight gain associated with undesirable pharmacological side effects, lesser variability of external weather conditions and different intergenerational or intrauterine/epigenetic-mediated effects[2].

In this context, it has been claimed that parental nutrition previous to conception, maternal perinatal feeding and early postnatal dietary intake are involved in the onset of some chronic conditions (usually accompanied by inflammatory manifestations) such as obesity, diabetes,

Abbreviations: miRNA, microRNA.

***Corresponding author**: J. Alfredo Martinez, fax +34 948425649, email jalfmtz@unav.es

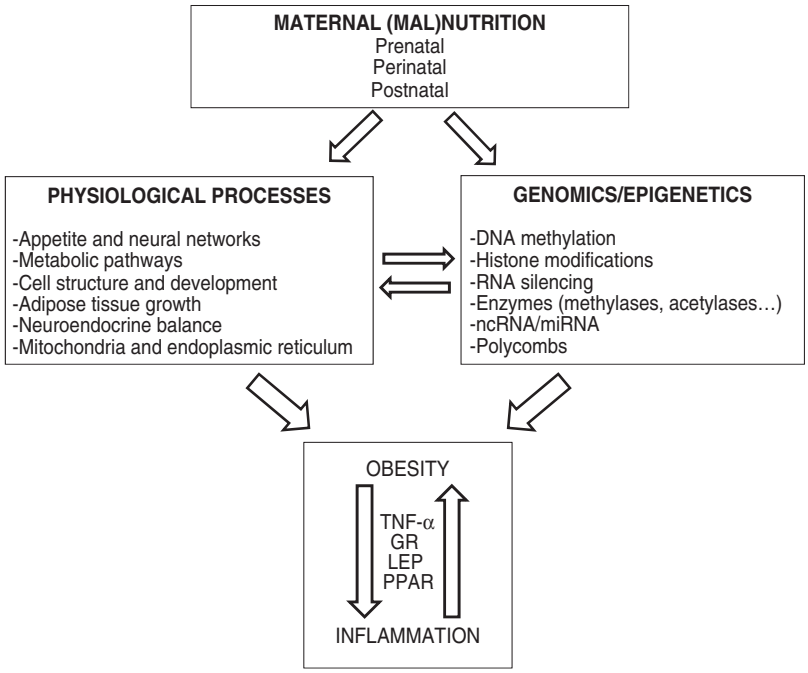

Fig. 1. Diagram showing how early-life nutrition could influence obesity–inflammation interactions in adulthood by physiological processes, and genomics and epigenetic mechanisms. ncRNA, non-coding RNA; miRNA, micro RNA; GR, glucocorticoid receptor; LEP, leptin.

hypertension, dyslipaemia, etc. in the life cycle, which has laid down the foundations of the offspring metabolic encoding[3]. In addition to perinatal programming studies, several investigations aiming to understand energy metabolism and fuel utilisation have been performed considering the interactions between genetics, inflammation phenomena and immunologically related mediators[4].

The term epigenetics was coined as a conceptual assumption for disentangling hither-to undiscovered relationships between environmental settings and the genetic background to produce a given phenotypical outcome[5]. Thus, an early definition for epigenetics involved 'the study of the mechanisms of temporal and spatial control of gene activity describing pathways different from those directly attributable to the underlying DNA sequence and with an influence on the adaptive reaction of an organism' overcoming the usual legacy assigned to DNA[6]. The 'epigenetic code' encompasses the chromatin information mainly encrypted by DNA involving methylation patterns in the nucleotide sequence, histone covalent modifications, microRNA (miRNA) profiles and polycombs, which constitutes 'the sum of the alterations to the chromatin template that collectively establish, modulate and propagate different patterns of gene expression and/or silencing from the same genome'[7]. Therefore, epigenetics can provide some creative insights into understanding genetic fetal programming, monozygotic twin differences, transgenerational outcomes and the onset of chronic diseases with associated inflammatory features such as obesity in the adult, which is requiring newer and elegant experimental models with a focus on phenomena affecting gene expression but not linked to the nucleotide sequence[8].

The Developmental Origins of Health and Disease hypothesis and nutritional programming

The Developmental Origins of Health and Disease hypothesis, which was initially based on epidemiological approaches, is now receiving steady back-up and boosted support through intensive genetically founded experimental research in both cell or animal models and through human genome-related findings[9].

The pioneer finding that poor fetal and infant growth are associated with a higher risk of suffering metabolic syndrome features in adulthood has allowed to sustain the thrifty phenotype hypothesis, which points out that early inadequate nutrition induces insulin resistance[10]. Additional studies conducted in a British Cohort[11], Danish subjects born between 1936 and 1983[12], Dutch famine or Leningrad siege affected children[13] have been consistent with the possibility of developmentally mediated origin of obesity[14].

Furthermore, the National Children Study, the Southampton's Women Survey, the Viva project and the Behavioural Perinatology Research Program together with other more recently launched investigations such as the Avon Longitudinal Study of Parents and Children[15] are contributing to identify critical processes underlying the interactions between retarded fetal growth and development with adiposity-related outcomes and obesity features[16].

Indeed, nutritional programming may explain the predisposition of some individuals to suffer non-communicable diseases in adulthood linked to *in utero*-deprived or infant development[17] (see Fig. 1.). Inheritance-oriented investigations concerning gene–nutrient interactions on

https://doi.org/10.1017/S0029665112000055 Published online by Cambridge University Press

energy homoeostasis processes and metabolic cell functions is extending to all clinically chronic relevant diseases such as diabetes and cardiovascular events as well as to obesity and associated inflammatory features[18,19]. Also, some studies have identified that inflammation and transient infections could be not only a comorbidity of obesity and diabetes[20] but also an aetiological agent[21,22].

The fetal or developmentally programmed genesis of adult sickness hypothesis settled that environmental factors and maternal lifestyles, particularly adverse nutritional disturbances, proceed in early life to drive the risks for the onset of metabolic diseases and excessive weight gain in later life stages[23]. Indeed, maternal nutrition can programme gene expression patterns to the embryo that persist into adulthood and may contribute to the appearance of typical metabolic syndrome features such as hypertension, insulin resistance, hyperlipaemia and abdominal obesity[24]. The parental conditions and lifestyles, which may involve maternal size/obesity, famine at perinatal periods, the use of nutritional supplements, alcohol or drug abuse as well as the administration of therapeutical agents in this critical period may alter specific processes with an impact on embryonic, placental and fetal growth, organogenesis or regulatory set points for system functions affecting adiposity, where inflammatory and immunologically mediated processes may be involved[25]. Interestingly, some of these epigenetically mediated signals may be not permanent but transient, which is of interest not only for prevention, but also as a target for developing future therapeutic focus[26].

Unfavourable environmental cues coming from the mother such as psychological stress, infection, over or undernutrition, smoking, neuroendocrine disruptors, trauma or diseases are signalled inputs negatively affecting the embryo, fetus or neonate[27]. The adaptive responses may involve growth stunting or tissue remodelling with an impact on physiological functions and metabolism being the trade-off and increased risk in later life[3]. The characteristics of the programmed outcomes depend upon the insult or stimuli, as well as on the timing of the exposure[28].

Understanding the maternal regulation of fetal development and programming involves a knowledge about the genome, baseline maternal body composition, dietary and metabolic status, uteroplacental blood flow and substrate transfer that may condition the nutrient balance and fetal malnutrition by inducing hypoxaemia or metabolic changes (cortisol, insulin and nutrient oxidation) and altering body composition in the newborns[29]. In this context, the term developmental plasticity has been used to define the aptitude of a unique genotype to produce a variable phenotype in response to changing environmental circumstances, even though they may be neither adaptive nor prognostic as stated by the developmental programming theory[30], but struggling for resources which may envisage or forecast future metabolic scenarios in an effort to tune gene expression to generate a better adapted phenotype to the predictable afterwards environment[31].

A number of mammal's models have been developed to examine the potential processes and mechanisms involved in perinatal programming that depend on nutrition[32]. The phenomena and manifestations ascribed to early nutritional programming have been explained through different mechanisms such as the involvement of the adipose tissue, the participation of different hormones and endocrine systems, enzymes, transcription factors and signalling mediators (glucocorticoids, insulin, PPAR family, adipokines, etc.), the regulation of specific nutrient-related metabolic pathways (lipogenesis, glyconeogenesis, etc.), the control of neural networks affecting the appetite system (specific orexigenic/anorexigenic neuropeptides and the hypothalamic–pituitary–adrenal axis) and the up/down feedback concerning the gene expression machinery and epigenetic marks[33,34].

The question if later obesity is induced *in utero* or early after birth has been repeatedly addressed and researched[35,36]. Thus, it seems that glucose, insulin and leptin coming from the mother's blood or taken from the breast milk are of relevance for the persistent programming of food intake control at least in the rodent[37] as well as for obesity-related peptides and hormones such as insulin[38]. Furthermore, hormonal and metabolic signals acting during the perinatal period could alter the structure and functions concerning the fat–brain axis or adipogenic genes in the adipose tissue that regulates the energy balance during later life[39]. Alternatively, adverse intrauterine exposures may produce long-term changes in mRNA levels leading to a thrifty phenotype with changes affecting liver, muscle and renal anatomy and physiology[14] as well as long-lasting changes in mitochondria that can be associated with obesity and insulin resistance in later life[40]. Other mechanisms that have been investigated in different animal models in order to clarify the role of the perinatal feeding on tissue structure have revealed an important impact of the maternal diet on proliferation and differentiation processes in the pancreas and in the brain involving an overexposure to glucocorticoids mediated by a reduced activity of the placental 11-β hydroxysteroid dehydrogenase[34]. Also, a maternal obese condition influences fetal growth and body composition with implications in the future offspring health depending on the genetic background, the intrauterine metabolic environment and the generated maternal metabolites[23]. Thus, a mild maternal overnutrition led to increased adiposity, glucose intolerance and altered brain appetite regulators in offspring[41], while food-deprived dams may transfer to the offspring patterns of increased hepatic gluconeogenesis, enhanced release and impaired oxidation of fatty acids from adipocytes, resistance to ketosis and changes in glucose uptake mediated by an increased insulin receptor expression[10]. On the other hand, intrauterine growth restriction due to perinatal impaired uteroplacental function or nutrient deficiency has been linked to lower leptin, normal or lower adiponeptin and higher ghrelin and visfatin levels, while contradictory results have been reported concerning apelin and resistin and other pro-inflammatory markers such as TNFα and IL-6[42]. Interestingly, maternal perinatal undernutrition attenuates T-cell function in adult male rat offspring[43].

Finally, epigenetic marks affecting a number of genes regulating energy metabolism, adipogenesis or inflammatory processes are providing new clues to understand the

https://doi.org/10.1017/S0029665112000055 Published online by Cambridge University Press

relationships between nutritional programming and obesity in adulthood[25,44].

Despite the general acceptance of the Developmental Origins of Health and Disease hypothesis, the terms of such proposal have not always been demonstrated in epidemiological surveys, with some inconsistent results being reported in animal models[27]. A systematic error in interpreting experimental data and a publication bias due to missing information are not ruled out.

Animal models and epigenetic regulation

There are a number of experimental interventions in animals concerning the role of nutrition in pregnancy and lactation including energetic deprivation, protein restriction and excess fat feeding[34]. Such investigations have proven a cluster of disorders affecting energy efficiency as well as the impairment of different metabolic pathways and adverse predisposition for suffering CVD, glucose intolerance and obesity in the offspring[8] and unfavourable inflammatory interactions[45].

A loss of diurnal variation in heart rate and blood pressure in adulthood has been described when maternal undernutrition is followed by postnatal overnutrition in rodents, while hyperphagia resulting from perturbed development of the hypothalamic circuitry devoted to food intake control may contribute to overweight and developmental changes in fat-cell precursors[46]. On the other hand, maternal obesity has an effect on pancreatic β-cells inducing a higher risk of diabetes[47]. The mitochondrial DNA content of the liver and skeletal muscle was reduced in fetal and early postnatal undernourished animals even when balanced nutrition was provided after weaning, which was accompanied by a decrease in mitochondrial DNA-encoded gene expression indicating that poor nutrition in early life causes long-lasting changes in mitochondria that may contribute to the development of insulin resistance in later life[40]. The adverse effects of an *in utero* low protein dietary intake have been associated with diabetes[48], increased systolic blood pressure[49], altered glucose tolerance[49], hyperisulaemia and reduced insulin signalling protein expression later in life[50]. Also, a reduced maternal protein consumption during pregnancy and lactation has window-of-exposure and sex-specific effects on offspring growth, adiposity, appetite, glucose utilisation and circulating leptin[51]. A programming of hepatic insulin-sensitive enzymes has been found in the offspring of rat dams fed a protein-restricted diet where glucokinase activity decreased (approximately 50%), whereas phosphoenolpyruvate carboxykinase activity increased (approximately 100%) with parallel changes in gene expression in both enzymes[52]. Indeed, the understanding of genetic and epigenetic factors in human nutrition and health is helping to translate basic biology into clinical applications[1,53] concerning perinatal nutrition and disease in adulthood.

Three genomic targets have been involved in the modulation of the gene expression changes in relation to disease susceptibility: epigenetic marks at the promoter regions of some epiobesogenes, transposable elements that lie adjacent to genes with metastable epialleles, and the regulation of imprinted genes[54]. In this context, epigenetic studies are contributing to unravel some putatively hidden phenomena that are not being explained by the accomplishment of the Human Genome Project in relation to obesity[55]. In the last few years, different examples of dynamic changes in DNA methylation patterns, histone covalent modifications and the involvement of non-coding RNA due to the restriction or supplementation with different nutrients have been reported[4,25,56], but also in relation to obesity[57]. Thus, the methylation pattern of the leptin promoter in adipocytes is affected by a high fat intake in rats following an inverse trend to body weight changes[58], while weight gain induced by an isoenergetic pair-fed high-fat diet produces a nutriepigenetic outcome on fatty acid synthase and NADH dehydrogenase ubiquinone 1β subcomplex subunit 6 gene promoters[59].

Interestingly, maternal supraphysiological methyl group (folate, cobalamine, choline and betaine) or genistein supply throughout pregnancy modifies DNA methylation of some key metabolic genes, with implications in adiposity[60,61], while protein restriction of pregnant rats induces DNA hypomethylation in the glucocorticoid receptor and PPARα genes in the liver of the newborns, which was prevented by folic acid supplementation[62]. Also, it has been found that a chronic high-fat diet in fathers epigenetically programmes β-cell dysfunction in female rat offspring[63]. These findings are in agreement with previous observations suggesting that transgenerational epigenetic inheritance may be sex-dependent for specific traits[64,65].

In addition to changes in methylation patterns, epigenetic transfer may involve histone modifications and miRNA-mediated mechanisms[66]. Thus, an energy-dense maternal diet driving to obesity epigenetically impairs fetal chromatin structure in primates via covalent modifications on histones[67], while a role for miRNA in the alternative expression of insulin-like growth factor 2 in fetal livers from high-fat fed dams has been reported[68,69].

All these data and experiments strongly suggest that epigenetic mechanisms may be boosted or impaired by dietary and environmental factors in the gestating mother and could be involved in obesity susceptibility in the offspring[9,36].

Obesity, inflammation and epigenetics

Inflammation is a protective complex biological response mounted by tissues to combat injurious stimuli in order to maintain cell homoeostasis[70], which include host defence, tissue remodelling and metabolic changes, and involve multiple mechanisms such as the contribution of immune cells (recruitment and activation of leucocytes, granulocytes, monocytes, B–T-lymphocytes and dendritic cells), the involvement of different mediators (IL, TNFα, leptin, adipokines, etc.) or the regulation of signalling pathways (insulin, glucose, lipids, etc.) and eventually the epigenetic regulation of the expression of some related genes[4,71]. Indeed, many important risk factors for obesity (overnutrition, low dietary fibre intake, sedentary lifestyles, sleep debts, neuroendocrine status or genetic make-up)

https://doi.org/10.1017/S0029665112000055 Published online by Cambridge University Press

have been found to be implicated in local or low-grade systemic inflammation[20]. Thus, an excessive adiposity has been considered either as a cause or as a consequence of chronic inflammatory disorders[21] and epimutations[72]. Interestingly, inflammatory signalling has been identified as mediator of epigenetic modulation in tissue-specific chronic inflammation[73].

One of the challenges in the epigenomics field is identifying and characterising the epigenetic marks and those stimuli modulating the expression of some specific genes (epiobesogenes) in pathways involving obesity/body weight homoeostasis and energy balance processes such as adipogenesis, inflammation, appetite, insulin signalling, thermogenesis or macronutrient turnover[25]. Indeed, a bioinformatics analysis of promoter regions for the search of epigenetic biomarkers of obesity, has identified putative methylation-prone sequence patterns in several obesity-related genes such as fibroblast growth factor 2, phosphatase and tensin homolog deleted on chromosome 10, cyclin-dependent kinase inhibitor 1A and oestrogen receptor 1, implicated in adipogenesis, suppressor of cytokine signalling 1/suppressor of cytokine signalling 3, in inflammation and cytochrome *c* oxidase 7A1 lipoprotein lipase, caveolin 1 and insulin-like growth factor binding protein 3, in intermediate metabolism and insulin signalling[74]. The characterisation of those individuals which at an early age could present changes in the methylation profiles of specific genes could help to predict their susceptibility to later develop obesity, which may make it possible to prevent and follow-up its progress, as well as to research and develop newer therapeutic approaches[75]. Thus, from approximately 760 human genes under putative epigenetic regulation, about 20% of them, defined as epiobesogenes, could be associated with obesity[74,76]. The knowledge of the modification of their methylation patterns due to different dietary factors, age, inflammation or some of the physiological aspects surrounding overweight, could be crucial to investigate the role of these mechanisms in the prevention, onset and therapy of obesity. Also, the reversibility/stability of the epigenetic code and the involvement of specific enzymes (methylases, acetylases, etc.) is of interest[55].

Epigenetically mediated signal-specific inflammatory mechanisms may operate through transcription factors (NF-κB family), kinases (IκB kinase-related kinases, salt-inducible kinase, protein kinase A, phosphoinositide 3-kinase, serine/threonine protein kinase, etc.), the endoplasmic reticulum (Ca), biochemical activation of DNA methyltransferases and histone modifier enzymes (histone deacetylase/histone acetyltransferase, histamine methyltransferase, sirtuin, etc.), changes in cellular pools of acetyl-CoA, NAD or methyl donors, all of them sensitive to oxidative stress, hyper- or hypoglycaemia and fatty acids load, and activated or inhibited by over-nutrition[69,77]. Furthermore, in addition to epigenetic processes involving methylation marks and histone modifications, also non-coding RNA are susceptible to dynamic inflammatory control[4].

The concept of epigenetic regulation is gradually being recognised as an important factor in inflammatory-related events such as obesity, diabetes and CVD[78]. Gene silencing in severe systemic inflammation has been associated with the reprogramming of acute pro-inflammatory genes, the intervention of NF-κB and the compartmentalisation of the epigenetic process[79]. In this context, the impact of inflammation on global DNA methylation has been demonstrated in chronic kidney disease, while an epigenetic regulation of high-glucose-induced pro-inflammatory cytokine production in monocytes has been described for the polyphenol curcumin involving NF-κB[80]. On the other hand, histone deacetylase inhibitors are emerging as possible epigenetic modulators of gene expression controlling the inflammatory response in some circumstances[81]. Also, an increased expression of DNA methyltransferase3A in obese adipose tissue has been reported[82], while the methylation of polycomb target genes may be mediated by inflammation[83]. Furthermore, redox modulation of chromatin remodelling may have an effect on histone acetylation/deacetylation modulating the expression of pro-inflammatory genes[84]. Finally, enhanced levels of miRNA125b are associated with increased expression of specific inflammatory genes in *db*/*db* mice[85]. A relevant locus-specific DNA methylation affecting inflammatory processes has been reported for at least the following genes: leptin, superoxide dismutase, glucocorticoid receptor, PPAR, TNFα, endothelial nitric oxide synthase and inducible nitric oxide synthase and hypoxia-inducible factor, and the understanding of their epigenetic machinery will contribute to the management of inflammation and associated disorders including obesity[4].

Obesity-associated adipose tissue enlargement is often associated with an elevated secretion of pro-inflammatory adipokines such as leptin and cytokines such as TNFα, whose epigenetic regulation has emerged as a potentially important determinant of gene expression[86]. Thus, at baseline, obese women with better response to an energy-restricted dietary intervention designed to induce weight loss showed lower promoter methylation levels of leptin and TNFα than the non-responder group, which suggests that leptin and TNFα methylation levels could be used as epigenetic biomarkers concerning the response to a low-energy diet[87]. Indeed, the methylation profile could help to predict the susceptibility to weight loss as well as to some comorbidities such as hypertension or type 2 diabetes[87,88]. Additional investigations concerning the interactions between obesity and inflammation under an epigenetic perspective have allowed identification of different CpG sites from Wilms tumour 1 and ATP10A genes, which show a differential response as a result of a hypoenergetic-diet-induced weight loss in human subjects by altering DNA methylation status of these specific genes indirectly related with inflammatory processes, suggesting that baseline DNA methylation patterns may be used as prognostic epigenetic markers that could help to predict weight loss[89].

Summing up, there is growing evidence suggesting that interindividual differences in obesity susceptibility depend not only on the DNA sequence (genetics) but also on epigenetic factors affecting gene expression such as DNA methylation, covalent histone modifications, chromatin folding and the regulatory actions of miRNA and

NS Proceedings of the Nutrition Society

polycomb complexes, in which inflammatory phenomena may be involved. Thus, epigenetics is providing novel insights into cellular identity, stem cell flexibility, tissue regeneration, tumorigenesis and aging and to understand monozygotic twin differences and interestingly the onset of chronic diseases in the adult such as obesity. The following aims are presently pursued in the ground of obesity and epigenomics: the early identification of epigenetic biomarkers concerned in individual's disease susceptibility and the description of weight lowering protocols for tailored dietary treatments/advice to avoid/neutralise likely adverse epigenomic events. Other questions that remain to be answered are to understand the regulation of epigenomic phenomena, the period(s) for intervention, the key nutritional factors and doses, which will allow diagnosis and prognosis implementation and will facilitate preventive/curative strategies in a personalised 'epigenomically' based manner to combat obesity.

Acknowledgements

The authors declare no conflict of interest. All the authors contributed to the preparation of the manuscript. This work was supported by 'Linea Especial de Investigación: Nutrición, Salud y Obesidad' from the University of Navarra (LE/97). Also the RETICS and CIBERobn schemes from Carlos III Institute are gratefully acknowledged.

References

1. Marti A, Martinez-Gonzalez MA & Martinez JA (2008) Interaction between genes and lifestyle factors on obesity. *Proc Nutr Soc* **67**, 1–8.
2. McAllister EJ, Dhurandhar NV, Keith SW *et al.* (2009) Ten putative contributors to the obesity epidemic. *Crit Rev Food Sci Nutr* **49**, 868–913.
3. Lillycrop KA (2011) Effect of maternal diet on the epigenome: implications for human metabolic disease. *Proc Nutr Soc* **70**, 64–72.
4. vel Szic KS, Ndlovu MN, Haegeman G *et al.* (2010) Nature or nurture: let food be your epigenetic medicine in chronic inflammatory disorders. *Biochem Pharmacol* **80**, 1816–1832.
5. Cordero P, Milagro F, Campion J *et al.* (2010) Nutritional epigenetic: a key piece in the puzzle of obesity. *Rev Esp Obes* **8**, 10–20.
6. Waddington C (1977) The epigenotype. *Endeavour* **1**, 18–22.
7. Bird A (2007) Perceptions of epigenetics. *Nature* **447**, 396–398.
8. Simmons R (2011) Epigenetics and maternal nutrition: nature v. nurture. *Proc Nutr Soc* **70**, 73–81.
9. Waterland RA & Michels KB (2007) Epigenetic epidemiology of the developmental origins hypothesis. *Annu Rev Nutr* **27**, 363–388.
10. Hales CN & Barker DJ (2001) The thrifty phenotype hypothesis. *Br Med Bull* **60**, 5–20.
11. Parsons TJ, Power C & Manor O (2001) Fetal and early life growth and body mass index from birth to early adulthood in 1958 British cohort: longitudinal study. *Br Med J* **323**, 1331–1335.
12. Rugholm S, Baker JL, Olsen LW *et al.* (2005) Stability of the association between birth weight and childhood overweight during the development of the obesity epidemic. *Obes Res* **13**, 2187–2194.
13. Silveira PP, Portella AK, Goldani MZ *et al.* (2007) Developmental origins of health and disease (DOHaD). *J Pediatr (Rio J)* **83**, 494–504.
14. Oken E & Gillman MW (2003) Fetal origins of obesity. *Obes Res* **11**, 496–506.
15. Fraser A, Tilling K, Macdonald-Wallis C *et al.* (2011) Associations of gestational weight gain with maternal body mass index, waist circumference, and blood pressure measured 16 y after pregnancy: the Avon Longitudinal Study of Parents and Children (ALSPAC). *Am J Clin Nutr* **93**, 1285–1292.
16. Wadhwa PD, Buss C, Entringer S *et al.* (2009) Developmental origins of health and disease: brief history of the approach and current focus on epigenetic mechanisms. *Semin Reprod Med* **27**, 358–368.
17. Bruce KD & Hanson MA (2010) The developmental origins, mechanisms, and implications of metabolic syndrome. *J Nutr* **140**, 648–652.
18. Stenvinkel P, Karimi M, Johansson S *et al.* (2007) Impact of inflammation on epigenetic DNA methylation – a novel risk factor for cardiovascular disease? *J Intern Med* **261**, 488–499.
19. Tamashiro KL & Moran TH (2010) Perinatal environment and its influences on metabolic programming of offspring. *Physiol Behav* **100**, 560–566.
20. Kolb H & Mandrup-Poulsen T (2010) The global diabetes epidemic as a consequence of lifestyle-induced low-grade inflammation. *Diabetologia* **53**, 10–20.
21. Moreno-Aliaga MJ, Campion J, Milagro F *et al.* (2005) Adiposity and proinflammatory state: the chicken or the egg. *Adipocytes* **1**, 1–16.
22. Van den Berghe G (2010) Increased blood flow by insulin infusion targeting normoglycemia in patients with severe sepsis: friend or foe? *Crit Care* **14**, 122.
23. Freeman DJ (2010) Effects of maternal obesity on fetal growth and body composition: implications for programming and future health. *Semin Fetal Neonatal Med* **15**, 113–118.
24. Symonds ME, Sebert SP, Hyatt MA *et al.* (2009) Nutritional programming of the metabolic syndrome. *Nat Rev Endocrinol* **5**, 604–610.
25. Campion J, Milagro F & Martinez JA (2010) Epigenetics and obesity. *Prog Mol Biol Transl Sci* **94**, 291–347.
26. Herrera BM, Keildson S & Lindgren CM (2011) Genetics and epigenetics of obesity. *Maturitas* **69**, 41–49.
27. Langley-Evans SC & McMullen S (2010) Developmental origins of adult disease. *Med Princ Pract* **19**, 87–98.
28. Oliver MH, Jaquiery AL, Bloomfield FH *et al.* (2007) The effects of maternal nutrition around the time of conception on the health of the offspring. *Soc Reprod Fertil Suppl* **64**, 397–410.
29. Godfrey KM & Barker DJ (2001) Fetal programming and adult health. *Public Health Nutr* **4**, 611–624.
30. McMillen IC, MacLaughlin SM, Muhlhausler BS *et al.* (2008) Developmental origins of adult health and disease: the role of periconceptional and foetal nutrition. *Basic Clin Pharmacol Toxicol* **102**, 82–89.
31. Godfrey KM, Lillycrop KA, Burdge GC *et al.* (2007) Epigenetic mechanisms and the mismatch concept of the developmental origins of health and disease. *Pediatr Res* **61**, 5R–10R.
32. Mostyn A & Symonds ME (2009) Early programming of adipose tissue function: a large-animal perspective. *Proc Nutr Soc* **68**, 393–400.
33. McMillen IC & Robinson JS (2005) Developmental origins of the metabolic syndrome: prediction, plasticity, and programming. *Physiol Rev* **85**, 571–633.

https://doi.org/10.1017/S0029665112000055 Published online by Cambridge University Press

34. McMullen S & Mostyn A (2009) Animal models for the study of the developmental origins of health and disease. *Proc Nutr Soc* **68**, 306–320.
35. Vickers MH (2007) Developmental programming and adult obesity: the role of leptin. *Curr Opin Endocrinol Diabetes Obes* **14**, 17–22.
36. Kemp MW, Kallapur SG, Jobe AH *et al.* (2011) Obesity and the developmental origins of health and disease. *J Paediatr Child Health* (Epublication ahead of print version).
37. McMillen IC, Adam CL & Muhlhausler BS (2005) Early origins of obesity: programming the appetite regulatory system. *J Physiol* **565**, 9–17.
38. Hietaniemi M, Malo E, Jokela M *et al.* (2009) The effect of energy restriction during pregnancy on obesity-related peptide hormones in rat offspring. *Peptides* **30**, 705–709.
39. McMillen IC, Rattanatray L, Duffield JA *et al.* (2009) The early origins of later obesity: pathways and mechanisms. *Adv Exp Med Biol* **646**, 71–81.
40. Park KS, Kim SK, Kim MS *et al.* (2003) Fetal and early postnatal protein malnutrition cause long-term changes in rat liver and muscle mitochondria. *J Nutr* **133**, 3085–3090.
41. Rajia S, Chen H & Morris MJ (2010) Maternal overnutrition impacts offspring adiposity and brain appetite markers-modulation by postweaning diet. *J Neuroendocrinol* **22**, 905–914.
42. Briana DD & Malamitsi-Puchner A (2009) Intrauterine growth restriction and adult disease: the role of adipocytokines. *Eur J Endocrinol* **160**, 337–347.
43. Badr G & Mohany M (2011) Maternal perinatal undernutrition attenuates T-cell function in adult male rat offspring. *Cell Physiol Biochem* **27**, 381–390.
44. Lillycrop KA & Burdge GC. (2010) Epigenetic changes in early life and future risk of obesity. *Int J Obes* (*Lond*) **35**, 72–85.
45. Marcos-Gomez B, Bustos M, Prieto J *et al.* (2008) Obesity, inflammation and insulin resistance: role of gp 130 receptor ligands. *An Sist Sanit Navar* **31**, 113–123.
46. Remacle C, Bieswal F, Bol V *et al.* (2011) Developmental programming of adult obesity and cardiovascular disease in rodents by maternal nutrition imbalance. *Am J Clin Nutr* **94**, 1846–1852.
47. Han J, Xu J, Epstein PN *et al.* (2005) Long-term effect of maternal obesity on pancreatic beta cells of offspring: reduced beta cell adaptation to high glucose and high-fat diet challenges in adult female mouse offspring. *Diabetologia* **48**, 1810–1818.
48. Sparre T, Reusens B, Cherif H *et al.* (2003) Intrauterine programming of fetal islet gene expression in rats – effects of maternal protein restriction during gestation revealed by proteome analysis. *Diabetologia* **46**, 1497–1511.
49. Langley-Evans SC, Phillips GJ & Jackson AA (1994) *In utero* exposure to maternal low protein diets induces hypertension in weaning rats, independently of maternal blood pressure changes. *Clin Nutr* **13**, 319–324.
50. Fernandez-Twinn DS, Wayman A, Ekizoglou S *et al.* (2005) Maternal protein restriction leads to hyperinsulinemia and reduced insulin-signaling protein expression in 21-mo-old female rat offspring. *Am J Physiol Regul Integr Comp Physiol* **288**, R368–R373.
51. Zambrano E, Bautista CJ, Deas M *et al.* (2006) A low maternal protein diet during pregnancy and lactation has sex- and window of exposure-specific effects on offspring growth and food intake, glucose metabolism and serum leptin in the rat. *J Physiol* **571**, 221–230.
52. Desai M, Byrne CD, Zhang J *et al.* (1997) Programming of hepatic insulin-sensitive enzymes in offspring of rat dams fed a protein-restricted diet. *Am J Physiol* **272**, G1083–G1090.
53. Stover PJ & Caudill MA (2008) Genetic and epigenetic contributions to human nutrition and health: managing genome-diet interactions. *J Am Diet Assoc* **108**, 1480–1487.
54. Jirtle RL & Skinner MK (2007) Environmental epigenomics and disease susceptibility. *Nat Rev Genet* **8**, 253–262.
55. Rodenhiser D & Mann M (2006) Epigenetics and human disease: translating basic biology into clinical applications. *Can Med Assoc J* **174**, 341–348.
56. Ford D, Ions LJ, Alatawi F *et al.* (2011) The potential role of epigenetic responses to diet in ageing. *Proc Nutr Soc* **70**, 374–384.
57. Marti A & Ordovas J (2011) Epigenetics lights up the obesity field. *Obes Facts* **4**, 187–190.
58. Milagro FI, Campion J, Garcia-Diaz DF *et al.* (2009) High fat diet-induced obesity modifies the methylation pattern of leptin promoter in rats. *J Physiol Biochem* **65**, 1–9.
59. Lomba A, Martinez JA, Garcia-Diaz DF *et al.* (2010) Weight gain induced by an isocaloric pair-fed high fat diet: a nutriepigenetic study on FASN and NDUFB6 gene promoters. *Mol Genet Metab* **101**, 273–278.
60. Dolinoy DC, Weidman JR, Waterland RA *et al.* (2006) Maternal genistein alters coat color and protects Avy mouse offspring from obesity by modifying the fetal epigenome. *Environ Health Perspect* **114**, 567–572.
61. Waterland RA, Travisano M, Tahiliani KG *et al.* (2008) Methyl donor supplementation prevents transgenerational amplification of obesity. *Int J Obes* (*Lond*) **32**, 1373–1379.
62. Lillycrop KA, Phillips ES, Jackson AA *et al.* (2005) Dietary protein restriction of pregnant rats induces and folic acid supplementation prevents epigenetic modification of hepatic gene expression in the offspring. *J Nutr* **135**, 1382–1386.
63. Ng SF, Lin RC, Laybutt DR *et al.* (2010) Chronic high-fat diet in fathers programs beta-cell dysfunction in female rat offspring. *Nature* **467**, 963–966.
64. Wu Q & Suzuki M (2006) Parental obesity and overweight affect the body-fat accumulation in the offspring: the possible effect of a high-fat diet through epigenetic inheritance. *Obes Rev* **7**, 201–208.
65. Cordero P, Gomez-Uriz AM, Milagro F *et al.* (2012) Maternal weight gain induced by an obesogenic diet affects adipose accumulation, liver weight and insulin homeostasis in the rat offspring depending on the sex. *Obes Metab-Milan* (In the Press).
66. Sinclair KD, Lea RG, Rees WD *et al.* (2007) The developmental origins of health and disease: current theories and epigenetic mechanisms. *Soc Reprod Fertil Suppl* **64**, 425–443.
67. Aagaard-Tillery KM, Grove K, Bishop J *et al.* (2008) Developmental origins of disease and determinants of chromatin structure: maternal diet modifies the primate fetal epigenome. *J Mol Endocrinol* **41**, 91–102.
68. Zhang J, Zhang F, Didelot X *et al.* (2009) Maternal high fat diet during pregnancy and lactation alters hepatic expression of insulin like growth factor-2 and key microRNAs in the adult offspring. *BMC Genomics* **10**, 478.
69. Heerwagen MJ, Miller MR, Barbour LA *et al.* (2010) Maternal obesity and fetal metabolic programming: a fertile epigenetic soil. *Am J Physiol Regul Integr Comp Physiol* **299**, R711–R722.
70. Medzhitov R (2008) Origin and physiological roles of inflammation. *Nature* **454**, 428–435.
71. Entringer S, Buss C & Wadhwa PD (2010) Prenatal stress and developmental programming of human health and disease risk: concepts and integration of empirical findings. *Curr Opin Endocrinol Diabetes Obes* **17**, 507–516.

NS Proceedings of the Nutrition Society

72. Baple EL, Poole RL, Mansour S *et al.* (2011) An atypical case of hypomethylation at multiple imprinted loci. *Eur J Hum Genet* **19**, 360–362.
73. Backdahl L, Bushell A & Beck S (2009) Inflammatory signalling as mediator of epigenetic modulation in tissue-specific chronic inflammation. *Int J Biochem Cell Biol* **41**, 176–184.
74. Campion J, Milagro FI & Martinez JA (2009) Individuality and epigenetics in obesity. *Obes Rev* **10**, 383–392.
75. Feinberg AP, Irizarry RA, Fradin D *et al.* (2010) Personalized epigenomic signatures that are stable over time and covary with body mass index. *Sci Transl Med* **2**, 49ra67.
76. Martinez JA, Milagro F & Campion J (2010) Obesity research and personalized nutrition: nutriepigenomics. *Nature* **468**, 998.
77. Hotamisligil GS (2010) Endoplasmic reticulum stress and the inflammatory basis of metabolic disease. *Cell* **140**, 900–917.
78. Wierda RJ, Geutskens SB, Jukema JW *et al.* (2010) Epigenetics in atherosclerosis and inflammation. *J Cell Mol Med* **14**, 1225–1240.
79. McCall CE & Yoza BK (2007) Gene silencing in severe systemic inflammation. *Am J Respir Crit Care Med* **175**, 763–767.
80. Yun JM, Jialal I & Devaraj S (2011) Epigenetic regulation of high glucose-induced proinflammatory cytokine production in monocytes by curcumin. *J Nutr Biochem* **22**, 450–458.
81. Faraco G, Pittelli M, Cavone L *et al.* (2009) Histone deacetylase (HDAC) inhibitors reduce the glial inflammatory response *in vitro* and *in vivo*. *Neurobiol Dis* **36**, 269–279.
82. Kamei Y, Suganami T, Ehara T *et al.* (2010) Increased expression of DNA methyltransferase 3a in obese adipose tissue: studies with transgenic mice. *Obesity* (*Silver Spring*) **18**, 314–321.
83. Hahn MA, Hahn T, Lee DH *et al.* (2008) Methylation of polycomb target genes in intestinal cancer is mediated by inflammation. *Cancer Res* **68**, 10280–10289.
84. Rahman I, Marwick J & Kirkham P (2004) Redox modulation of chromatin remodeling: impact on histone acetylation and deacetylation, NF-kappaB and pro-inflammatory gene expression. *Biochem Pharmacol* **68**, 1255–1267.
85. Villeneuve LM, Kato M, Reddy MA *et al.* (2010) Enhanced levels of microRNA-125b in vascular smooth muscle cells of diabetic *db/db* mice lead to increased inflammatory gene expression by targeting the histone methyltransferase Suv39h1. *Diabetes* **59**, 2904–2915.
86. Hermsdorff HH, Puchau B, Zulet MA *et al.* (2010) Association of body fat distribution with proinflammatory gene expression in peripheral blood mononuclear cells from young adult subjects. *Omics* **14**, 297–307.
87. Cordero P, Campion J, Milagro FI *et al.* (2011) Leptin and TNF-alpha promoter methylation levels measured by MSP could predict the response to a low-calorie diet. *J Physiol Biochem* **67**, 463–470.
88. Campion J, Milagro FI, Goyenechea E *et al.* (2009) TNF-alpha promoter methylation as a predictive biomarker for weight-loss response. *Obesity* (*Silver Spring*) **17**, 1293–1297.
89. Milagro FI, Campion J, Cordero P *et al.* (2011) A dual epigenomic approach for the search of obesity biomarkers: DNA methylation in relation to diet-induced weight loss. *FASEB J* **25**, 1378–1389.

https://doi.org/10.1017/S0029665112000055 Published online by Cambridge University Press