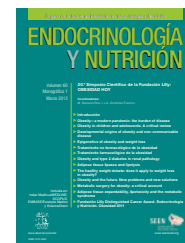


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20.º SIMPOSIO CIENTÍFICO OBESIDAD HOY

Epigenetics of obesity and weight loss

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The huge health burden accompanying an excessive fat accumulation resulting in obesity is not only a gluttony or sloth problem due to inadequate dietary and sedentary lifestyle habits. In addition to a predisposed genetic make-up to easier gain weight and fat deposition, a number of recognized scientific evidences have theorized about the roles of other putative determinants. Thus, several investigations aiming to understand energy metabolism have been performed considering the potential involvement of epigenetics as well as perinatal programming. Indeed, inheritance-oriented investigations concerning gene-nutrient interactions on energy homeostasis processes and metabolic cell functions are being extended to all clinically chronic relevant diseases such as diabetes and cardiovascular events as well as to obesity and associated features.

The word *epigenetics* was launched as a conceptual model seeking to explain putative unrevealed interactions between genes and environmental surroundings to produce a phenotype. 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 response of an organism”. The “epigenetic code” encompasses the chromatin information mainly encrypted by histone signatures or DNA methylation profiles and other epigenetic marks, and represents “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”. A number of epigenetic changes appear to occur within the course of each individual organism’s lifetime, but some epigenetic information might

be inherited from one generation to the next. Therefore, epigenetics can provide some insights to understand genetic foetal programming, monozygotic twin differences and chronic disease onset in the adult, which is requiring newer and appropriate experimental models.

Specific epigenetic processes include imprinting, position effect, bookmarking, X chromosome inactivation, gene silencing, reprogramming, maternal effects, DNA methylation, histone modifications or chromatin folding (euchromatin vs. heterochromatin) and, in general, all those phenomena eventually affecting gene expression patterns (iRNAs, DNA repair, transposons, chaperones, copy number variations, etc.). Two characteristic and outstanding features of epigenetic processes are the ability for cellular memory transmission or transgenerational heritability as well as the involvement in spacial and temporal cell differentiation from totipotent cells. Therefore, epigenetics can provide some insights not only to unsolved mysteries such as cellular identity, stem cell plasticity, tissue regeneration, tumorigenesis and aging, but also to understand genetic fetal programming, monozygotic twin differences and chronic disease onset in the adult, which interact with dietary intake and environmental factors. Actually, epigenetic research will contribute to explain the way that cells/organisms carrying identical nucleotide sequences can generate different responses under the same nutrient exposure through mechanisms such as DNA methylation, small and non-coding RNAs and chromatin architecture changes. These mechanisms together with other transcriptional regulatory events ultimately regulate gene activity and expression during development and differentiation or in response to nutritional and environmental stimuli (Fig. 1).

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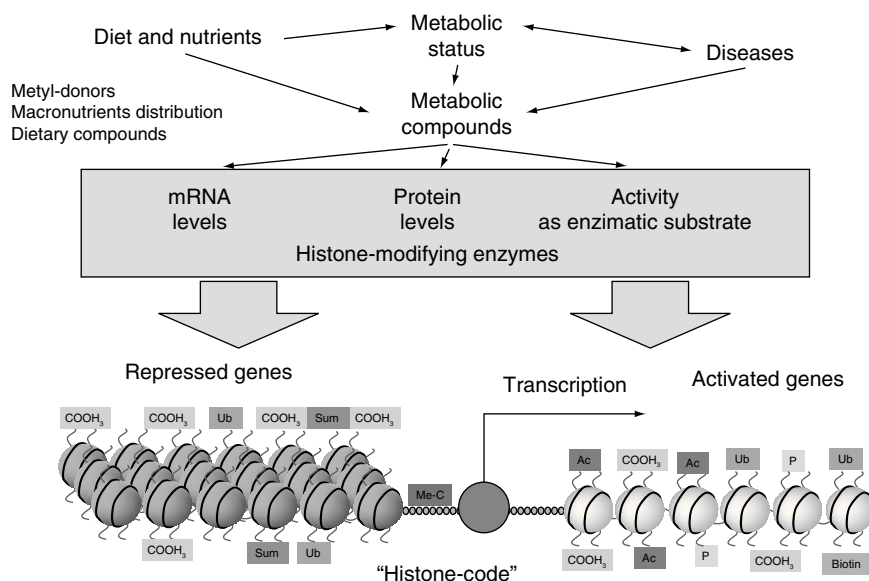


Figure 1 From Handbook of Epigenetics: The New Molecular and Medical Genetics. Tollefsbol T. ed. Dietary and metabolic compounds affecting chromatin dynamics/remodelling, Milagro FI, Campion J, Martinez JA. Ed. Elsevier Academic Press (San Diego, USA), ISBN 13: 978-0-12-375709-8 (2010).

In the last years, different examples of dynamical changes in DNA methylation patterns due to the restriction or supplementation with different nutrients during pregnancy have been reported, suggesting that epigenetic mechanisms may be boosted or impaired by dietary factors in the mother and could be involved in obesity susceptibility in the offspring.

Indeed, one of the challenges for investigators researching in the epigenetics field is identifying and characterizing the epigenetic marks and those stimuli modulating the expression of some specific genes (defined as epiobesogenes) in pathways involving obesity/body weight homeostasis and energy balance processes, such as adipogenesis, inflammation, appetite, insulin signalling, thermogenesis or macronutrient turnover. A bioinformatics analysis of promoter regions for the search of epigenetic biomarkers of obesity, have identified affected methylation patterns on several obesity-related genes such as *FGF2*, *PTEN*, *CDKN1A* and *ESR1*, implicated in adipogenesis, *TNF* and *SOCS1/SOCS3*, in inflammation, and *COX7A1*, *LPL*, *CAV1* and *IGFBP3*, in intermediate metabolism and insulin signalling. The characterization of those individuals that 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 allow to prevent and follow-up its progress, as well as to develop and implement newer therapeutic approaches. The knowledge of the modification of their methylation patterns due to different dietary factors, age, inflammation or some of the physiological aspects surrounding overweightness (oxidative stress, hypoxia, physical activity,...), could be crucial to investigate the role of these mechanisms in the prevention, onset and therapy of obesity (Table 1).

In this context, our research group has reported that diets rich in fat and sugar and situations of excessive body weight in rodents are associated with changes in DNA methylation patterns, affecting the promoter region of different genes

Table 1 Some putative epiobesogenes involved in obesity-related processes, such as adipogenesis, inflammation, energy metabolism, lipid turnover, insulin signalling, appetite regulation

Process	Genes
Adipogenesis	<i>PTEN</i> , <i>CDKN1A</i> , <i>FGF2</i> , <i>PPARG</i> , <i>PPARA</i> , <i>ESR1</i> , <i>CEBPA</i>
Apoptosis	<i>CASP9</i>
Energy homeostasis	<i>COX7A1</i> , <i>FTO</i>
Lipid turnover	<i>FABP4</i> , <i>LPL</i> , <i>FASN</i>
Insulin signalling	<i>CAV1</i> , <i>PIK3CG</i> , <i>SSTR2</i> , <i>IRS1</i> , <i>INS</i> , <i>IGFBP3</i> , <i>HSD11B2</i> , <i>GLUT4</i>
Appetite regulation	<i>LEP</i> , <i>POMC</i> , <i>NPY</i> , <i>MC4R</i>
Inflammation, hypoxia and oxidative stress	<i>TNF-α</i> , <i>IL6</i> , <i>IFNG</i> , <i>SOD3</i> , <i>SOCS1</i> , <i>SOCS3</i> , <i>HIF1A</i> , <i>NR3C1</i> , <i>PPARGC1</i>

involved in energy homeostasis and obesity, such as leptin, *TNF* and *NDUFB6*. On the other hand, different epigenetic biomarkers have been identified predicting body weight maintenance after weight loss in humans, including the methylation percentage of cytosines in *TNF*, *ATP10A* and *CD44*.

In summary, it is becoming evident that interindividual differences concerning the outcomes of nutritionally-related chronic diseases and obesity depend not only on the dietary intake and the subject's DNA sequence, but also on the inherited epigenome and on different nutritional influences (during the intrauterine or the adult periods) that modify the epigenetic marks and are able to affect gene expression. DNA methylation, covalent histone modifications, chromatin folding and the regulatory action of miRNAs are the main epigenetic processes involved. Epigenetic marks are envisaged to have applications not only as predictors of obesity, but also as prognostic markers of weight loss and in

the personalization of the treatment of obesity-related comorbidities.

Conflicts of interest

The authors declare that they have no conflicts of interest in this article.

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