

The Role of Epigenetics in the Etiology of Obesity: A Review

Raquel Patrícia Ataíde Lima^{1*},
Daisuke Neto Hayashi²,
Keylha Querino de Farias Lima³,
Nadjeanny Ingrid Galdino Gomes³,
Marina Ramalho Ribeiro³,
Patrícia Oliveira Prada³ and
Maria José de Carvalho Costa³

Abstract

Obesity is highly prevalent in developed countries and contributes to a substantial burden of morbidity and mortality. Increased adiposity is often accompanied by comorbidities such as insulin resistance, type 2 diabetes, hypercholesterolemia, cardiovascular disease, fatty liver disease, low-grade inflammation, immune disorders, endocrine complications, and sleep apnea, which may require specific dietary and pharmacological interventions. The current obesity epidemic requires a better understanding of the underlying mechanisms through which genetic and epigenetic factors interact to determine metabolic characteristics. Epigenetic studies are dynamic; tags with reversible potential can be influenced by genetics and environment attributing phenotypic variations. There are large knowledge gaps regarding how human epigenetic changes are related to obesity and its consequences. Therefore, the present study elucidates the role of epigenetics in the etiology of obesity. Recent studies suggest that the epigenetic regulation of gene expression (DNA methylation and histone modifications) could be a major contributor to the variation of susceptibility to diseases such as obesity. The identification of genes that determine obesity susceptibility can provide information on the pathophysiological mechanisms underlying body weight regulation, food intake control and fat distribution, which in turn can lead to new approaches to treatment and prevention of obesity.

Keywords: Obesity, DNA methylation; Immune disorders; Inflammatory disorders

Received: November 01, 2017; **Accepted:** November 09, 2017; **Published:** November 11, 2017

Introduction

Obesity is highly prevalent in developed countries and contributes to a substantial burden of morbidity and mortality [1]. It is a complex multifactorial disease, which makes a better understanding of the mechanisms underlying the interactions between lifestyle, environment, and genetics necessary for the development of effective prevention and treatment strategies [2]. The quality of the macronutrients and their content in foods consumed, as well as the sedentary lifestyle, affects the energy balance equation, which can potentially lead to the unhealthy accumulation of fat and obesity [3,4]. Increased adiposity is often accompanied by comorbidities, such as insulin resistance, type 2 diabetes, hypercholesterolemia, cardiovascular disease, fatty liver disease, low grade inflammation, immune disorders, endocrine complications and sleep apnea, all of which may require specific dietary and pharmacological interventions [3]. The treatment of obesity is currently based on calorie-restriction diets to reduce

- 1 Department of Nutritional Science, Health Sciences Center (Centro de Ciências da Saúde - CCS), Federal University of Paraíba (Universidade Federal da Paraíba), Brazil
- 2 Department of Nutrition, School of Applied Sciences, Faculdade de Ciências Aplicadas, State University of Campinas (Universidade Estadual de Campinas – UNICAMP), Brazil
- 3 Graduate Program in Nutritional, Sport Sciences and Metabolism-CNEM, Federal University of Paraíba, Brazil

***Corresponding author:**
Raquel Patrícia Ataíde Lima

✉ raquelpatriciaal@hotmail.com

Department of Nutritional Science, Health Sciences Center (Centro de Ciências da Saúde - CCS), Federal University of Paraíba (Universidade Federal da Paraíba), Castelo Branco, João Pessoa, PB 58059-900, Brazil.

Citation: Lima RPA, Hayashi DN, Lima KQDF, Gomes NIG, Ribeiro MR, et al. (2017) The Role of Epigenetics in the Etiology of Obesity: A Review. J Clin Epigenet. Vol.3 No.4:41

the consumption of high energy foods (mainly the ones rich in fat and sugar), as well as recommending a greater intake of fiber and protein to induce satiety, which can be complemented by physical activity or behavioral programs and additional programs to induce weight loss [5].

In a society where foods with high energy density are abundant and physical-activity levels are low, there is a great variation in the vulnerability of individuals to developing obesity and metabolic health problems [6]. Studies estimate the heritability of the body mass index (BMI) of 40% to 70% in children and adults, as well as of other anthropometric measures of obesity and body fat distribution [waist circumference and waist: hip ratio (WHR)] show similar heritability [7]. However, a large portion of heredity remains unexplained [8].

Factors such as changes in gut microbiota, infections, epigenetic marks, perinatal nutrition, postponement of maternal age, superior fecundity among overweight women, associative mating within obese people, sleep problems, endocrine and inflammatory disorders, pharmacological side effects, variability of temperature variability environment, availability of environmental oxygen, and intrauterine effects have all been considered as contributors to the increasing obesity rates worldwide [9].

The obesity epidemic requires a better understanding of the mechanisms through which genetic and epigenetic factors interact to determine metabolic characteristics of individuals. Epigenetic studies are dynamic. Marks with the potential for reversibility may be influenced by genetics and the environment, attributing phenotypic variations in individuals [10]. There are large knowledge gaps about how human epigenetic changes relate to obesity and its consequences [1]. Therefore, the present study elucidates some of the role of epigenetics in the etiology of obesity.

Epigenetic Mechanisms

Epigenetic changes during embryonic development are a result of "causal interactions between genes and their products that contribute to changes in the phenotype". The epigenome acts as a bridge between genetics and the environment, and the epigenetic code modifies gene expression to determine the final phenotype without changing DNA sequences. Epigenetic changes may alter the disease phenomenon, directly affecting the target gene, as a response to environmental cues and pathological states, such as diet, exercise, toxins, oxidative stress, inflammation and metabolic alterations [11].

Epigenetic changes have an important effect on embryo formation and development, X chromosome inactivation, genomic imprinting, cell identity and differentiation, stable inheritance of gene expression, immune cell function, as well as stem cell and cellular plasticity. Histone modifications and DNA methylation, along with non-coding RNAs, are collectively known as epigenetic marks that contain the necessary epigenetic information for the stable inheritance of gene expression prototypes in differentiated cells [11,12]. The main epigenetic mechanisms in mammalian cells are carbon methylation of cytosine residues in

the CpG dinucleotide; covalent modifications of histones, such as methylation, acetylation, phosphorylation, and ubiquitination; and the production of non-coding RNAs (microRNAs) [13]. Among the epigenetic mechanisms, DNA methylation is the most well-known epigenetic mark [1,14,15] because its assays and interpretations are easier than changes in histone modifications [16] and generally occurs in cytosine-phosphate-guanine dinucleotides (CpG), where one of the numerous specific methyltransferase enzymes adds a methyl group to the cytosine at the 5' carbon of a CpG dinucleotide. Also, DNA methylation is potentially hereditary [15,17-19]. Methylation can affect gene expression and chromosomal stability and potentially influence the health and disease phenotype. Epigenetic profiles are influenced by genetics [20], aging and environmental factors, including diet, chemicals products and smoking habit [21].

DNA Methylation occurs with the covalent transfer of a methyl group from S-adenosyl-L-methionine to cytosines in CpG dinucleotides [16]. These CpG dinucleotides can be grouped into regions known as CpG islands. In general terms, hypermethylation of CpG within the gene promoters is associated with inactivation of transcription, causing stable silencing of gene expression while the unmethylated (hypomethylated) promoters are potentially transcriptionally active [12,18,19,22].

Epigenetics in the etiology of obesity

Recent studies suggest that the epigenetic regulation of gene expression (DNA methylation and histone modifications) could be a major contributor to varying susceptibility to diseases such as obesity [23-24].

Human obesity usually arises from the combined effects of interactions between multiple genes, environmental and behavioral factors, and this complex etiology makes management and prevention of human obesity especially challenging. There is a genetic basis for obesity that has proven to be an arduous task [25]. Genetic epidemiological methods for the genetic discovery of complex traits such as obesity can be divided into two broad classes: hypothesis-based approaches (candidate gene or biological pathway) and non-hypothesized approaches (genome-wide link and genomic association - GWAS), these analyzes in GWAS are responsible for evaluating the association of millions of genetic variants without a previous hypothesis [26].

The identification of genes that determine obesity susceptibility can provide information on the pathophysiological mechanisms underlying body weight regulation, food intake control and fat distribution, which in turn can lead to new approaches to treatment and prevention [27].

These studies are still starting, but the results so far have shown promise to help explain the variation in susceptibility to obesity. There is growing evidence that obesity has its origins, such as exposure to a nutrient below ideal in the fetal or early childhood period and is associated with an increased risk of obesity and metabolic disease in adulthood [28]. Initially, animal studies demonstrated that a range of early-onset nutritional exposures, especially those with early gestational experience, could induce

epigenetic changes in the underlying metabolic tissues of the offspring that persisted after birth and result in permanent changes in the function of the gene [29].

Evidence of the role of epigenetics in obesity comes mainly from animal models [30] and few are still, studies with humans. For example, children born to women who became hungry during the first half of pregnancy during the Dutch famine were at a significantly greater risk of developing obesity than comparable subjects; This was later related to epigenetic modifications. This intergenerational study suggests that nutritional deprivation of pregnant women may have lasting non-genetic effects on next generation body weight. An individual epigenetic pattern is established early during gestation and is subject to transformations through environmental factors throughout life, with epigenetic mechanisms being very important in the development and transgenerational transmission of chronic non-communicable diseases (NCDs), including obesity [31,32]. Still in the maternal phase and its relation with obesity, it is the exposure in this period to several chemical products (the so-called obesogênicos), which has been associated to the increase of the BMI in the offspring, also suggesting that the obesity is being programmed prenatal or early childhood, and discontinuation of normal epigenetic regulation altering the expression of key genes is probably involved in the adipogenic pathways [33]. Research on monogenic obesity has revealed the biology of obesity in the general population. Molecular mapping of mutations that caused monogenic obesity in mice was one of the first strategies to investigate genes that control body weight. Prominent results of this approach include genes encoding leptin (*LEP*) and its receptor (*LEPR*), melanocortin 4 receptor (*MC4R*) and pro-opiomelanocortin (*POMC*), among others; These genes affect body weight through pathways in the central nervous system [34]. Large-scale, genome-wide association studies (GWAS) identified >300 genetic loci for obesity traits. The first major success of GWAS was the discovery of the locus F7978, 79. A set of non-coding variants common in *FTO* showed a highly significant association with the risk of obesity [35]. Two other large-scale epigenetic studies, involving 10,000 and 7,800 individuals, respectively, identified a large number of DNA methylation loci associated with BMI being 187 in the first and 83 in the second study [36].

The biology that underlies this association is slowly being resolved. The *FTO* locus can regulate the expression of proximal *RPGRIP1L* or distant *IRX3-IRX5* to influence body weight, regulating appetite, thermogenesis, adipocyte, and obesity-related epigenetic mechanisms [37]. Additional GWAS identified genetic loci associated with traits of adiposity, BMI and waist-hip ratio [38,39].

One relevant factor, which modulates this epigenetic profile, is the environmental influence on the epigenetic marks that can lead to obesity remain rather rudimentary. For example, the *FTO* gene codes for an enzyme that is capable of removing methyl groups from DNA [33] and a long-term exposure to the high-fat

diet may decrease methylation of the melanocortin-4 receptor gene (*MC4R*) [40].

Obesity induced by a high-fat diet can modify the methylation patterns of leptin (Milagro et al.). Expression of the *PPAR γ* gene, a key regulator of adipocyte differentiation, has been reduced due to the methylation of the DNA of its promoter in adipocytes of visceral adipose tissue in mammals [40].

In one study it was observed that methylation of the regulatory DNA of the essential fatty acid binding protein in lipid metabolism was also associated with traces of the metabolic syndrome in 517 individuals in more than 40 families [41]. In addition, methylation patterns of three clock genes of circadian rhythm participation (*CLOCK*, *BMAL1* e *PER2*) were found to be associated with anthropometric traits such as BMI and adiposity [42], further narrowing the relationship between DNA methylation and obesity.

In a study carried out by Lima et al., [43] it was evidenced that methylation levels were influenced by dietary factors, such as the consumption of monounsaturated and polyunsaturated fat that contributed to the reduction of methylation levels of the *ADRB3* gene. Results of this research may be used in the future in the prevention and management of complications of obesity, since the *ADRB3* gene was related to obesity.

Several other genes involved in adiposity have promoters that appear to be epigenetic targets for obesity (epi-obesogenic genes). One of the first genome-wide methylation studies revealed increased methylation levels at one CpG site (*UBASH3A* gene) and reduced methylation levels at one CpG site (*TRIM3* gene) in obese individuals compared to controls, providing evidence that obesity is associated with epigenetic changes [44]. Although collectively, such studies could indicate that epigenetic changes are associated with obesity, it is not really clear whether they predict or precede obesity [45].

Since obesity arises from combined effects between genes, environment and behavior, the study of epigenetics comes to identify genes that can determine the susceptibility of individuals to obesity by providing pathophysiological mechanisms for weight regulation, food intake control and fat distribution. And thus, improve public policy actions and guidelines to better guide strategies for prevention and treatment of obesity.

Acknowledgements

We thank all the authors and collaborators for contributing with this publication.

Authors' Contributions

All authors were responsible for the draft of the work or critical revision for important intellectual content. All authors read and approved the final manuscript.

Competing Interests

The authors declare that they have no competing interests.

References

- Mendelson MM, Marioni RE, Joehanes R, Chunyu Liu, Hedman AK, et al. (2017) Association of Body Mass Index with DNA Methylation and Gene Expression in Blood Cells and Relations to Cardiometabolic Disease: A Mendelian Randomization Approach. *Plos Med* 14: e1002215.
- WHO - World Health Organization (2013) Obesity and overweight. Media Cent. Fact sheet N 311.
- Benjamin EJ, Blaha MJ, Chiuve SE, Cushman M, Das SR, et al. (2017) Heart Disease and Stroke Statistics-2017 Update: A Report From the American Heart Association. *Circulation* 135: e146-e603.
- Johnson AA, Akman K, Calimport SR, Wuttke D, Stolzing A, et al. (2012) The role of DNA methylation in aging, rejuvenation, and age-related disease. *Rejuvenation Res* 15: 483-494.
- Perumpail BJ, Cholankeril R, Yoo ER, Kim D, Ahmed A (2017) An Overview of Dietary Interventions and Strategies to Optimize the Management of Non-Alcoholic Fatty Liver Disease. *Diseases* 5.
- Baker K, Loughman A, Spencer SJ, Reichelt AC The impact of obesity and hypercaloric diet consumption on anxiety and emotional behavior across the lifespan. *Neurosci Biobehav Rev* 83: 173-182.
- Barczyk A, Kutkowska-Kaźmierczak A, Castaneda J, Obersztyn E (2017) The genetics of obesity- pathogenetic, clinical and diagnostic aspects. *Dev Period Med* 21: 186-202.
- Locke AE, Kahali B, Berndt SI, Justice AE, Pers TH, et al. (2015) Genetic studies of body mass index yield new insights for obesity biology. *Nature* 518: 197-206.
- Solas M, Milagro FI, Urbistondo DM, Ramirez MJ, Martinez JA (2016) Precision Obesity Treatments Including Pharmacogenetic and Nutrigenetic Approaches. *Trends Pharmacol Sci* 37: 575-593.
- Castillo-Fernandez JE, Spector TD, Bell JT (2014) Epigenetics of discordant monozygotic twins: implications for disease. *Genome Med* 6: 60.
- Sun J, Wang Y, Cui W, Lou Y, Sun G, et al. (2017) Role of Epigenetic histone modifications in diabetic kidney disease involving renal fibrosis. *J Diabetes Res* 1-11.
- Lopomo A, Burgio E, Migliore L (2016) Epigenetics of obesity. *Prog Mol Biol Transl Sci* 140: 151-184.
- Foma AM, Aslani S, Karami J, Jamshidi A, Mahmoudi M (2017) Epigenetic involvement in etiopathogenesis and implications in treatment of systemic lupus erythematosus. *Inflamm Res* 66: 1057-1063.
- Relton CL, Davey SG (2010) Epigenetic epidemiology of common complex disease: prospects for prediction, prevention, and treatment. *Plos Med* 7.
- Schubeler D (2015) Function and information content of DNA methylation. *Nature* 517: 321-326.
- Crider KS, Yang TP, Berry RJ, Bailey LB (2012) Folate and DNA methylation: A review of molecular mechanisms and the evidence for folate's role. *Adv Nutr* 3: 21-38.
- Afman LA, Muller M (2012) Human nutrigenomics of gene regulation by dietary fatty acids. *Prog Lipid Res* 51: 63-70.
- Lillicrop KA, Hoile SP, Grenfell L, Burdge GC (2014) DNA methylation, ageing and the influence of early life nutrition. *Proc Nutr Soc* 73: 413-421.
- Vel szic KS, Declerck K, Vidakovi M, Berghe WV (2015) From inflammaging to healthy aging by dietary lifestyle choices: is epigenetics the key to personalized nutrition? *Clin Epigenetics* 7: 33.
- Mckay JA, Groom A, Potter C, Coneyworth LJ, Ford D, et al. (2012) Genetic and non- genetic influences during pregnancy on infant global and site-specific DNA methylation: role for folate gene variants and vitamin B₁₂. *PLoS One* 7: 1-9.
- Christensen BC, Houseman EA, Marsit CJ (2009) Aging and environmental exposures alter tissue-specific DNA methylation dependent upon CpG island context. *PLoS Genetics* 5: 1-13.
- Sproul D, Meehan RR (2013) Genomic insights into cancer-associated aberrant CpG island hypermethylation. *Brief Funct Genomics* 12: 174-190.
- Macartney-Coxson D, Benton MC, Blick R, Stubbs RS, Hagan RD, et al. (2017) Genome-wide DNA methylation analysis reveals loci that distinguish different types of adipose tissue in obese individuals. *Clin Epigenetics* 9: 48.
- Schwenk RW, Jonas W, Ernst SB, Kammel A, Jähnert M (2013) Differences in Promoter Methylation accompany diet-dependent Alterations of Hepatic Scd1 Expression. *Horm Metab Res* 45: 786-794.
- Cheung WW, Mao P (2012) Recent Advances in Obesity: Genetics and Beyond. *ISRN Endocrinol* 2012: 536905.
- Rao KR, Lal N, Giridharan NV (2014) Genetic & epigenetic approach to human obesity K. *Indian J Med Res* 140: 589-603.
- González-Muniesa P, Martínez-González MA, Hu FB, Després JP, Matsuzawa Y, et al. (2017) Obesity. *Nat Rev Dis Primers* 3: 17034.
- Van Dijk S, Tellam RL (2015) Recent developments on the role of epigenetics in obesity and metabolic disease. *Clin Epig* 7: 66.
- BOURET S, LEVIN BE, OZANNE SE. Gene-Environment Interactions Controlling Energy and Glucose Homeostasis and the Developmental Origins of Obesity. *Physiology Reviews*, doi: 10.1152/physrev.00007.2014, 2015.
- Loche E, Ozanne SE (2016) Early nutrition, epigenetics, and cardiovascular disease. *Current Opinion in Lipidology* 27: 449-458.
- Heijmans BT, Tobi EW, Stein AD, Putter H, Blauw GJ, et al. (2008) Persistent epigenetic differences associated with prenatal exposure to famine in humans. *Proc Natl Acad Sci USA* 105: 17046-17049.
- Choi KM, Lee YS, Sin DM, Lee S, Lee MK, et al. (2013) Sulforaphane inhibits mitotic clonal expansion during adipogenesis through cell cycle arrest. *Obesity (Silver Spring)* 20: 1365-1371.
- Janesick A, Blumberg B (2012) Obesogens, stem cells and the developmental programming of obesity. *Int J Androl* 35: 437-448.
- Levian C, Ruiz E, Yang X (2014) The pathogenesis of obesity from a genomic and systems biology perspective. *Yale J Biol Med* 87: 113-126.
- Frayling TM, Timpson NJ, Weedon MN, Zeggini E, Freathy RM, et al. (2017) A common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity. *Science* 316: 889-894.
- Do C, Shearer A, Suzuki M, Terry MB, Gelernter J (2017) Genetic-epigenetic interactions in cis: a major focus in the post-GWAS era. *Genome Biol* 18: 120.
- Claussnitzer M, Hui CC, Kellis M (2016) FTO obesity variant and adipocyte browning in humans. *The N Engl J Med* 374: 192-193.
- Locke AE, Kahali B, Berndt SI, Justice AE, Pers TH, et al. (2015) Genetic studies of body mass index yield new insights for obesity biology. *Nature* 518: 197-206.
- Winkler TW, Justice AE, Graff M, Barata L, Feitosa MF, et al. (2015)

- The influence of age and sex on genetic associations with adult body size and shape: a large-scale genome-wide interaction study. *PLoS Genet* 11: e1005378.
- 40 Widiker S, Karst S, Wagener A, Brockmann GA (2010) High-fat diet leads to a decreased methylation of the *Mc4r* gene in the obese BFMI and the lean B6 mouse lines. *J Appl Genet* 51: 93-197.
- 41 Zhang Y, Kent JW, Lee A, Cerjak D, Ali O, et al. (2013) Fatty acid binding protein 3 (*fabp3*) is associated with insulin, lipids and cardiovascular phenotypes of the metabolic syndrome through epigenetic modifications in a northern european family population. *BMC Medical Genomics* 6: 9.
- 42 Milagro FI, Gómez-Abellán P, Campión J, Martínez JA, Ordovás JM, et al. (2012) CLOCK, PER2 and BMAL1 DNA methylation: association with obesity and metabolic syndrome characteristics and monounsaturated fat intake. *Chronobiol Int* 29: 1180-1194.
- 43 Lima RPA, Nascimento RAF, Luna RCP (2017) Effect of a diet containing folate and hazelnut oil capsule on the methylation level of the *ADRB3* gene, lipid profile and oxidative stress in overweight or obese women. *Clin Epigenetics* 9: 110.
- 44 Wang Y, Luk AO (2010) Independent predictive roles of eotaxin Ala23Thr, paraoxonase 2 Ser311Cys and beta-adrenergic receptor Trp64Arg polymorphisms on cardiac disease in Type 2 Diabetes—an 8-year prospective cohort analysis of 1297 patients. *Diabet Med* 27: 376-383.
- 45 Franks PW, Ling C (2010) Epigenetics and obesity: the devil is in the details. *BMC Medicine* 8: 88.