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

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

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...
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 embryonic 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 FTO79, 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 RPRGIP1L 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 PPARγ 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.

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Competing Interests
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References


