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Clinical applicability of epigenetics in obesity

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Abstract

Recent findings in the field of epigenetics have shown that obesity, like other metabolic diseases, is regulated by epigenetic mechanisms and that certain therapies currently in clinical use, such as bariatric surgery and nutritional interventions for weight loss, are capable of reversing the obesity-related epigenome. Despite the evidence for the role of epigenetic regulation in obesity, it is currently unknown whether the epigenetic mechanisms associated with obesity are a cause or a consequence of excess adiposity. However, there is sufficient evidence to support the usefulness of the study of these epigenetic mechanisms as tools in the detection of predisposition to the development of obesity and its associated diseases and they can also act as possible therapeutic targets, useful in the field of nutriepigenomics and pharcoepigenomics. This review will present the most updated scientific evidence on the implication of epigenetic regulation in the field of obesity, with a special emphasis on DNA methylation marks and their usefulness in the prevention, diagnosis and treatment of obesity and its associated diseases.

Keywords:

- Epigenetics
- Adipose tissue
- Bioactive compounds
- Personalized medicin

Introduction

Epigenetics is an emerging field of science that serves as the bridge between genotype and phenotype, determining the complex interactions that occur between the genome and the environment and that affect the health of organisms. Several applications of epigenetic marks have been demonstrated for personalized medicine in the field of oncology; however, in the fields of endocrinology and nutrition, epigenetics remains a very young science. The latest findings in the field of epigenetics have revealed that obesity, like other metabolic diseases, is regulated by epigenetic mechanisms, and that certain therapies currently used in clinical practice, such as bariatric surgery and nutritional interventions for weight loss, are capable of reversing the obesity-related epigenome[1]. Obesity is a multifactorial disorder that is directly influenced by the effect exerted by certain external agents, to a greater extent than by each person's own genetics[2]. The molecular mechanisms involved in the connection between environmental factors and gene expression are called epigenetic mechanisms, and the science that studies these mechanisms is epigenetics. These epigenetic mechanisms consist of chemical marks that bind to DNA and regulate gene expression, without modifying the DNA sequence. Like genetic mutations, these epigenetic marks are heritable, but unlike genetic mutations, they are reversible. The main relevant molecular mechanisms involved in epigenetic regulation are the following: DNA methylation, post-translational modifications of histones (PTMs), and non-

coding RNAs (ncRNAs), including microRNAs (miRNAs) and long non-coding RNAs (lncRNAs). (Fig. 1).

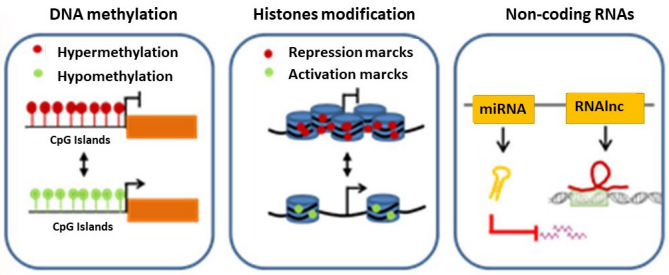

Figure 1. Main Epigenetic Mechanisms. DNA methylation, post-translational modifications of histones, and non-coding RNAs play a fundamental role in the regulation of gene expression, acting at different stages of an individual's life. DNA: deoxyribonucleic acid; RNA: ribonucleic acid; lncRNA: long non-coding RNA; miRNA: microRNA; CpG: cytosine-phosphodiester-guanine dinucleotide. Modified from 51.

In this review, the most current scientific evidence regarding the involvement of epigenetic regulation in the field of obesity will be presented, with a special emphasis on DNA methylation marks and their utility in the prevention, diagnosis, and treatment of obesity and its associated diseases.

Epigenetics and obesity: the chicken or the egg?

Despite the evidence regarding the role of epigenetic regulation in obesity, it is currently unknown which comes first: whether the pathology of obesity regulates epigenetic mechanisms, or if epigenetic regulation induced by environmental factors promotes the development of obesity and its associated diseases. In other words, it is currently unclear whether epigenetic mechanisms associated with obesity are a cause or a consequence of excess adiposity.

Epigenetics and obesity

Here it is reviewed the evidence supporting the hypothesis that epigenetic changes can induce obesity, which in turn leads to dysfunction in other organs and conditions susceptibility to obesity-related diseases. Specific patterns of epigenetic factors, including DNA methylation, have been found associated with obesity in analyses of DNA methylation in leukocytes and adipose tissue at a whole-genome level[3–5] , as well as in analyses of specific genes such as clock genes (e.g., CLOCK; circadian clock regulator, BMAL1; aryl hydrocarbon receptor nuclear translocator, and PER2; circadian period 2), whose methylation status in human leukocytes is associated with obesity [6]. This specific epigenetic profile associated with obesity can be induced by environmental factors in somatic cells, but several studies also demonstrate that ancestral environmental exposure can promote transgenerational epigenetic inheritance of obesity through epimutations in the germ line, i.e., the transgenerational transmission in the germ line (sperm or egg) of epigenetic marks that influence physiological parameters and diseases, in the absence of direct environmental exposures[7]. For example, a recent study demonstrated the presence of differentially methylated regions in the sperm of F3 generation male rodents with ancestral exposure to the insecticide dichlorodiphenyltrichloroethane (DDT), and several previously identified obesity-associated genes correlated with the identified epimutations[8]. This transmission of obesity-associated epimutations in rodents was also observed following exposure to endocrine disruptors derived from plastics (bisphenol-A, diethylhexyl phthalate, and dibutyl phthalate)[9] or hydrocarbons from airplane fuel[10]. It is noteworthy that therapeutic strategies aimed at counteracting excess body weight can remodel DNA methylation profiles while reducing body weight. DNA methylation levels and the expression of various genes related to metabolic processes and mitochondrial functions (e.g., peroxisome proliferator-activated receptor gamma coactivator 1-alpha, PGC-1α, and pyruvate dehydrogenase kinase isoenzyme 4, PDK4) are altered in the skeletal muscle of obese individuals and after Roux-en-Y gastric bypass (RYGB), a type of weight-loss surgery, and were normalized to levels observed in healthy normal-weight controls[11]. A 6-month exercise intervention can induce changes in DNA methylation patterns at the whole-genome level in human adipose tissue that potentially affect adipocyte metabolism[12]. Similar results have been observed in the muscle of patients with T2D; in these patients, exercise altered the DNA methylations of genes involved in retinol metabolism and calcium signaling pathways known to function in muscle and T2D[13]. The DNA methylation status of specific genes in human leukocytes[14] and adipose tissue can be altered by calorie restriction interventions[15]. Furthermore, it has been shown that responses to weight loss treatments can be influenced and predicted by the DNA methylation status before starting treatment; that is, differences in DNA methylation patterns of specific genes have been found between individuals with

low and high response to weight loss therapy[14,15] as well as between patients prone to weight regain and those able to maintain weight loss over a lifetime free-living period after dieting[16]. In this regard, the existence of an obesogenic memory has been proposed, leading to resistance to weight loss or to the regain of lost weight following a weight loss treatment[17]. This obesogenic memory is acquired over time due to exposure to environmental factors inherent to the lifestyle of our modern Western societies, where a chronically positive energy balance is very common. This is a consequence of a stressful lifestyle, sedentary behavior, and excessive consumption of appealing, energy-dense foods rich in saturated fats and processed sugars. Ultimately, prolonged exposure of an individual to this obesogenic environment allows their biology to adapt to this situation, leading to the development of overweight and obesity[17]. This obesogenic memory can also be transmitted to subsequent generations, both from the mother and the father[18] and can even be modulated depending on nutrition and exposure to environmental factors during the early days of life[19]. In this sense, it has been proposed that epigenetic mechanisms may play a relevant role in maintaining this obesogenic memory[17].

Obesity and epigenetics

Here we review the evidence supporting the hypothesis that obesity induces epigenetic alterations, which in turn may increase susceptibility to the development of other diseases. Along with an imbalance in energy homeostasis, obesity is characterized by a state of chronic low-grade inflammation that promotes oxidative stress due to dysfunction of adipose tissue and alterations in the secretion of adipocyte-derived hormones and cytokine synthesis[20]. In addition to its primary role as a fuel reservoir, adipose tissue is a highly active metabolic and endocrine organ that secretes factors such as leptin, adiponectin, and other cytokines[21], as well as new signals that have been identified through proteomics approaches[22]. Additionally, adipose tissue is a major site of metabolism for sex steroids and glucocorticoids [23]. Obesity is strongly associated with changes in the physiological function of adipose tissue, leading to its dysfunction. This, in turn, results in elevated systemic levels of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-alpha), interleukin 6 (IL-6), C-reactive protein, and matrix metalloproteinases[24]. Chronic inflammation induced by adipocyte dysfunction leads to increased release and accumulation of reactive oxygen species (ROS). Additionally, obesity itself induces excessive ROS generation due to inefficient energy metabolism[25]. It has been hypothesized that this obesity-related inflammatory and oxidative stress is a link between obesity and its comorbidities[26].

Likewise, several enzymes involved in epigenetic modifications use cofactors or substrates that are crucial metabolites in central intermediary metabolism pathways, such as acetyl-CoA, glucose, α-ketoglutarate (α-KG), nicotinamide adenine dinucleotide (NAD+), flavin adenine dinucleotide (FAD), ATP, or S-adenosylmethionine (SAM)[27]. Histone acetylation primarily depends on the cytosolic reserves of acetyl-CoA derived from glucose. This chromatin modification allows a positive feedback control mechanism for the selective expression of genes that regulate cellular function[27]. Therefore, alterations in energy metabolism, as occurs in obesity, could also lead to stable epigenetic changes that are maintained through the germline or occur in adult tissues and affect the health of the organism, as previously reviewed[27].

Oxidative stress induces DNA damage (e.g., base modifications, deletions, strand breaks, and chromosomal rearrangements) that reduces the DNA's capacity to be methylated by DNA methyltransferases (DNMTs), resulting in global hypomethylation[28,29]. Additionally, ROS can induce the hypermethylation of certain tumor suppressor genes and thus promote carcinogenesis[30,31]. Additionally, oxidative damage has been implicated in the regulation of histone modifications and microRNA expression[32–34]. Inflammation also induces epigenetic changes in tissues that are associated with disease manifestations, as revealed by recent therapeutic interventions using histone deacetylase and DNMT inhibitors, the effects of certain anti-inflammatory dietary elements on DNA methylation and chromatin remodeling, and the actions of various inflammation-related transcription factors, such as nuclear factor kappa B (NFκB)[35].

This epigenetic impact of obesity on the function of other organs can be divided into two areas: somatic effects and effects on the germline. Obesity-related factors can induce epigenetic alterations in adult tissues and target cells, but they can also induce an epigenetic phenotype in germline cells. This not only impairs gamete function and contributes to infertility, but it can also be transmitted to the next generation.

Although the idea that epigenetic marks are transmitted across generations remains controversial because it is

unclear whether such epigenetic inheritance exists and to what extent[36], in recent years accumulating evidence suggests that transgenerational epigenetic inheritance occurs in mammals [7,37–39]. In this sense, obesity status can exert an epigenetic impact on the germline, as demonstrated by the effect of parental obesity on the reproductive health of subsequent generations[40]. Relatedly, a recent study observed that diet-induced paternal obesity modulates sperm microRNA content and germline cell methylation status (which are potential signals programming offspring health) and adversely affects metabolic health in future generations[41]. Similarly, maternal obesity negatively affects oocyte quality, embryo development, and offspring health. The DNA methylation status of several imprinted genes and genes related to metabolism appears to be the underlying mechanism responsible for the adverse effects of maternal obesity on oocyte quality and embryonic development in offspring. These findings have recently been corroborated in oocytes from a mouse model of obesity and in oocytes and liver tissue from their offspring[42]. The results of this study revealed that the DNA methylation patterns of several genes related to metabolism are not only altered in the oocytes of obese mice, but also in the oocytes and liver of their offspring[42].

Clinical applications of epigenetics in obesity

DNA methylation as biomarkers of disease

All levels of epigenetic regulation appear to have wide-ranging effects on development and health and may be reversible. Anomalous epigenetic regulation has been described in many human diseases, including cancer[43], obesity[35], type 2 diabetes[44], atherosclerosis[45] and cardiovascular diseases[46], neurodegenerative and neurological diseases[47,48], as well as various inflammatory processes such as inflammatory bowel disease, autoimmune diseases, and rheumatoid arthritis[49]. Therefore, epigenetic marks could explain the link between lifestyle and disease risk and have been proposed as sensitive biomarkers of diseases and potential therapeutic targets for disease management [50].

Molecular biomarkers are innate characteristics that help identify or monitor a specific pathological process or disease. These may reflect prior environmental exposures, predict the onset or progression of a disease, or determine how a patient responds to therapy. Epigenetic changes possess these characteristics, with DNA methylation serving as the basis for most epigenetic biomarkers discovered to date [1].

The main challenge in the search for epigenetic biomarkers is obtaining suitable samples. Epigenetic marks are tissue-specific, so ideally, they should be analyzed in biopsy samples from the primary tissues affected by the disease. However, this may be impractical when evaluating biomarkers in healthy individuals, in sensitive populations such as children, in hard-to-access target tissues like the brain, or in longitudinal studies[51]. In this context, studies are being conducted to identify epigenetic marks in non-invasive samples, such as blood cells or buccal mucosa, as well as in cell-free samples such as plasma[52].

Besides blood samples, an increasing number of clinical studies are now examining the relationship between DNA methylation in saliva and various pathological conditions[53,54]. This is because saliva samples are easy to obtain, can be stored at room temperature, and allow for the expansion of epidemiological studies, including the longitudinal follow-up of the same patient over time.

Another innovative approach is the detection of epigenetic marks in circulating cell-free DNA from cell-free samples. Cell-free DNA refers to extracellular DNA present in various body fluids such as plasma[55]. This DNA can be released into peripheral blood from various tissues and organs during apoptosis and necrosis. By identifying the characteristics of circulating DNA derived from different tissues and organs in the plasma, it is possible to track and assess pathological changes in the corresponding tissue [55]. Thus, the analysis of DNA methylation profiles in plasma among patients and control subjects, which includes DNA fragments from various tissues and organs, holds great potential for identifying disease-related methylation changes. This tool can enable accurate diagnosis and personalized treatment strategies[56].

. In the identification of epigenetic biomarkers based on DNA methylation, multiple studies have utilized a candidate gene approach, analyzing methylation sites associated with known genes that have relevant functions in a specific disease[51]. For this type of studies, DNA methylation can be analyzed using qualitative or quantitative methods based on bisulfite conversion, including pyrosequencing. Pyrosequencing is a DNA sequencing method based on the “sequencing by synthesis” principle, and it allows quantification of DNA methylation levels at specific CpG sites. This methodology

is useful when targeting a specific gene whose biological function in the studied tissue is already known. In some cases, gene selection is based on prior analysis of gene expression differences.

On the other hand, whole-genome methylation analyses based on arrays have the advantage of examining the entire genome[51]. However, candidate gene analysis is useful to confirm the results obtained in whole genome methylation analyses. Currently, methylation analysis is becoming more complex with the study of base-nucleotide resolution methylation using next-generation whole genome sequencing approaches. Thanks to all these technical approaches, several genes are already known to exhibit differential methylation in obesity and associated diseases such as cancer or insulin resistance. (Fig 2).

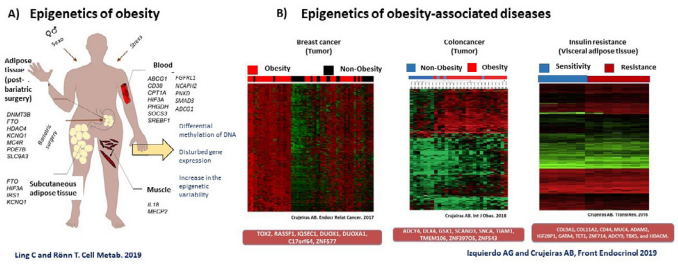

Figure 2. Examples of Epigenetic Marks in Obesity Pathology. A) Examples of DNA Methylation Marks Associated with Obesity. Modified from 77. B) Evidence of DNA methylation marks related to obesity-associated diseases. Modified from 78

DNA methylation and obesity diagnosis

Several studies have explored methylation sites in or near known candidate genes, providing evidence that obesity is associated with altered epigenetic regulation of several metabolically important genes, such as tumor necrosis factor alpha (TNFα), leptin (LEP), proopiomelanocortin (POMC), melanin-concentrating hormone receptor 1 (MCHR1), and the imprinting region IGF2/H19, as previously reviewed[1]. Furthermore, with the recent development of whole-genome methods to quantify DNA methylation at specific sites, studies are underway investigating associations between many genes and CpGs. These approaches identify differentially methylated sites associated with obesity, enriched in candidate obesity genes and genes with various other functions or even unknown properties related to obesity or adipose tissue function[57]. Thus, specific patterns of epigenetic factors, including DNA methylation, have been found to be associated with obesity. This association has been observed in genome-wide DNA methylation analyses in leukocytes and adipose tissue[57], as well as in analyses of specific genes such as those involved in the circadian clock (e.g., CLOCK; circadian locomotor output cycles kaput, BMAL1; aryl hydrocarbon receptor nuclear translocator-like protein 1, and PER2; period circadian regulator 2), whose methylation status in human leukocytes is linked to obesity[57]. The DNA methylation and expression of HIF3A in adipose tissue were also examined[5], reporting a significant inverse correlation and highlighting the potential functional relevance of the epigenetic variation at the identified locus. This finding is relevant as it suggests that assessing DNA methylation in whole blood can identify a robust and biologically relevant epigenetic variation associated with BMI. Thus, it presented the first systematic analysis of the association between DNA methylation variation and body mass index[5]. HIF3A encodes a component of the hypoxia-inducible transcription factor that regulates cellular response to hypoxia by modulating the expression of numerous genes. Findings suggest that increased CpG methylation at three different sites within the HIF3A locus occurs as a consequence of increased BMI and may play a role in the development of metabolic dysfunction associated with obesity. Similarly, another study demonstrated that an obesity-associated DNA methylation pattern specific to adipose tissue can be reflected in circulating leukocytes. This study showed that methylation levels of the genes FGFRL1, NCAPH2, PNKD, and SMAD3 could constitute an epigenetic signature of adipose tissue dysfunction associated with obesity, assessed in blood leukocytes as a surrogate for target tissue[51] . The methylation of these genes showed an 80% ability to discriminate between samples from individuals with obesity and healthy individuals with normal weight

DNA methylation and diseases associated with obesity

Some examples in the literature on epigenetic biomarkers, mainly DNA methylation, in diseases associated with obesity include a genome-wide epigenetic analysis of visceral adipose tissue from patients with severe obesity, which identified an epigenetic signature of insulin resistance encompassing the genes COL9A1, COL11A2, CD44, MUC4, ADAM2, IGF2BP1,

GATA4, TET1, ZNF714, ADCY9, TBX5, and HDACM[58] Another study showed that the methylation levels of 478 CpG sites in blood leukocytes were differentially methylated according to the HOMA-IR cutoff of 3 units, and these were good predictors of insulin resistance[59]. In blood leukocytes, a specific DNA methylation pattern related to metabolic syndrome was also found, being particularly consistent for the ABCG1 gene [60].

Obesity is also associated with the development and progression of non-alcoholic fatty liver disease (NAFLD). Epigenetics has been proposed to play a significant role in the onset of NAFLD. In this regard, several differentially methylated regions (DMRs) were found based on the hepatic fibrosis status. These DMRs were associated with metabolic pathways and reversed following weight loss [61].

Epigenetic regulation was also evidenced in the association between obesity and cancer by identifying a specific methylome in postmenopausal breast cancer[62] and in human colorectal cancer (CRC)[63] and obesity-associated hepatocellular carcinoma[64]. This role of epigenetic regulation in obesity was also highlighted during the COVID-19 pandemic. A study revealed a global increase in methylation levels related to obesity in the ACE2 gene sequence, which encodes the primary entry factor of the SARS-CoV-2 virus, in visceral adipose tissue of patients with obesity, independently of obesity-associated comorbidities[65]. An important finding is that the methylation profile of ACE2 was altered following weight loss induced by nutritional therapy, but not following bariatric surgery. Two CpG sites were identified in the ACE2 gene promoter that were proposed as potential biomarkers for monitoring the risk of COVID-19 related to obesity and its progression using a non-invasive sample (blood leukocytes)[65].

DNA methylation and response to obesity treatment

Currently, the main challenge in the treatment of obesity not only lies in achieving weight loss that improves health parameters, but also in preventing the regain of lost weight[66]. The response to obesity treatment is influenced by a physiological adaptation determined by multiple factors, such as genetic, hormonal, and environmental factors[66]. There has been accumulating scientific evidence supporting the use of epigenetic marks, such as DNA methylation, to predict treatment response before initiating it. For instance, it has been observed that patients who respond better to behavioral interventions for weight loss have lower levels of

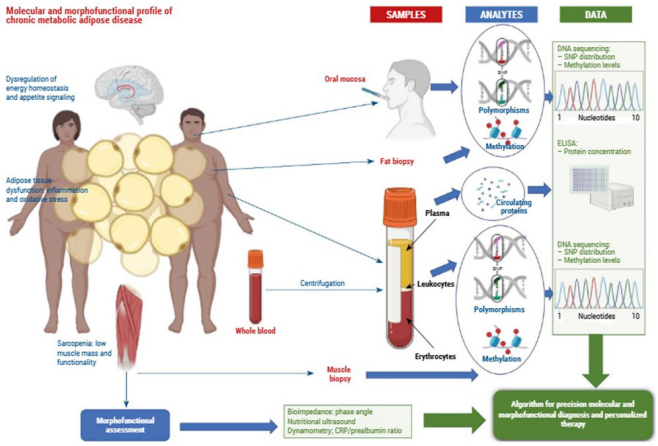

Figure 3. Proposal for the clinical applicability of epigenetics in obesity. Samples, analytes, and useful data in the molecular diagnosis of obesity, including epigenetic marks along with other clinical, genetic, and lifestyle parameters specific to each individual that could be effectively implemented in clinical practice for precision diagnosis and personalized therapy of obesity. Modified from 79

methylation in the promoter region of the HTR2A gene, which encodes the 5-hydroxytryptamine receptor 2A (HTR2A) in circulating leukocytes[67]. In another study, baseline levels of LINE-1 DNA methylation were significantly higher in patients with high response compared to those with low response to energy restriction, suggesting that high LINE-1 methylation could predict a better response to hypocaloric diet[68].

Regarding predisposition to weight regain, several studies have found differences in gene methylation between patients who successfully maintain weight loss and those who regain weight in the short to medium term after treatment. For instance, varying levels of methylation in genes such as NPY and POMC, involved in appetite regulation, were associated with the ability to sustain lost weight at 32 weeks post completion of the caloric restriction nutritional treatment[16]. As well, in women with severe obesity undergoing bariatric surgery, baseline methylation levels of the MFSD3 gene, involved in metabolism regulation, were significantly higher in those who regained weight after three years compared to those who did not[69].

In summary, current scientific evidence suggests that DNA methylation marks could be useful biomarkers for predicting the response to weight loss treatment in patients with obesity. However, additional studies in large population

cohorts are needed to establish cutoff points and the optimal combination of epigenetic biomarkers. This, along with other specific clinical, genetic, and lifestyle parameters of each individual, will enable the effective implementation of these tools in clinical practice. (Fig 3).

Epigenetic therapy in obesity: pharmacoepigenomics and nutriepigenomics.

As research in epigenetics has advanced, epigenetic therapies targeting different epigenetic mechanisms have also been developed, taking advantage of a key characteristic of epigenetic marks that genetic mutations do not have: reversibility. In this regard, the clinical application of epigenetics is approached from both nutriepigenomics and pharmacoepigenomics. (Fig. 4).

Regarding nutriepigenomics, various nutrients and dietary compounds have been identified that can slightly modify the epigenetic patterns of different cell lines and tissues, which could help overcome metabolic diseases. Numerous studies have demonstrated the effects on DNA methylation of B vitamins, proteins, micronutrients, components of functional foods, and overall nutritional status. Dietary changes can directly influence the epigenetic processes that affect health or disease and can also program metabolism and future responses to nutrition. The epigenetic diet has been proposed as an important mechanism that can modulate and potentially slow the progression of age-related diseases, such as cardiovascular diseases, cancer, and obesity. This is due to the introduction of bioactive compounds such as sulforaphane, curcumin, and resveratrol, among others, which are believed to help extend lifespan. Healthy eating patterns like the Mediterranean Diet or the Atlantic Diet have also been proposed as potential epigenetic diets that promote health, prevent diseases, and support healthy aging by regulating epigenetic mechanisms[70].

Regarding epigenetic modification in the treatment of obesity, it is important to highlight that therapeutic strategies to counteract excess weight can remodel DNA methylation profiles along with reducing body weight. DNA methylation and the expression levels of various genes related to metabolic processes and mitochondrial functions are modulated in adipose tissue after bariatric surgery, often normalizing to levels observed in healthy, normal-weight controls. Physical exercise can also induce changes in the DNA methylation patterns of adipose tissue and human muscle

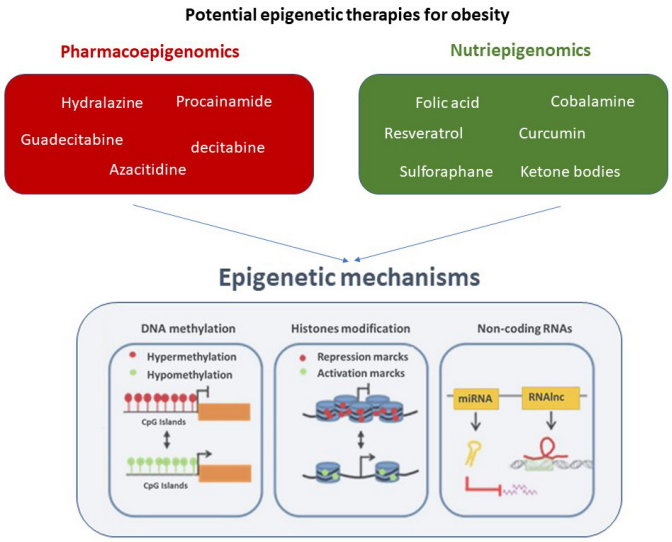

Figure 4. Epigenetic Therapies in Obesity

that affect metabolism. Similarly, the DNA methylation of specific genes in adipose tissue can be altered with caloric restriction interventions. Similar results of reversibility in the methylation of certain genes have been observed in the DNA of peripheral blood leukocytes after bariatric surgery, after nutritional treatment with a balanced hypocaloric diet, or after physical exercise. A relevant example is the nutritional treatment based on a very low-calorie ketogenic diet (VLCKD), which can reverse the methylome of obesity to values similar to those observed in healthy individuals with normal weight, thanks to nutritional ketosis and the weight loss induced by the VLCKD[71].

Finally, little is known about the potential effect of new anti-obesity drugs on the regulation of the obesity epigenome and the utility of epigenetic marks to predict and monitor the response to pharmacological treatment of obesity. Currently, no epigenetic drugs have been approved for the treatment of metabolic diseases, although they have been approved for other diseases such as cancer. Considering DNA methylation, there are currently drugs capable of inhibiting this mechanism through inhibitors of DNA methyltransferase enzymes (DNMTi), which modulate the methylation levels of specific genes. Examples of DNMTi agents include azacitidine and guadecitabine, hydralazine, procainamide, and decitabine. It has been observed that the inhibition of DNA methylation by azacitidine leads to a lower accumulation of lipid droplets in 3T3-L1 cells at the early differentiation stage and suppresses

adipogenesis[72–74]. Additionally, a relevant finding is that this inhibition of DNA methylation can induce browning of white fat, which in turn may act as mechanisms of resistance to obesity, demonstrating a potential application of epigenetic drugs in anti-obesity therapy[75]. Other DNMTi drugs such as hydralazine, procainamide, or decitabine are capable of alleviating diseases associated with obesity such as chronic kidney disease, type 2 diabetes mellitus, or hypertension[76] . Together, these scientific evidences suggest that epigenetic marks could be useful as therapeutic targets for specific nutritional supplementation with bioactive compounds, dietary patterns, physical activity, or even epigenetic drugs. (Fig. 4).

Conclusions

Despite it is still unclear whether obesity-associated epigenetics is a cause or a consequence of the pathophysiology of this disease, one could hypothesize that obesogenic environmental factors regulate epigenetic mechanisms, leading to the obese state that results in adipose tissue dysregulation and appetite regulation systems. These dysregulated factors associated with obesity, in turn, regulate epigenetic mechanisms that promote obesity-associated diseases. In this regard, epigenetics holds a promising future yet to be fully explored in the field of metabolic diseases. Given the new horizon of anti-obesity drugs, studies are needed to assess the potential epigenetic effect of such drugs to decode obesogenic memory, as well as to evaluate differences in epigenetic marks levels between responders and non-responders to these drugs prior to treatment initiation. This information could be applied to prescribe personalized and precision anti-obesity pharmacotherapy based on epigenetic profiles.

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Conflict of Interest Statement

The author declares no conflict of interest regarding the content of this review

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