Chapter

Environmental Epigenetics and Obesity

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Abstract

In recent years, increasing interest on the effects of dietary components on epigenetic processes and, consequently, on the regulation of gene expression and metabolic responses has led clinical efforts worldwide to approach obesity. When inadequate, food consumption leads to chronic and non-communicable diseases (CNCD) including obesity. Among the dynamic changes in cellular responses by nutritional interventions, epigenetic control represents a master regulator underlying both positive and negative effects of diet on body mass, including DNA methylation, histone post-translational modifications and microRNA expression signatures. Indeed, mechanistical studies of the relationship between environment, diet and differential epigenetic landscapes are gaining attention on functional pathways involved in cell growth, DNA-repair, lipogenesis, senescence, inflammation, tumor suppression, apoptosis and oncogenesis. Being the dynamic interplay between epigenetics and obesity so complex, moreover considering a detrimental environment context, this chapter will discuss the state-of-the-art evidence showing the pollution impact on the different epigenetic mechanisms regulating an obese phenotype, and how these molecular events determine the organic interplay upon metabolic alterations, and finally we will introduce recent epidrugs and biocompounds of therapeutic interests due to their potential to modulate and even revert obesity-inducing epigenetic mechanisms.

Keywords: toxicants, chromatin, ncRNAs, DNA methylation, endocrine disruptor

1. Introduction

Obesity epidemics has become pandemic in the last decade, placing a significant burden on the global health system. Although the heritability of the disease is high, all identified genetic variants associated with obesity represent a very small percentage of the phenotypic variation. Thus, the origins of obesity cannot be explained exclusively by genetic factors. In recent years, epigenetic studies have provided valuable information for a deeper understanding of the significant increase in global rates. Specific factors have related obesity to fundamental epigenetic changes, such as intrauterine environment, nutrition, circadian rhythms, psychosocial inputs, lifestyles, and a set of environmental stimuli. Therefore, health

is itself the result of the interaction of the social (agriculture, industry, and energy production, use and management of water and waste, urbanization, income distribution, public services), the physical–chemical (soil, air, water, food, pathogens, climate, pollutants) and the biological environment (flora, fauna, habitats including reservoirs and vectors). Obesity-related environmental pollutants function in the body as endocrine disruptors, altering body weight, adipose tissue expansion, circulating lipid profiles, and adipogenesis through epigenetic mechanisms. To mention some introductory examples, it has been reported that widely diffused toxins, mainly bisphenol A, phthalates and pesticides, can promote obesity in children and adults, by acting on the differentiation pathway that unites multipotent stromal stem cells with mature adipocytes, modulating epigenetic factors and influencing in a series of mechanisms that ultimately lead to altered eating habits, increased adipocyte formation and fat storage.

2. A "Globese" reality

Currently it exists a debate that attempts to redefine the concept of obesity (**Figure 1**). Until now, obesity was considered as the Body Mass Index (BMI) equal

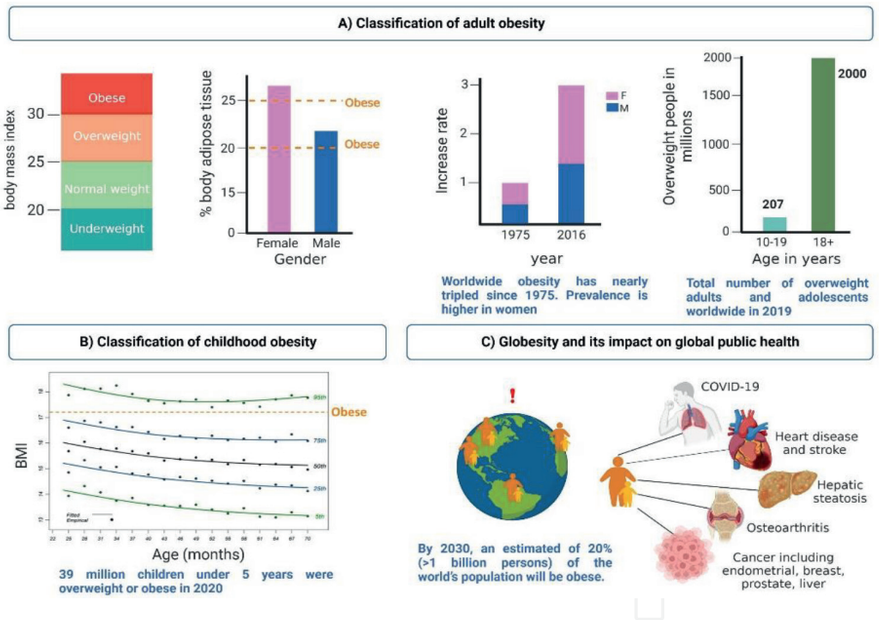

Figure 1.
Globesity. (A) Adult obesity is the body mass index (BMI) equal to or greater than 30 kg/m² and based on the percentage of body adipose tissue, when it exceeds 20% in men and 25% in women [1–3]. (B) Childhood obesity (under 5 years of age) is the BMI percentile equal to or greater than 95 according to the World Health Organization (WHO)'s growth standards [4–7]. (C) "Globesity" is a concept that refers to the obesity pandemic and an invitation by the WHO to create social awareness about its impact on global public health [8], since its health impacts range from an enhanced risk of premature death to significant chronic illnesses that diminish the overall quality of life. After smoking, it is the most important predisposing factor for the global burden of disease, contributing to the morbidity and mortality of COVID-19, type 2 diabetes mellitus, cardiovascular diseases, non-alcoholic fatty liver disease, hepatic steatosis, rheumatoid osteoarthritis, gout, musculoskeletal injuries, metabolic syndrome; as well as cancer types such as breast, endometrial, esophageal, colon, kidney and prostate; chronic respiratory diseases, sleep apnoea, fertility problems in both sexes, chronic kidney disease, neurodegenerative disorders, and maternal complications, according to the world obesity atlas** [9–12]. "Globesity" is higher in the afro-descendant and Hispanic population, and the increase in prevalence is more prominent in women [13, 14]. *https://www.who.int/toolkits/child-growth-standards/standards/body-mass-index-for-age-bmi-for-age, **https://www.worldobesity.org/resources/resource-library/world-obesity-atlas-2022).*

to or greater than 30 kg/m2 [1, 2]. However, due to the lack of tissue specificity, there is another definition of obesity related to the percentage of adipose tissue in the body, established at a maximum limit of 20% for men and 25% for women [3]. In the case of childhood obesity, the criteria are not so specific, but it is still considered as a basis that the body weight exceeds the relationship with the height of the child or adolescent [4, 5]. In this regard, the Center for Disease Control and Prevention of the National Public Health Agency of the United States recommends BMI charts for people from 2 to 20 years of age, which are color-coded based on the BMI percentile: 5 (red), 5–85 (green), 85–95 (yellow) and 95 (red). Thus, overweight is diagnosed between percentiles 85 to 95, and obesity with percentiles above 95 [6, 7].

Obesity is currently one of the most alarming pathological conditions due to its exacerbated prevalence (**Figure 1**) [15, 16]. Due to this reason the World Health Organization has proposed the term "globesity" [8] to raise awareness on the damage to global health caused by this disease in the last 50 years [17]. Prevalence is higher in the Afro-descendant and Hispanic population, and the increase in prevalence is more prominent in women [13, 14]. Obesity reduces both quality of life and life expectancy. After smoking, it is the most important predisposing factor for the global burden of disease, contributing to the morbidity and mortality of COVID-19, type 2 diabetes mellitus, cardiovascular diseases, non-alcoholic fatty liver disease, hepatic steatosis, rheumatoid osteoarthritis, gout, musculoskeletal injuries, metabolic syndrome; as well as cancer types such as breast, endometrial, esophageal, colon, kidney and prostate; chronic respiratory diseases, sleep apnoea, fertility problems in both sexes, chronic kidney disease, neurodegenerative disorders, and maternal complications [9–12] (**Figure 2**).

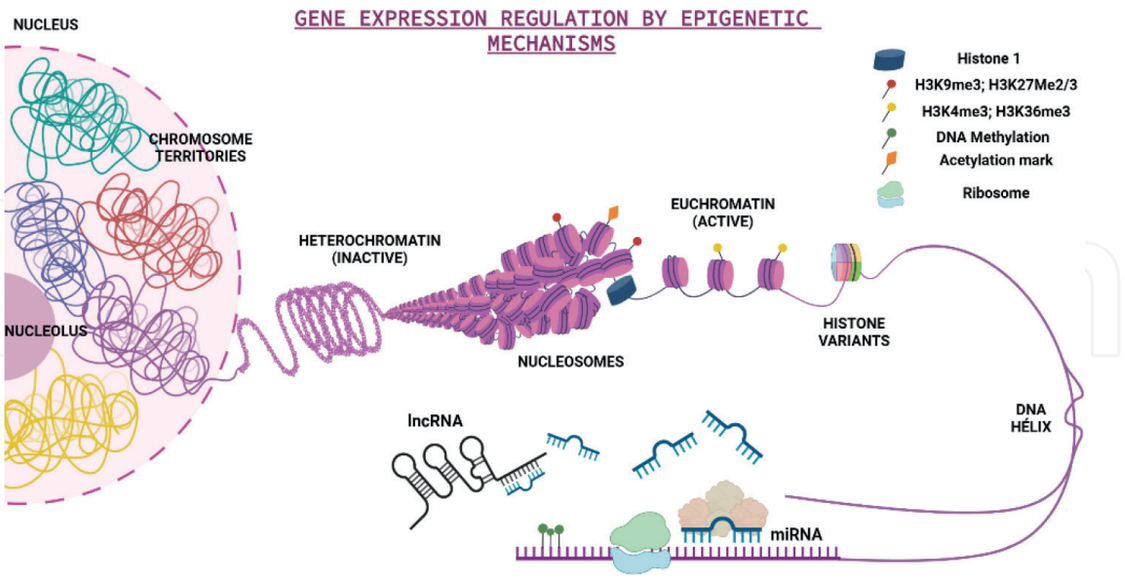

Figure 2.
Epigenetic mechanisms and topological structure of the nucleus. Gene expression can be regulated by non-genetic heritable genomic modifications without alterations in DNA sequence. Epigenetic mechanisms include DNA methylation, histone modifications and non-coding RNAs (ncRNAs), all regulating gene activity at the transcriptional, post-transcriptional, translational, and post-translational level. Moreover, lncRNAs participate in numerous biological activities, including cell cycle control, cytoplasmic and nuclear trafficking, splicing, transcription, translation, imprinting, epigenetic regulation, and more recently shown, in the arrangement of functionally different nuclear sub-compartments such as nucleolus and chromosomal territories. Thus, specific 3D nuclear topology or architecture is strongly related with normal cell functions.

3. Environmental pollution and its impact on epigenetics

Environmental change on our planet is a natural and ancient phenomenon that has occurred for over 4 billion years. However, the human being has left an ecological footprint affecting planet Earth, especially from the 20th century onwards [18, 19]. Environmental pollution is one of the most serious problems facing biodiversity, ecosystems and human health. It is widely defined as the introduction of toxins that alter the physical and biological components of the environment. Pollutants can be liquids, solids and harmful gases produced in concentrations that exceed the levels allowed by the World Health Organization (WHO), reducing the quality of life and the environment [20]. Specifically, air pollution is defined as the release of harmful particles into the air by one or more harmful gases. The six main air pollutants are: airborne fine particulate matter 10 microns or less in diameter (PM10) and 2.5 microns or less in diameter (PM2.5); ozone, carbon monoxide, lead, nitrogen dioxide and sulfur dioxide [20, 21]. Two main types of air pollution are considered: outdoor pollution as the pollution of the ambient air, and indoor pollution as the pollution generated by domestic combustion [20].

According to the United Nations, Educational, Scientific and Cultural Organization (2021), one in nine people in the world consumes water from unimproved and unsafe sources. 90% of wastewater in countries with developing economies is discharged directly into untreated water bodies. Moreover, wastewater is reused in agriculture, while important for livelihoods, it is associated with serious health risks (International Initiative on Water Quality, IIWQ, UNESCO, 2021). 99% of the world population breathes air that exceeds the maximum limits for air pollutant levels. Currently, more than 6000 cities in 117 countries monitor air quality, but their inhabitants still breathe unhealthy levels of fine particulate matter and nitrogen dioxide, with people in low- and middle-income countries experiencing the highest exposures (The report and WHO air quality database 2022). Additionally, the WHO declared airborne fine particulate matter the number one global environmental health concern in October 2021 [22]. Moreover, soil contamination by heavy metals has become a global health problem. According to The United States Environmental Protection Agency (2021), the sources of pollution in indoor environments are enlisted in **Table 1** [23].

In recent years, scientific evidence linking air pollution with obesity has been published by international groups, proposing several key biological pathways acting as a functional bridge [24, 27]. It is known that the exposome (exposure to environmental compounds and factors such as stress, habits, diet, exercise, lifestyle) can affect molecular pathways and cellular processes that increase the susceptibility to develop several diseases including obesity, because of abnormal epigenetic modifications [21, 28]. Early in the forties, Conrad Waddington first introduced the term "epigenetics" to describe environment-gene interactions that could not be explained by traditional Mendelian genetics [29]. Nowadays, epigenetics is defined as the study of non-genetic heritable genomic modifications that regulate gene expression without alterations in DNA sequence. Epigenetic mechanisms include DNA methylation, histone modifications and non-coding RNAs (ncRNAs), all regulating gene activity at the transcriptional, post-transcriptional, translational, and post-translational level (**Figure 2**) [21, 30].

DNA methylation is the most studied and characterized epigenetic mechanism, using as effectors the DNA methyltransferases (DNMT1, DNMT3A, DNMT3B, and DNMT3). These enzymes transfer a methyl group from S-adenosylmethionine (SAM) onto the C5 position of the cytosine to form 5-methylcytosine (5mC), the major

	Air pollution	**Water pollution**	**Soil pollution**
DEFINITION	Release of harmful particles into the air by one or more harmful gases. Two main types are considered: outdoor pollution as the pollution of the ambient air, and indoor pollution as the pollution generated by domestic combustion [20].	Deterioration of water quality worldwide due to the acceleration of industrialization.	Accumulation of organic and inorganic contaminants leading to unbalanced availability of nutrients to plants, changes in the abundance and structure of the soil microbial community, degradation of the soil ecosystem, and contamination of groundwater; further affecting the quality and safety of crops and human health.
SOURCES OF EXPOSURE	Indoor air [23]:	Contamination of waterbodies by waste from the agricultural, industrial, mining and energy sectors.	Agricultural production, the quality of cultivated land and environmental hygiene habits of the population.
	Combustion processes: heating, cooking food, smoking and fireplaces.		
	Cleaning products, paints, insecticides, and other commonly used products.		
	Building materials, either through degrading materials (i.e. asbestos fibers) or new materials (i.e. chemical off-gassing from pressed wood products).		
	Other substances such as radon, mold, and pet dander.		
	Outdoor air [23]:		
	Contaminants entering indoors through open doors and windows, ventilation systems, and cracks in structures.		
	Power plants, refineries, petrochemicals, chemical and fertilizer industries, metallurgical plants, and municipal incineration.		
	Mobile sources: automobiles, railways, airplanes, and other types of vehicles.		
	Natural sources: wildfires, volcanic eruption, dust storms, and agricultural burns.		

	Air pollution	**Water pollution**	**Soil pollution**
COMPOUNDS	The six main air pollutants are: airborne fine particulate matter 10 microns or less (PM_{10}) and 2.5 microns or less in diameter ($PM_{2.5}$); ozone, carbon monoxide, lead, nitrogen dioxide and sulfur dioxide [20, 21].	Agrochemicals, pathogens, nutrients and metals: Cr, Al, Ba, Cu, Mo, Ni, Pb, Se, As and Zn.	Agrochemicals, pathogens and heavy metals such as Cd, Pb, Cr, Zn, and Cu.
RISK FACTORS	Industrialization, population explosion, and fossil fuel economy [24]. The most prominent risk factor is long-term exposure, but there is no operational definition in terms of distance and time established by regulatory bodies, such as the World Health Organization. Regarding exposure to $PM_{2.5}$, several authors agree on the distance between the residence and the nearest highway or main road. A study reports the distance as 7 km between the residence with the automatic station for monitoring air quality from which the verified data was obtained, other studies coincide with the sites measurement methods mentioned above, establishing the exposure distance of 30 km, 10 km, 1.2 km or 1 km. 99% of the world population breathes air that exceeds the maximum limits for air pollutant levels. Currently, more than 6000 cities in 117 countries monitor air quality, but their inhabitants still breathe unhealthy levels of fine particulate matter and nitrogen dioxide, with people in low- and middle-income countries experiencing the highest exposures (WHO air quality database, 2022). Additionally, the World Health Organization declared airborne fine particulate matter the number one global environmental health concern in October 2021 [22].	Toxins with a greatest risk are metals and can be ingested by humans in crops that were irrigated with contaminated water. 1/9 people in the world consumes water from unimproved and unsafe sources. 90% of wastewater in countries with developing economies is discharged directly into untreated water bodies. Moreover, wastewater is reused in agriculture, while important for livelihoods, it is associated with serious health risks (International Initiative on Water Quality, IIWQ, UNESCO, 2021). Heavy metals in drinking water can induce genetic and epigenetic modifications that affect gene expression in growth control genes such as DNA-repair, tumor suppressor, apoptotic or oncogenes [25]. Susceptibility depends on surface and ground water use for drinking, cooking, washing, among others as part of their daily routine [26].	Concentrations of heavy metals in urban soils vary significantly depending on the city, the type of land used, the population density and the volume of traffic.

Table 1.
Sources of pollution in air, water and soil.

form of DNA modification. 5mC is present mainly in CpG sites on gene promoters, with relevant roles in development and disease, and conventionally associated with gene silencing or transcriptional repression [31]. The methylation repressive effect is caused by the attraction or the repulsion of certain DNA-binding proteins. Repressor complexes have been observed to be recruited to methylated promoter regions by a class of proteins known as methyl-CpG binding domain proteins (MBDs), which are attracted to and bind DNA-containing methylation CpG dinucleotides [32]. In addition, exposure to toxicants found in the environment may promote differential DNA methylated regions (DMR), potentially contributing to the obese phenotype [33, 34].

Histone modification is another well-known epigenetic mechanism [35]. Since DNA is packaged in the form of chromatin, its basic unit the nucleosome contains 147 bp of DNA wrapped around an octamer of histone proteins formed of two dimers of H2A and H2B, and a tetramer of H3 and H4 proteins, and an H1 as linker of adjacent nucleosomes [36]. Histone tails (N- and C- terminal) can be post-translationally modified by methylation, acetylation, phosphorylation, ubiquitylation, ADP-ribosylation, citrullination, sumoylation, carbonylation and proline isomerization, among others, thus, directly regulating chromatin structure [36, 37]. Methylation and acetylation are the most studied mechanisms occurring on histone tails. Methylation marks can cause either transcriptional repression (i.e., H3K9me3 and H3K27me2/3) or activation (i.e., H3K4me3, H3K36me3 and H3K79me3) and occurs mainly in arginine and lysine residues catalyzed by histone methyltransferases (HMTs). Reactions can be reverted by several histone demethylases (HDMs) such as KDM1 or AOF [38]. Like methylation, histone acetylation regulates chromatin remodeling (euchromatin and heterochromatin) and affects gene expression by dynamic changes through the action of histone acetyltransferase (HATs), also known as "writers", and histone deacetyltransferases (HDACs), also called "erasers" [26474904]. HDACs are divided into four classes, class I (HDACs 1, 2, 3 and 8), II (HDACs 4, 5, 6, 7, 9 and 10), III or sirtuins, and IV with HDAC11 as unique member. Each group harbors specific functions, i.e. HDACs class I play a role in adipocyte differentiation as well as in establishing the metabolic characteristics of these cells [39, 40].

Around 98% of the transcriptome consists of non-coding RNAs (ncRNAs) that cannot be translated into proteins, so they contribute to the physiological complexity of mammals. Non-coding RNAs are classified as 1) small-ncRNAs (20–30 nucleotides length) and 2) long-ncRNAs (lncRNAs, >200 nucleotides length), which are subclassified based on their biosynthesis and effector proteins. The main functions of small-ncRNAs are related to gene expression at transcriptional, post-transcriptional and translational levels. Moreover, they can be grouped in small interfering RNAs (siRNAs), Piwi-interacting RNAs (piRNAs) and microRNAs (miRNAs) as the most study biotypes [41]. Meanwhile, lncRNAs participate in numerous biological activities, including cell cycle control, cytoplasmic and nuclear trafficking, splicing, transcription, translation, imprinting, epigenetic regulation, and more recently shown, in the arrangement functionally different nuclear sub-compartments and their impact on nuclear topology or architecture [42, 43]. Hence, several human diseases like obesity are linked to alteration of ncRNA biosynthesis and function.

3.1 Pollution impact on DNA methylation

Environmental epigenetics explains the biological pathways that are altered by environmental factors that modify epigenetic mechanisms [44]. These changes include as main mechanisms DNA methylation, histone post-translational

modifications, ribonucleic acid-based mechanisms, and chromatin remodeling [45]. DNA methylation is an epigenetic mechanism that consists of the covalent transfer of a methyl group to the C5 position of the DNA cytosine ring by DNA methyltransferases (DNMT1, DNMT3A, DNMT3B, and DNMT3) [46, 47]. In mammals, methylation occurs primarily at the cytosine residues of cytosine and guanine dinucleotides (CG), but CG dinucleotides within promoters are usually free of methylation [46, 48].

Furthermore, the functions of DNA methylation differ depending on its location. In promoter regions, it confers gene repression, whereas, throughout the gene body, it is associated with transcriptional activation. Methylation levels also depend on genetic sequence and DNA-binding factors. Therefore, there is no general rule that can be applied to all biological situations, reflecting the high complexity of DNA methylation-dependent regulatory pathways [46, 49]. During all stages of human life, DNMTs can add or remove methyl groups by ten-eleven translocation enzymes (TETs), and because the methylome (global genome methylation state) operates at the interface between the genome and the environment, it can be modified in response to environmental stimuli, such as exercise, diet, smoking, or pollutants [48]. Altered patterns of DNA methylation have been associated with obesity and other chronic degenerative pathologies [50].

A large percentage of individuals worldwide are exposed to high arsenic (As) concentrations (10 ppb) in drinking water [51]. A revealing study was made in mononuclear cells of peripheral blood from individuals exposed to well-water. Araihazar's concentrations (0.1–960 μg/L), a region constituted by 10,000 wells near to Dhaka, Bangladesh. Forty participants were divided in two groups: low water concentration of As (median 55 μg/L, range 50–81 μg/L) and high concentration (median: 216 μg/L; range:150–500 μg/L) [52]. Interestingly, they found that As exposure influenced histone marks in a gender specific manner. H3K18ac and H3K27ac levels were higher in males than in females; in contrast, H3K27me3 and H3K4me3 increased in females. A probable explanation is that As has an endocrine disruptor role by mediating the estrogenic receptor (*ER*) expression. Also, these histone marks are known as estrogenic-sensitive which may have a relationship with the As effect. However, they did not fully characterize specific genes and pathways that were modified by As chronic exposure [52].

On the other side, chlorination by-products of drinking water (i.e. triethyltin, chloroform, dichloroacetic acid, trichloroacetic acid, bromodichloromethane, chlorodibromomethane and bromoform) have shown carcinogenic properties, modifying the methylation profile in liver and kidney in mice [53]. In this line of ideas, a human normal hepatic cell line treated with 0.1–0.9 mM trichloroacetic acid showed lower expression levels of Histone deacetylases (HDACs, mainly *HDAC2* and *HDAC3*) after 24 h compared to control treated cells. Intracellular H3K9ac levels increased and PCAF was maintained at low levels, resembling a DNA methyltransferase inhibitor (5-aza-dC) effect. Remarkably, TCA effect in HDACs was reversed after 72 h, which suggests that TCA long exposure cause DNA hypomethylation in promoter regions of *HDACs* genes, therefore activating their expression. As discussed by the authors, *HDACs* and H3K9ac levels could represent early epigenetic biomarkers useful for toxicity evaluation to prevent disease development upon TCA exposure [54]. Nevertheless, it is necessary to elucidate the relationship between early and long TCA effect on histone acetylation and DNA methylation.

In addition, a cyanobacterial toxin called cylindrospermopsin (CYN) is uptaken for humans while drinking water and through contaminated food by bioaccumulation. Recent studies characterizing the transcriptomic profile of the colorectal

adenocarcinoma cell line Caco-2 showed chromatin remodeling events after CYN exposure. Precisely, 2911 differentially expressed genes appeared between CYN treated and control cells. Among these genes, authors identified enzymes forming the RNA polymerase II complex (*POLR2D*, *POLR2L*, *POLR3E* and *POLR1C*), transcription co-activation factors (*MED6*, *MED10*, and *MED21*), enzymes involved in RNA maturation, acetyl transferases (*MYST1*, *KAT5*) and methyl transferases (*EHMT2*). Also, they confirmed a CYN-increased gene expression for *POLR2D*, *POLR2L*, *MED6*, *DDX20*, *KAT5*, *MYST1* AND *EHMT2*, as well as a differential level of proteins KAT5, MYST1, and EHMT2. Interestingly, different histone marks were modified in the same conditions, for example acetyl-histone H2A (Lys5), methylLys4 and Lys9 on histone H3 reflecting the activity of EHMT2, and dimethyl-Lys4 on histone H3. In this manner, important determinations were made in the context of environmental epigenome reprogramming in CYN-treated CaCo cells [55].

3.2 Pollution impact on histone post-translational modifications

Covalent histone modifications have a significant role during gene expression, inducing open chromatin for active transcription, and condensate chromatin for inactive transcription [54]. In recent years, the term obesogens has emerged referring to compounds that interrupt lipid homeostasis and promote adipogenesis. Several obesogens like heavy metals, solvents, pesticides, PCBs, organic phosphates, phthalates, organotin and diethylstilbestrol (DES) remodel histone marks associated to inflammatory and stress responses [56].

Systemic inflammation is widely linked to air pollution and obesity [57, 58]. However, the mechanism that connect both processes is poorly understood. Monocytes from obese individuals have shown elevated levels of IL6 and H3K9/H3K18 acetylation, associated to EP300, transcription factors and RNA Polymerase II recruitment to *IL6* promoter regions. EP300 silencing, and inhibition of histone acetyltransferase attenuated this effect. In this sense, a cohort study with individuals exposed for long periods to particulate matter (PM) (aerodynamic diameter $\leq$ 2.5, 2.5–10, and $\leq$ 10 μm) and gaseous air pollutants confirmed the increased *IL6* levels compared to short exposures. These studies provided crucial highlights about histone code changes in response to environmental pollutants during inflammatory events [59].

AMP-activated protein kinase (AMPK) is a known sensor of cellular energy homeostasis. AMPK phosphorylates targets involved in lipid homeostasis, mitochondrial biogenesis, and glycolysis, upon its stimulation above low energy conditions [60]. Recently, it was reported the genome-wide transcriptional profile and chromatin landscape of pancreatic islets from mice fed high-fat diet (HFD) treated with O304, a pan-AMPK activator. O304 treatment on HFD abrogated *Aldh1a3* expression, a β-cell stress marker, and *Ins1* mRNA levels, whereas it restored the glucose transporter *Slc2a2* expression, a target of impaired glucose response and insulin secretion. Screening of histones marks in O304-treated pancreatic islets indicated an ~58% active chromatin marks and preserved ~27% of H3K27Ac, compared to regions in HFD islets. Particularly, HFD-O304 cells diminished H3K27Ac in the *Aldh1a3* promoter as well as two distant upstream regions (~ 70 kb and ~ 114 kb) [60]. Tetrabromobisphenol A (TBBPA)-exposed human adenocarcinoma hepatic cells and Cr (IV)-treated neutrophils increase ROS production which mediate AMPK activation and promote cellular proliferation and apoptosis [61, 62]. In the case of transcriptomic analysis in TBBPA-exposed adenocarcinoma liver cells revealed differential expression in growth factors *FGF17* and *EFN5A*, Ras signaling pathway

activators, involved in cell detoxification mechanism, lipid and vitamin metabolic rate regulation [61]. On the other hand, Cr (IV)-exposed neutrophils showed the reduction on myeloperoxidase (*MPO*) and *H3* expression, which inhibited neutrophil extracellular traps (NETs) formation, a deconcentrated chromatin scaffolds complex. Interestingly, metformin treatment in Cr (IV)-exposed neutrophils attenuated heavy metal effect on ROS levels through nuclear factor (erythroid-derived 2)-like 2 (*NFE2L2*) induction, a key transcription factor of antioxidant genes, apoptosis, NETs formation, and protein imbalance [62]. Taken together, O304, a pan-AMPK activator and metformin treatment may benefit restoration of glucose homeostasis and insulin sensitivity in obesity patients after chromatin remodeling by toxicants exposure.

3.3 Pollution impact on ncRNAs

Implementation and integration of omics data, such as epigenomics, transcriptomics, proteomics, and metabolomics, is increasingly used to detect early and subtle molecular responses to environmental compounds. Thus, multi-omics profiles such as, circulating miRNAs, blood DNA methylation marks, gene expression, proteins, urine and serum metabolites, may provide a broad perspective on all cellular activities [63]. Regarding to epigenomics, DNA methylation may be more useful for epidemiological research that compare certain individuals based on a single measurement, whereas ncRNAs profiles may provide more valid information for studies that analyze individual trajectories across time [63]. Despite the importance of epigenetic modifications that occur directly on the DNA strand, noncoding RNAs (ncRNAs) represent a wide and well-orchestrated regulatory mechanism of gene expression. Most (98.5%) of the eukaryotic genome is transcribed into ncRNAs, including microRNAs (21–25 nucleotides in length) and long noncoding RNAs (lncRNA, > 200 nucleotides in length, or lacking an open reading frame of >100 amino acids) [64, 65]. Although miRNAs are supposed to act mainly in the cytosol by inhibiting translation, recent research has shown their location, activity and relevance in the nucleus of cells as direct regulators of cell phenotype [66–69]. MicroRNAs guide Argonaut (Ago) proteins to specific target mRNAs leading to their destabilization or translational repression. The mature miRNA acts to guide not only Ago but also the RNA-induced silencing complex (RISC) ribonucleoprotein complex. On the other hand, lncRNAs are important regulators of different biological processes in the nucleus, such as providing a framework for the assembly of defined chromatin structures at specific loci, thereby modulating gene expression, centromere function, and silencing of DNA repetitive elements [70].

Non-coding RNAs are RNA molecules that are not translated into proteins but that importantly modulate gene expression in specialized cellular processes such as adipogenesis [71]. Several works provide evidence regarding the potential role of microRNAs in metabolic disorders, specifically type 2 diabetes and obesity [71]. For instance, Kunej et al. identified 221 miRNAs to be dysregulated in distinct species. Among them 14 miRNAs, including *let-7a, let-7b*, *let-7c, let-7e, let-7f*, *mir-103*, *mir-10b*, *mir-125a*, *mir-125b*, *mir-143*, *mir-23a*, *mir-23b*, *mir-26a*, and *mir-99b* directly impact fat accumulation in cattle, rats, mice and humans [72]. In humans, diet and lifestyle directly influence the expression of microRNAs such as *miR-17/20/93*, *miR-21/590-5*p, *miR-200b/c*, *miR-221/222*, *let-7/miR-98* and *miR-203* families are the most dysregulated in this setting [73].

ncRNAs have also the potential to mediate the cellular response to environmental toxicants. Environmental stressors or environmental obesogens [74] may be strongly related with obese phenotype by aberrant miRNAs expression [75]. For instance,

phthalates, a class of plasticizers, are widely employed in a variety of everyday items. Recent research implicating butyl benzyl phthalate (BBP) as an obesogen has increased public health concerns [76]. Meruvu et al. demonstrated that the expression of *miR-34a-5p* and its target genes, *NAMPT* and *SIRT1*, is perturbed when developing 3 T3-L1 cells are exposed to varying concentrations of BBP without external adipogenic stimuli [77]. Exposure to BBP increased the expression levels of *miR-34a-5p*, resulting in a reduction in *NAMPT* and *SIRT1* and a subsequent rise in adipogenesis [77]. Moreover, Mcllwraith et al. recently demonstrated that *miR-708-5p* mediates the effects of BPA in hypothalamic cells through the reduction of neuronatin levels and the increase in orexigenic Neuropeptide (Npy) [78]. Contrarily, Rahmani et al. showed revealed that the expression of *miR-375*, *miR-676*, *miR-126-a*, and *miR-340-5p* was significantly disrupted by BPA, resulting in aberrant β-cell metabolism and diabetes [79]. More interestingly, the interplay between environment and gene expression seems to be a coordinated action of different ncRNA biotypes, at least lncRNAs and miRNAs. In the case of chronic exposure of human primary adipocytes from Caucasian females to BPA, but also other structural analogs like bisphenol F (BPF) or S (BPS), long intergenic non-coding RNAs (upregulated *LINC01140* and *LINC01088*, downregulated *LINC01048*), small nucleolar RNAs and miRNAs (*MIR-4655-3p,* upregulated *MIR-30c*, downregulated *MIR-136*) were differentially expressed in a coordinated manner with conventional genes related with adipocyte differentiation (*LPL*, *PLIN1/4*, *ADIPOQ* and *FABP4*) [80].

Not only the direct cell-cell contact is used endogenously to induce tissue-specific responses upon harmful stimuli. The release of extracellular membrane vesicles (EVs) has been on the scope during the recent years as a potential modifiable scenario in terms of pathological tissue reprogramming. DNA, RNA, protein and lipids-containing EVs are released in all body fluids, and importantly, their cargo miRNAs dysregulation can induce phenotypic changes on a distant target tissue. EVs and EV-associated miRNAs (EV-miRNAs), such as *let-7c-5p*, *miR-106a-5p*, *miR-143-3p*, *miR-185-5p*, *miR-218-5p*, *miR-331-3p*, *miR-642-5p*, *miR-652-3p* and *miR-99b-5p* have been considered as mediators of the detrimental effects of PM10 exposure, since their levels are reduced in EVs after short-term exposure and correlate with elevated fibrinogen levels and subsequent cardiac injury [81].

3.4 Impact on genome 3D structure

Recently developed Chromosome Conformation Capture (3C) technology, based on Hi-C, ChIA-PET, and Hi-C capture approaches, have revealed important hints about the role of chromosomal organization and compaction for transcription mechanisms. Precisely large, gene-poor chromosomes are frequently located in the nuclear periphery, whereas small, gene-rich chromosomes are located at the internal side of the nucleus. Chromosomes are divided into A compartments with active chromosome domains, and B compartments with inactive chromosome domains. For example, lamin-associated domains (LADs). These compartments have several topologically associated domains (TADs). TADs are multiple regulatory loops that include DNA sequences exhibiting significantly higher contact frequency with other DNA sequences, among distal enhancers and promoters, within a range from 500 kb to 1 Mb. TADs are mediated by CCCTC-binding factor (CTCF)/cohesin complex. In this case, altered CTCF occupancy is associated with several diseases due to aberrant chromosome looping between distal cis-regulatory elements and their target promoter(s), inducing altered gene expression [82].

Aberrant pancreas and adipose tissue function contributes with metabolic alterations triggering obesity-related diseases as diabetes, and insulin resistance [82, 83]. Gene expression signature in adipocytes is influenced by gene interactions with proximal and distal *cis* regulatory elements, which are mediated by 3D chromosome architecture maintenance in adipose tissue [82]. High-resolution maps of chromatin architecture of porcine livers under a high-fat diet-induced obesity demonstrated changes in genome 3D structure by similarities in Hi-C contact maps, compartmentalization strength, largely conserved TAD boundaries and intra-TAD contact intensities. Also, in terms of metabolic adaptation to excessive energy intake in pigs, even in comparison with variations in liver pig development. Among 160 genes exhibited significant expression changes, 126 was non-alcoholic fatty liver disease-related genes, including *ADIPOQ, CYP2E1, IL6, LEP, TNF*, and target genes of HNF4α and C/EBPα. In addition, it was observed hepatic morphology modifications, increase in lipid accumulation, and serum concentrations of five metabolic indicators (triglyceride (TG), low-density lipoprotein (LDL), high-density lipoprotein (HDL), cholesterol and glucose) which did not have significant changes in livers of pigs fed with HFD compared to pigs fed normal adult diets. These results suggested that pigs resist to 'diabetogenic' environments and increase their tolerance to chronic damage from obesity in the liver [84].

Recently, a research group studied metabolic adaptation to chronic obesity and NAFLD on male C57BL/6 mice with hypercaloric diet. The evaluation of transcriptomic profile showed 2066 genes overregulated in obese animals on the lipid-rich diet, and 1663 genes overregulated on the carbohydrate-rich diet. Interestingly, lipid-rich diet suppresses *de novo* lipogenesis in comparison with a carbohydrate-rich diet. In general, obese animals by lipid-rich diet showed differential expressed genes (DEG) involved in fatty acid metabolism such as type I acyl-CoA thioesterases (*Acot2, Acot3, Acot4, Acot5, Acot6)*, and type II acyl-CoA thioesterases (*Acot7, Acot8, Acot9, Acot13*); beta oxidation of fatty acids like acyl-CoA dehydrogenases (*Acadm*, *Acads*, *Acadvl*), enoyl-CoA hydratase (*Ehhadh*), and hydroxyacyl-CoA dehydrogenase (*Hadh*), as well as mitochondrial carnitine-dependent lipid transporter, *Cpt1.* The evaluation of 3D chromosome architecture revealed that TADs and their boundaries are largely conserved in both diet groups. Furthermore, they identified lipid-rich diet enriched H3K27ac regions that corresponded to known consensus binding sequences for ETS (*ETS1, EHF*), bZIP (*FOSL2, JUN-AP1, and ATF3*), and C/EBP (*C/EBPA, C/EBPB, and C/EBPE*) transcription factors. C/EBP family participates in lipogenesis regulation. Motifs for the bZIP family transcription factors and nuclear receptors (*HNF1, HNF6*) involved in lipid and carbohydrate metabolism regulation for loci were found enriched upon carbohydrate-rich diet. On the other hand, promoter-chromatin interactions evaluation revealed 34,982 significant chromatin interactions in liver from animals on lipid-rich diet, and 37,185 from animals on carbohydrate-rich diet. Notably, they confirmed the association between promoter-interacting regions (PIRs) and H3K27ac enrichment with high gene expression. As a result, they established a promoter-interaction landscape in liver under different dietary regimens in response to obesity and metabolic stress [85].

Glyphosate is a widely used herbicide in agricultural activities. A study made in blood samples from workers exposed occupationally detected concentrations of 0.05–0.5 mM, even in people who was not directly exposed to this herbicide, with concentrations between 0.435 ± 0.167 μM. Peripheral blood mononuclear cells (PBMCs) treated with glyphosate and aminomethylphosphonic acid (AMPA), significantly increased gene expression of *DNMT1* and *DNMT3A*, involved in DNA methylation, as well as *HDAC3*-associated histone deacetylation [86].

Lately, a research group traced the offspring from pregnant mouse females (F0) exposed to BPA via intraperitoneal injection. Curiously, second generation of male and female mice without exposure (BPA-F2) increase their body weight, showed a large accumulation of visceral white adipose tissue, increased number of adipocytes and accumulation of lipid droplets, compared to control F2 animals, but these effects were completely lost in BPA-F7 animals. They performed *in vitro* fertilization confirming that median weight of males and females from the embryo transfer experiment was significantly higher than in controls. In this way, the authors confirmed that the overweight phenotype is due to epigenetic modifications in the germline rather than external factors. Then, they observed a dramatic redistribution of transcription factor (TFs) and increase of interactions in sperm exposed to BPA F1-F3, indicating the formation of new CTCF loops, adjacent to *Steap1* and *Steap4*, genes involved in obesity in humans. Also, among 1327 differential sites, 107 are conserved in germ lines through generations, whereas other sites disappear. 69 BPA-gained sites in distal intergenic regions or introns corresponded to motifs for several TFs such as *Znf143, Foxa1,* and nuclear hormone receptors*,* including *Esr1/2, AR, and Ppar.* In sperm from BPA-F3 males, 1428 hypomethylated regions and 648 hypermethylated regions were identified to persist in a transgenerational manner. Furthermore, these 69 enriched sites interacted with 610 gene promoters and enhancer regions, involved in obesity, corresponding with the enrichment of H3K27ac. These results suggested that BPA, directly or indirectly, promote the binding of CTCF and various transcription factors at genomic sites that are normally methylated. These gene promoters become activated at a higher frequency in exposed sperm BPA. This occurs mainly through interactions between proximal *Fto* enhancer and target promoters including *Rpgrip1l, Irx3, Irx5, Slc6a2, and Mmp2*, known to regulate body size and obesity by affecting appetite and food consumption. According to this meta-analysis, intron 8 of *Fto* gene seems to be an important element responsible for the transgenerational transmission of obesity after BPA exposure. Even though these findings, it is poorly understood if the exposure to other environmental toxicants can lead heritable or reversible modifications in epigenetic landscape that modify gene expression contributing with obesity or other pathologies.

4. Organic interplay between pollution and obesity

4.1 Digestive systems

Pollutants that enter the body through the oral route first affect the digestive tract and then, when they reach the systemic circulation, the rest of the body's homeostasis [87, 88]. The World Health Organization (2022) states that the contamination of food and drinking water by chemicals from the environment represents a threat to human health [89]. These chemical compounds belong to the groups of polycyclic aromatic hydrocarbons (PAHs), metals and metalloids, perfluorinated compounds (PFCs), persistent organic pollutants (POPs), and consumer products [90]. These compounds may disturb digestive tract and its normal functioning by affecting the normal microbiota (**Figure 3**).

The microbiota is the set of microorganisms hosted in a specific niche [91]. The human intestinal microbiota is made up of 1014 microorganisms that include bacteria, viruses, archaea and fungi. Intestinal bacteria in healthy individuals are made up of four phyla *Proteobacteria, Actinobacteria, Bacteroidetes* and *Firmicutes*. The

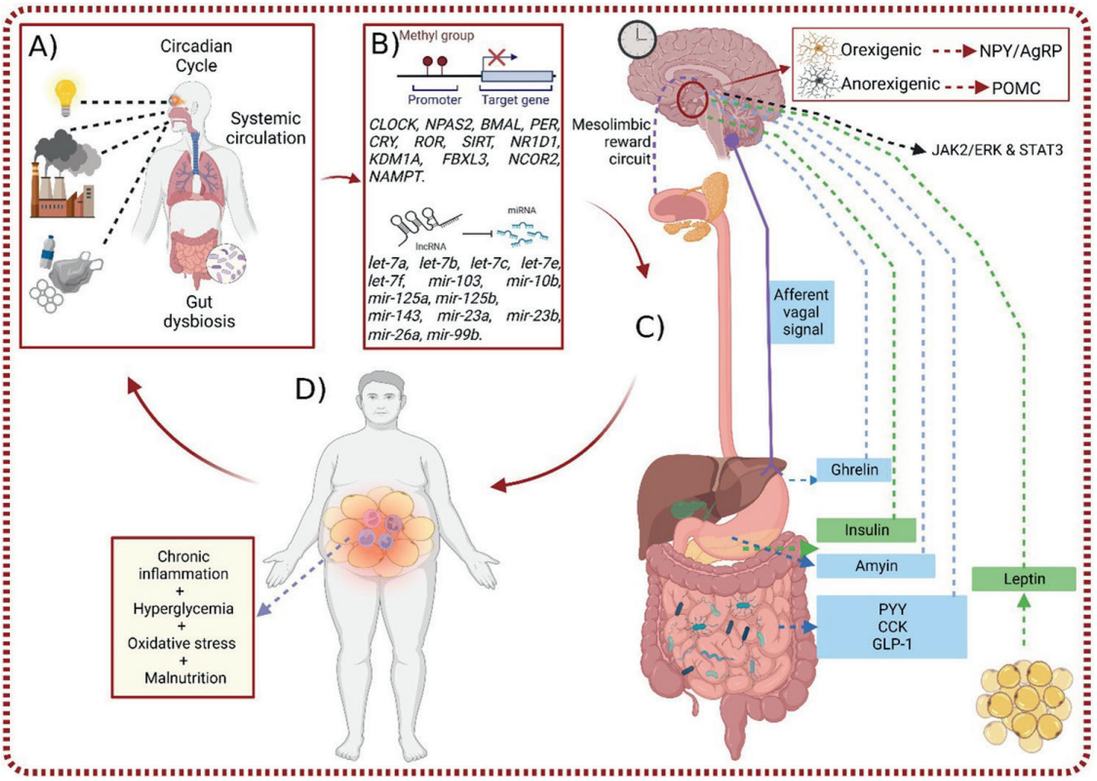

Figure 3.
Functional interaction between pollution, epigenetics and obesity. (A) Environmental contaminants such as PAHs, BPA, PFCs, POPs, light, particulate matter, among others, enter the body through respiratory, oral and ocular routes. (B) At the cellular level, pollutants cause changes in epigenetic landscapes that affect the expression profile of genes encoding proteins involved in energy homeostasis and obesity. (C) The above events alter the dynamic (blue) and static (green) signals of the hunger-satiation circuit in the neuroendocrine axis. In addition, they cause intestinal dysbiosis and, in cases of light pollution, alteration of the circadian cycle. (D) Endocrine disruption impacts metabolic pathways, mainly accelerating lipogenesis, which causes adipocyte hypertrophy and hyperplasia, increasing paracrine and endocrine activities driven by the adipose tissue. Therefore, pollution affects body systems through various epigenetic mechanisms that contribute to the global increase in obesity.

colon harbors a high density of the bacterial families *Prevotellaceae, Bacteroidaceae, Lachnospiraceae, Rikenellaceae*, and *Ruminococcaceae* [92, 93]. Intestinal microbiota has metabolic, immunological and trophic functions, fermenting indigestible dietary components, particularly undigested carbohydrates, to generate short-chain fatty acids [94, 95].

A direct relationship has been reported between exposure to fine particulate matter suspended in the air with intestinal dysbiosis and with obesity [96–98], which affects host adiposity through a comprehensive signaling pathways [99]. Environmental pollutants can influence the variety of microbiota, and their metabolites influence the activity of epigenetic enzymes. The mechanisms of action of environmental pollution also include the interaction between different niches of the human microbiota, such as the lung-gut axis [96, 100] (**Figure 3**).

4.2 Neural

Recently, artificial light at night has been suggested as an environmental factor that favors the appearance of obesity. Because most living things have developed circadian rhythms that are in sync with the daily cycle of light and dark, constant exposure to artificial light can disrupt the circadian rhythm and alter the secretion

of various hormones, leading to disease metabolic, including obesity [101, 102]. The circadian rhythm is the internal manifestation of the solar day that allows adaptations to predictable environmental temporal changes. These ~24 h rhythms are controlled by molecular clockwork mechanisms in the hypothalamus that are reset daily to a precise 24 h by exposure to the light–dark cycle [103, 104].

Clock-controlled genes regulate circadian rhythms and the most important ones, as well as their products respectively, include: circadian locomotor kaput cycles (*CLOCK*) and its neuronal paralogous protein with PAS domain 2 (*NPAS2*), nuclear translocator of the brain aryl hydrocarbon receptor and muscle such as Arntl (*BMAL*), dot (*PER*), cryptochrome (*CRY*), retinoic acid-related orphan receptor (*ROR*), sirtuin (*SIRT*), nuclear receptor subfamily 1 group D member 1 (*NR1D1* or *REV -ERBα*), lysine-specific demethylase 1A (*KDM1A*), histone deacetylases (*HDACs*), ubiquitin ligases, F-box and leucine-rich protein repeat 3 (*FBXL3*), corepressor of nuclear receptor 2 (*NCOR2*), and nicotinamide phosphoribosyltransferase (*NAMPT*). These participate in various regulatory circuits designed to maintain the stability of the organism [105, 106].

There are reports describing different nutritional and environmental factors, including obesity, which can affect the DNA methylation pattern of clock genes that regulate the circadian rhythm in the hypothalamus and peripheral tissues. Insufficient sleep (short-term sleep or insomnia) has also been reported to be associated with loss of DNA methylation, which could be associated with alterations in pathways related to neuroplasticity, neurodegeneration, and cardiometabolic condition [107, 108].

Another neurological pathway of interest is the mesolimbic reward system. In this dopamine (DA) regulates pathological food intake. DA, which is synthesized from the amino acid tyrosine, exerts widespread effects both in neuronal tissues, as a neurotransmitter, and also in non-neuronal tissues as an autocrine or paracrine agent [109]. Dopamine reaches 80% of the total catecholamine levels in the mammalian brain. There are many subtypes of D1 and D2 receptors in the central nervous system; however, both types of dopamine receptors are implicated in neurobiological and behavioral disorders. There is evidence that food cues increase extracellular DA of the striatum. Therefore, dopamine plays a role in the non-hedonic motivational properties of food [110, 111]. Moreover, dopamine is suggested to encode the stimulatory properties of foods. The basis for this notion is that dopamine depletion or dopamine receptor blockade does not decrease pleasurable responses to palatable foods in animals or humans. People with obesity have been reported to have decreased levels of dopamine D2 receptors in the striatum, like observations in subjects with addictions. Dopamine deficiency can promote compensatory pathological eating to activate reward circuits [110, 112]. For instance, in 2013 it was suggested that epigenetic changes in adolescents contribute to long-lasting neurobiological consequences associated with early administration of ethanol (found in gasoline and adulterated alcoholic beverages) by causing brain region-specific changes in dopamine signaling [110].

4.3 Endocrine

The increased global prevalence of obesity is related with the use of industrial chemicals, and along the broad spectrum of these obesogenic elements, the endocrine disrupting compounds (EDCs) comprise up a sizable fraction [113]. EDCs were defined by the U.S. Environmental Protection Agency (EPA) as exogenous substances that disrupt the body's normal production, secretion, transport, metabolism, binding action, or elimination of blood-borne hormones that are necessary for homeostasis, reproduction, and developmental processes. Therefore, anormal exposure to EDCs,

either natural or synthetic, impacts the hormonal and homeostatic systems which provide the organism the capacity to interact with its surroundings [114].

Several studies have considered dichlorodiphenyltrichloroethane (DDT) [115, 116] tributyltin (TBT) [117], diethylstilbestrol (DES) [118], perfluorooctanoic acid (PFOA) [119], and plastic derived like bisphenol-A (BPA), bis(2-ethylhexyl)phthalate (DEHP) and dibutyl phthalate (DBP) among others as EDCs [120]. Most of DES are molecular analogues of natural estrogens, having a high affinity for estrogenic and androgenic receptors (ERs). Additionally, it is currently known that the hypothalamus-pituitary gland-gonads (HPG), hypothalamus-pituitary gland-thyroid (HPT), and hypothalamus-pituitary gland-adrenal (HPA) are the principal EDC targets [121–123]. Hence, endocrine disruptors impair the endocrine and reproductive systems through a few mechanisms contributing to the global rise in diseases such as cancer, diabetes, neurological disorders and obesity [124–127].

Several works indicate that epigenetic alterations serve as a bridge between the harmful effects of EDCs and the onset of obesity in vulnerable individuals and during crucial developmental stages, starting from fetal life through infancy and puberty, even in pregnancy [28]. In this manner, and because of tissue accumulation and binding to hormone receptors, EDCs disrupt normal metabolic mechanisms altering adipose cells phenotype (increasing number and size) and adipocytokine (molecules primarily secreted by WA that function with paracrine and endocrine activity) production, therefore reducing basal metabolic rate and altering the control of satiety [122].

BPA is very used in industry for polycarbonate and plastics manufacturing, so it is one of the most studied EDC in both, *in vitro* and *in vivo* models [128]. By using a mouse BPA exposure model, it has been suggested that long-term BPA exposure increases lipid (including cholesterol) synthesis, improving hepatic lipid accumulation due to an hypomethylation over *Srebf1* and *Srebf2* [129]. These genes enhance its expression in early life comparable with aging animals, contributing to the early onset of metabolic disorders [129] like insulin resistance [130] linked to a reduction in adipokines (i.e., *ADIPOQ*, *FABP4*) [131] and adiponectin secretion and an elevated *resistin* expression [132]. Moreover, BPA can reduce global hepatic DNA methylation by a reduced activity of DNMTs as suggested by others [133]. Conversely, some other authors indicate that, although BPA can disturb lipid accumulation, it cannot affect adiponectin and leptin secretion [134], thus, the effects of BFA on endocrine systems require further investigations.

In addition, to elucidate how epigenetic mechanisms may explain the onset of obesity, to study the possible transgenerational actions of relevant EDCs has taken importance in last years. For example, the insecticide DDT has been used in rats to demonstrate that subsequent generations (F0: rats exposed to DDT & F3: great grand-offspring) can promote the obese phenotype (high body weight and abdominal adiposity) without a direct exposure, mainly in a critical gestating period [135]. As authors mentioned, this hereditary disease could be related with low CpG sites identified in F3 generation sperm compared with non-exposed male rats [135]. CpG demethylation characterize *leptin* promoter region and is highly expressed in differentiated adipocytes [136]. Obesity is followed by an increase in leptin secretion, modifying the action of leptin through the leptin receptor (LEPR) to reduce hunger by activating neurons that contain proopiomelanocortin (POMC) [137], which promoter has shown hypermethylation associated with 1) weight regain after dietary treatment [138] and 2) a high BMI [139].

4.4 Reproductive

Ovarian steroidal hormones control endometrial decidualization as a prerequisite for implantation during menstrual cycle trough epigenetic regulation. Bisphenol A (BPA) is a biologically compound active due to its property to bind directly with hormone receptors. BPA induce aberrant processes involved in reproduction and cells development at low concentrations. It is known that BPA has short lifespan within the organism, however, endometrial cells can retain BPA. Precisely, BPA-treated stromal cells reduced decidualization-related genes *PRL*, *IGFBP*-1 and *HOXA10*, related to a decrease of histone-3, lysine-4 trimethylation (H3K4me3) and an increase of histone-3, lysine-27 trimethylation (H3K27me3) in promoter regions. This effect was consisted with higher levels of *MLL1* and *EZH2*, histone methyltransferases responsible for the above histone modifications. These results suggested the epigenetic changes induced by BPA exposure impairing stromal cell decidualization, consequent embryo implantation failure and infertility [140]. Complementary studies demonstrated in human adipose tissue the enrichment of H3K4me3 histone mark in adipogenic, lipid metabolism and inflammatory promoter genes (*E2F1*, *LPL*, *SREBF2*, *SCD1*, *PPARG* and *IL6-IL9*) associated with Body Mass Index (BMI) and insulin resistance in morbid obese subjects with prediabetes compared to lean subjects [141]. Based on these findings, pollutants could induce metabolic deterioration by histone remodeling.

Bisphenol A (BPA) is widely used for polycarbonate plastics and resins production. Also, BPA is an agonist that binds with nuclear hormonal receptors causing endocrine disruption. Among BPA exposure consequences in female reproduction system are aberrant hypothalamic–pituitary hormonal production, oocyte quality reduction, defective uterine receptivity, polycystic ovary syndrome, premature puberty, and endometriosis development [142]. Di-(2-ethylhexyl) phthalate (DEHP) exposure affect male reproductive organ function and obesity triggering male secondary hypogonadism in High fat diet (HFD) mice due to oxidative stress induction [143].

A cohort study in women exposed to particulate matter with a diameter less than 2.5 μm (PM2.5, 13.4 μg/m3), black carbon (1.29 μg/m3), and nitrogen dioxide (17.98 μg/m3) during entire pregnancy demonstrated a positive correlation with cord blood histone H3 lysine 4 trimethylation (H3K4me3) levels. Precisely, this effect was significant after long exposure for black carbon and nitrogen dioxide, whereas cord blood histone H3 lysine 36 trimethylation (H3K36me3) levels inversely correlated in entire pregnancy, only for PM2.5 exposure [144]. In this regard, it is necessary to specify associated pathways to these histone modifications as potential markers for effective evaluation or even diagnosis in pregnant women in environmental risk zones.

Recent works have focused in elucidate ancestral environmental exposure on transgenerational epigenetic reprogramming of adipocytes. The methylation profile analysis in F3 generation of rats ancestrally exposed to DDT and atrazine demonstrated differential methylation regions (DMR) in 73% of genes (492/674), which corresponded between DDT obese male and atrazine lean male. The metabolic pathways related to these epigenetic changes was insulin signaling, adipogenesis, adipocyte browning, insulin resistance, and lipolysis. The adipocyte and metabolic genes in common between control and treatments were *Caln1, Ikzf1, Iqsec3, Kcnma1, Ksr2, Mychp2, Myo16, Negr1, Nr1h5, Rbms3*, highly associated with obesity, type 2 diabetes, and metabolic syndrome predisposition. These results revealed that epigenetic alterations promoting by pollution contribute with obesity pathogenesis and metabolic diseases [145].

4.5 Immune

The fully functional immune system integrates organs, cells, pathways, and molecules in such an interconnected, sometimes circular, process that they often act synergistically to defend us from both internal and external aggressions [146]. When we refer to obesity and adverse environmental stimuli, such as pollution, from the immunological perspective we land in a crucial cellular process, inflammation. This process is promoted in the host through epigenetic alterations that mostly involve DNA methylation modifications [147]. Inflammation caused by adipose tissue in obese patients contributes to pathological conditions such as Diabetes Mellitus II (DM2) [148]. Recent studies have attempted to elucidate the specific role of B cells in obese patients after contrasting them with those in obese diabetic patients. Remarkably, the secretion of IL-6 and TNF-a increased in both groups, while a defect in the up-regulation of *IL-10* as well as higher concentrations of IgM and IgG was detected in obese diabetic subjects, in addition to poor response to stimulation with new antigens through vaccination against influenza [149]. This is extremely important as it shows the "snowball" effect in patients with these characteristics.

Adipose tissue is an immunologically active organ which contributes to systemic inflammation, especially the so-called white adipose tissue (WAT) in which subjects with obesity show phenotypic changes, due to inflammation, adipocyte dysfunctionality and infiltration of immune cells in vascular stromal fraction [150]. Furthermore, obesity involves chronic activation of the innate immune system and consequent local and systemic inflammation, activation of TP53 [151] and telomere shortening, a phenotype similar to aging [152]. In addition, an excess of fat mass is associated with several respiratory pathological conditions, such as asthma, obstructive sleep apnea, and chronic obstructive pulmonary disease [153]. It was recently found that obesity may be one of the missing pieces between pollution and severe clinical presentation in patients diagnosed with COVID-19 [154], representing another example of an additive action with environmental factors.

Air pollution exposure has been shown to increase the risk of obesity and metabolic dysfunctions in animal models and human studies [155]. An important finding is that higher exposure to near-roadway air pollution (NRAP), especially off-highway NRAP, was associated with higher concentrations of glycerol and metabolites related to oxidation of non-esterified fatty acids (NEFA). Besides this fact, plasma levels of NEFA and its oxidation by-products are associated with increased adiposity and insulin resistance. However, the association between air pollution exposure and serum NEFA concentration was not statistically significant, suggesting that the young population may still have adequate mitochondrial capacity to compensate environmental stressors [155]. In this line, NRAP exposure can stimulate pulmonary and systemic inflammation through activation of immunomodulatory receptors, such as Toll-like receptors (TLRs) [155].

5. Current and future epidrugs against environmental-pollution effects

Several studies support that aberrant epigenetic mechanisms are strongly related with human diseases, mainly by affecting protein expression and therefore the functionality of proteins that determine, in part, the epigenetic signature of diet-related diseases such as obesity [156]. Some of the most deregulated proteins are those encoded by leptin (*LEP*), melanocortin 4 receptor (*MC4R*), proopiomelanocortin (*POMC*) and insulin-like growth factor 2 (*IGF2*), as some causal genes for obesity due

to epimutations. For instance, studies made in children and adults described a relationship between *POMC* intron hypermethylation (key element for food intake and energy balance regulation) and obesity. In addition, *IGF2* hypomethylation associates with higher BMI which also negatively correlates with specific lncRNAs levels like *lncRNA-p5549* and *lncRNA-p21015* [157].

It is necessary to remark that alterations in epigenetic landscapes are consequences of environmental factors like pharmacologicals, unhealthy habits, diet, and exposure to chemical stressors [157]. Certain exposure concentrations to chemical stressors or pollutants such as heavy metals, air pollution (PAHs, PM2.5, NO2) and EDCs during prenatal period are strongly related with high risk to overweight and obesity in childhood [158]. Metabolic disorders are also due to inflammatory responses characterized by immune cells infiltration promoted by pro-inflammatory cytokine release (i.e., TNF, IL-6, IL-1β, CCR2 and CCL2) [159]. The expression of inflammatory cytokines is also regulated by epigenomic regulators as in the case of CCL2 (CC chemokine ligand), which secretion is regulated by miRNAs in both positively (*miR-145*) and negatively (*miR-26a, miR – 92a, miR – 126, miR – 143, miR – 193a/b, miR – 652,* and miR*let-7a/d*) manners [159].

As mentioned, the diet is a pivotal factor for epigenetic reprogramming, thus, a healthy early-life dietary nutrition is crucial for the correct human developmental fate. Some bioactive dietary compounds largely studied in epigenetics are polyphenols and vitamins, also considered as phytochemicals, found in fruits, spices, teas and vegetables (**Figure 4**). They have been shown to have protective functions leading to

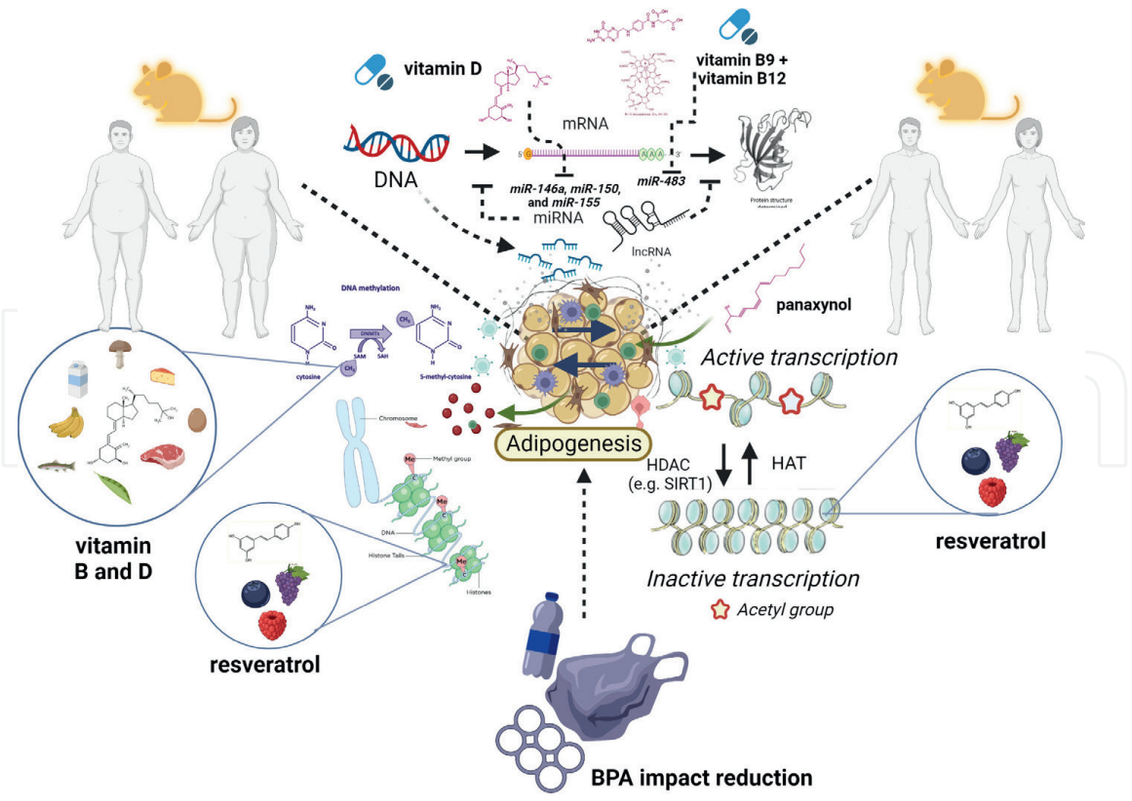

Figure 4.
Epidrugs (e.g., resveratrol, vitamin B and D, panaxinol) modulate adipogenesis preventing or attenuating obesity induced by pollutants. DNA: Desoxirribonucleic acid, SAM: S-adenosyl-methionine HDAC: Histone deacetylase, HAT: Histone acetylase, red dots: Adiponectin, vitamin D: Vitamin-D2 and -D3, 1α, 25-dihydroxyvitamin D3(1,25(OH)$_2$D3, bioactive form, calcitriol, vitamin B9: Folate and vitamin B12:Cobalamin.

healthy outcomes against to pollution-related diseases [160, 161]. Resveratrol (RSV) is a polyphenolic compound with anti-inflammatory, antioxidant and anticancer properties through DNA methylation and histone deacetylation modulation. In contrast, vitamin D has effects at DNA demethylation and histone acetylation levels promoting antitumoral processes [162]. Moreover, B vitamins are classified as methyl group donors, acting as precursors of SAM, therefore, when are included in diet they can counteract hypomethylation caused by BPA and diminish aberrant epigenetic inheritance [162].

Several bioactive dietary agents that potentially reverse epimutations and prevent or delay obesity, are of interest in the field of biomedicine because they can be propose as *epi-drugs* [163]. Due to their effects in modulating epigenetic mechanisms in human diseases, phytochemicals downregulate adipogenesis and upregulate fat oxidation preventing weight gain. For instance, resveratrol, which is found in plants, peanuts, berries, and grapes, can inhibit DNMTs activity and alter histone post-translational modifications by SIRT1 (HDAC Class III) activation [163]. In addition, it has been shown that resveratrol avoids adipocyte proliferation and preadipocyte differentiation through adipocyte-specific genes downregulation (*PPARγ*, *SREBP-1c*, *C/EBPa*, hormone-sensitive lipase, and lipoprotein lipase-*LPL*) in 3 T3-L1 adipocytes [164].

To ameliorate or to revert adipocyte differentiation could be an efficient therapy to inhibit the early onset of obesity-related diseases. In this sense, adiponectin, mainly secreted by white adipose tissue, has been proposed as a therapeutic target due to their crucial role in adipogenesis [165]. Adiponectin is secreted into the bloodstream as three oligomeric complexes, a trimer (67 kDa), a hexamer (140 kDa) and a high molecular weight (HMW, 300 kDa) formed by two trimers modified by hydroxylation and glycosylation, important for its metabolic-related downstream signaling functions [161]. A high circulating adiponectin expression protects against insulin resistance, alleviates lipotoxicity of lipid accumulation and it is associated with reduced age-related tissue inflammation [166], effects that are enhanced by peroxisome proliferator-activated receptor-γ PPARγ trough up-regulating *RUVBL2* (molecular chaperone for vesicle transport) expression as shown in 3 T3-L1 cells [167]. As mentioned, downregulation of *PPARγ* could diminish adipocyte differentiation, therefore it is crucial to identify effective agonists functioning as epidrugs that potentiate circulating adiponectin levels, such as panaxynol, isolated from *Saposhnikovia divaricata*, that can restore HMW adiponectin secretion affected by palmitic acid [168].

Nutriepigenomics is a promising field because gives important clinical information about certain ways to use phytochemichals and vitamins or to improve nano-engineering (vitamin formulations) as possible epidrugs to counteract the detrimental effects of environmental pollutants exposure (**Figure 4**) [169]. For this purpose, understanding the molecular mechanisms of vitamin-mediated epigenetic regulation by analyzing epidemiological, observational, *in vivo* and *in vitro* studies is crucial to identify effective bioactive compounds for human diseases treatments [170]. Vitamin D (VD) is a type of secosterol produced endogenously in the skin and obtained by diet, exists in two forms vitamin-D2 and -D3 and the bioactive form is 1α, 25-dihydroxyvitamin D3(1,25$(OH)_2$D3, calcitriol) involved in DNA methylation, in histone modifications and in miRNAs regulation [171]. Studies in mice have shown that a deficiency of maternal VD increases WA inflammatory responses in adults [172], thus, VD intake can limit inflammation and leukocyte infiltration by decreasing *miR-146a*, *miR-150*, and *miR-155* after a high fat (HF) diet supplemented with VD [173]. Additionally, combination of vitamins intake in defined doses could have

greater benefits as epidrugs compared with single intake, since an adequate dietary of both vitamin B9 (folate) and vitamin B12 (cobalamin) may protect against metabolic imbalance [174]. As seen in female mice after fed them with both vitamins, expressed significant lower *miR-483* levels compared with mice fed with an altered dietary ratio, a high *miR-483* is linked to insulin resistance and DMT2 by impair lipid storage in adipose tissue [174]. Finally, both vitamins and phytochemicals (specially polyphenols) are now attracting the attention as the most promising bioactive compounds for a preventive anti-obesity and obese-related diseases therapy [160].

6. Conclusions and perspectives

"Globesity" has become a pandemic in the last years, adding a significant burden on the global health system. Although heritability of the disease is high and ethnicity-dependent, identified genetic variants associated with obesity represent a very small percentage of phenotypic variation. In recent years, epigenetic studies intend a deeper understanding of the molecular basis underlying the dramatic increase in global obesity rates. Existing evidence indicates that even environmental exposures induce alterations in the epigenome, leading to the transmission of obesity propensity across generations. In this chapter we have synthesized the effect of different pollution sources on epigenetic modulators. Therefore, as our understanding of epigenetics continues to advance, as do experimental approaches and sequencing techniques (already at the level of three-dimensional characterization of chromatin structure), biochemical and structural studies will become more imperative for unraveling novel catalytic-dependent and catalytic-independent functions of epigenetic regulators that together coordinate their actions on to induce diseases transcriptional landscapes.

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