Review article

Epigenetic processing in cardiometabolic disease

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HIGHLIGHTS

- Epigenetic modifications are emerging as potent modulators of gene activity.
- Epigenetic networks derail transcriptional programs involved in cardiometabolic features.
- Epigenetic signals acquired during life are heritable and may foster early cardiometabolic traits in the offspring.
- Unveiling the epigenetic landscape in obesity and type 2 diabetes may furnish new diagnostic and therapeutic tools.

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ABSTRACT

Albeit a consistent body of evidence supports the notion that genes influence cardiometabolic features and outcomes, the "non-genetic regulation" of this process is gaining increasing attention. Plastic chemical changes of DNA/histone complexes – known as epigenetic changes – critically determine gene activity by rapidly modifying chromatin accessibility to transcription factors. In this review, we describe the emerging role of chromatin modifications as fine tuners of gene transcription in adipogenesis, insulin resistance, macrophage polarization, immuno-metabolism, endothelial dysfunction and metabolic cardiomyopathy. Epigenetic processing participates in the dynamic interplay among different organs in the cardiometabolic patient. DNA methylation and post-translational histone modifications in both visceral and subcutaneous adipose tissue enable the transcription of genes implicated in lipo- and adipogenesis, inflammation and insulin resistance. Along the same line, complex networks of chromatin modifying enzymes are responsible for impaired nitric oxide bioavailability and defective insulin signalling in the vasculature, thus leading to reduced capillary recruitment and insulin delivery in the liver, skeletal muscle and adipose tissue. Furthermore, changes in methylation status of *IL-4*, *IFN*γ and Forkhead box P3 (*Foxp3*) gene loci are crucial for the polarization of immune cells, thus leading to adipose tissue inflammation and atherosclerosis. Cell-specific epigenetic information could advance our understanding of cardiometabolic processes, thus leading to individualized risk assessment and personalized therapeutic approaches in patients with cardiometabolic disturbances. The development of new chromatin modifying drugs indicates that targeting epigenetic changes is a promising approach to reduce the burden of cardiovascular disease in this setting.

1. Metabolic disturbances and cardiovascular risk

Prevalence of obesity and type 2 diabetes (T2D) is skyrocketing across the globe and, most importantly, the number of affected people continues to climb, also among children [1–3]. This scenario mostly results from the adoption of poor lifestyle habits as well as exposure to an array of environmental factors (intrauterine milieu, pollution, cigarette smoking, urban noise) over the course of life [4]. The *International Diabetes Federation* has recently estimated that almost 500 million people will be obese by the year 2040, whereas 1.1 billion will be overweight [1]. Increased body weight and visceral adiposity cluster in most cases with several cardiovascular (CV) risk factors, namely arterial hypertension, insulin resistance, low-grade inflammation, and dyslipidaemia, all conditions which contribute to amplify morbidity and mortality in these patients [3,5]. Most importantly, overweight and obesity are potent predictors of incident T2D [6]. The progression from prediabetes to T2D occurs along a "continuum", not necessarily linear with time, and leads to different intermediate dysmetabolic phenotypes

and increased risk of atherosclerotic vascular disease. High insulin and glucose concentrations among obese patients associate with increased CV risk, regardless of diabetes [7]. A pooled analysis of 65 trials showed that the Homeostasis Model Assessment IR (HOMA-IR), an index which incorporates both glucose and insulin concentrations, is strongly associated to CVD risk as well as to post-procedural myocardial injury and clinical outcome after a percutaneous revascularization with drug-eluting stents [8,9]. Along the same line, high waist circumference values, a hallmark of visceral adiposity, are associated with an adjusted relative risk of 29% for CV death, 27% for myocardial infarction, and 35% for total mortality [10]. Moreover, the combination of hyperglycemia and insulin resistance has shown to exert a detrimental, synergic effect [11]. This concept is also outlined by the notion that patients with the combination of T2D and visceral obesity display worse myocardial function than patients having T2D or obesity alone [12]. A better understanding of the intersection between maladaptive metabolic processes and CVD is of paramount importance for the unveiling of new molecular targets and therapies to fight cardiometabolic diseases.

2. Environment and the epigenetic landscape

Albeit a consistent body of evidence supports the notion that genes influence cardiometabolic features and outcomes, the "non-genetic regulation" of this process is gaining increasing attention [13]. The advent of new technologies for the study of chromatin has led to the identification of additional biological layers which regulate gene expression regardless of our genetic background. Plastic chemical changes of DNA/histone complexes – known as epigenetic changes or (epi) mutations – critically determine gene activity by rapidly modifying chromatin accessibility to transcription factors. Such epigenetic tags – which do not alter DNA sequence – have the ability to license regions of the genome for expression while shutting down others [14]. In other words, our genetic code can be imagined as the "music sheet", while epigenetics is the orchestra director who decides "how" and "when" to play that given music. Several lines of evidence suggest the essential role of epigenetics in determining phenotypic and behavioural changes. Genetically identical twins who are raised under different environmental conditions have different lifespans or different risk of developing diabetes or hypertension [15,16]. Along the same line, caloric restriction has shown to delay age-dependent onset of diseases mostly via an epigenetic reprogramming, suggesting that environmentally-driven epigenetic signals may heavily affect gene expression trajectories during life [17].

Epigenetic changes can be classified into three main categories: i) DNA methylation; ii) post-translational histone modifications; iii) non-coding RNA (ncRNA) [14]. Methylation of DNA – where a methyl group is added to the carbon-5 position in the CpG dinucleotide sequences – represses gene activity by preventing the binding of transcription factors to gene promoters or by favoring the recruitment of chromatin modifying enzymes [18]. The process of DNA methylation is catalyzed by three different DNA methyltransferases (DNMTs): DNMT1, which maintains methylation status during replication, as well as DNMT3a and DNMT3b, involved in *de novo* methylation [19]. Together with DNA-related changes, posttranslational modifications of histones - which include methylation, acetylation, ubiquitination and phosphorylation - may cluster in different patterns to regulate chromatin architecture [20]. Unlike DNA methylation, the impact of histone modifications on gene expression may vary depending on the specific chemical modification [21]. For example, lysine mono-methylation of histones generally enables gene transcription while di- or tri-methylation while di- or trimethylation can either enhance gene transcription (e.g. H3K4me3) or induce gene silencing (e.g. H3K9me3) [22]. Different chemical modifications on histones tails are operated by different families of enzymes. Acetylation is modulated by histone acetyltransferases (HATs) and histone deacetylases (HDACs), whereas histone

methylation is mediated by different methyltransferases (HTMs) and demethylases (HDMs) [23]. Non-coding RNAs - including microRNAs (miRNAs) and long non-coding RNAs (lncRNAs) - do not directly affect chromatin architecture but play an essential role in post-transcriptional regulation of gene expression [24]. Interestingly, the non-coding genome strictly cooperates with both methyl- or acetyl-writing and erasing enzymes (i.e. HDACs) to edit chromatin conformation and gene activity [25]. MicroRNAs have shown to regulate the expression of chromatin modifying enzymes as well as enzymes involved in *de novo* promoter methylation (i.e. DNMT3a and DNMT3b). On the other hand, chromatin changes may affect the transcription of non-coding RNAs [26]. This complex and fine-tuned regulation of gene expression is also cell-specific [27]. Different cell types (i.e. adipocytes, endothelial cells, macrophages) may carry different epigenetic information, which is being translated into specific transcriptional programs relevant to cell differentiation, identify and fate. Micro and macro-environmental factors have clearly shown to induce cell-specific changes of the epigenetic landscape [28]. The acquired epigenetic make-up accounts for most of phenotypic alterations of otherwise genetically identical cells [16]. Understanding how environmental signals remodel the cell epigenome is invaluable to prevent hallmarks of cardiometabolic disease such as macrophage polarization, adipose tissue inflammation, insulin resistance as well as liver and cardiac lipotoxic damage. Environmental cues may induce specific changes in nutrition or fluctuations in metabolism which lead to dynamic modifications of chromatin-associated proteins and homeostatic transcriptional responses. Chromatin modifications that occur in response to metabolic signals are dynamic or stable and might even be inherited transgenerationally. Hence, epigenetic processes can be seen as an adaption to the environment. These emerging concepts have biological relevance to tissue homeostasis and may be heavily implicated in the etiological pathway linking environmental factors to cardiometabolic disturbances [29]. The present review will focus on the role of chromatin modifications (DNA/histone complexes) as key drivers of dysmetabolic processes and CVD.

3. Epigenetic plasticity in cardiometabolic traits

3.1. Insulin resistance and adipogenesis

Progressive loss of insulin sensitivity is perhaps one of the most important features observed in the cardiometabolic patient [4]. Recent studies indicate that epigenetic mechanisms may be involved in this phenomenon (Fig. 1). Genome-wide epigenetic analysis in visceral adipose tissue (VAT) from obese patients with and without insulin resistance (IR) revealed important variations in the methylation of CpG sites at the promoter of several genes, namely *COL9A1, COL11A2, CD44, MUC4, ADAM2, IGF2BP1, GATA4, TET1, ZNF714, ADCY9, TBX5,* and *HDACM* [30]. Specifically, the zinc finger protein 714 (*ZNF714*) was found as the gene with the largest methylation fold-change among insulin resistant and insulin sensitive patients. Hypomethylation of *ZNF714* promoter was associated with higher gene expression in insulin resistant patients. Given the key role of zinc finger proteins in adipogenesis, T2D and insulin resistance, these results provide hints on the importance of epigenetic remodelling in the modulation of insulin signalling in VAT [30]. A study comparing adult monozygotic BMI-discordant twin pairs unveiled several differentially methylated genes in subcutaneous adipose tissue (SAT) [31]. Epigenetic signatures in SAT were associated with altered transcription of genes implicated in lipo/adipogenesis, inflammation and extracellular matrix remodelling. Interestingly, methylation of CpG sites in SAT correlated with visceral and liver fat, as well as with IR, dyslipidaemia and low-grade inflammation [31]. DNA methylation in peripheral blood leukocytes was found to correlate with the severity of IR in monozygotic twins [32,33]. Collectively, these data strengthen the notion that epigenetic modifications acquired overtime may account for different "metabolic destinies" in subjects with identical genetic backgrounds [34]. A main question to be
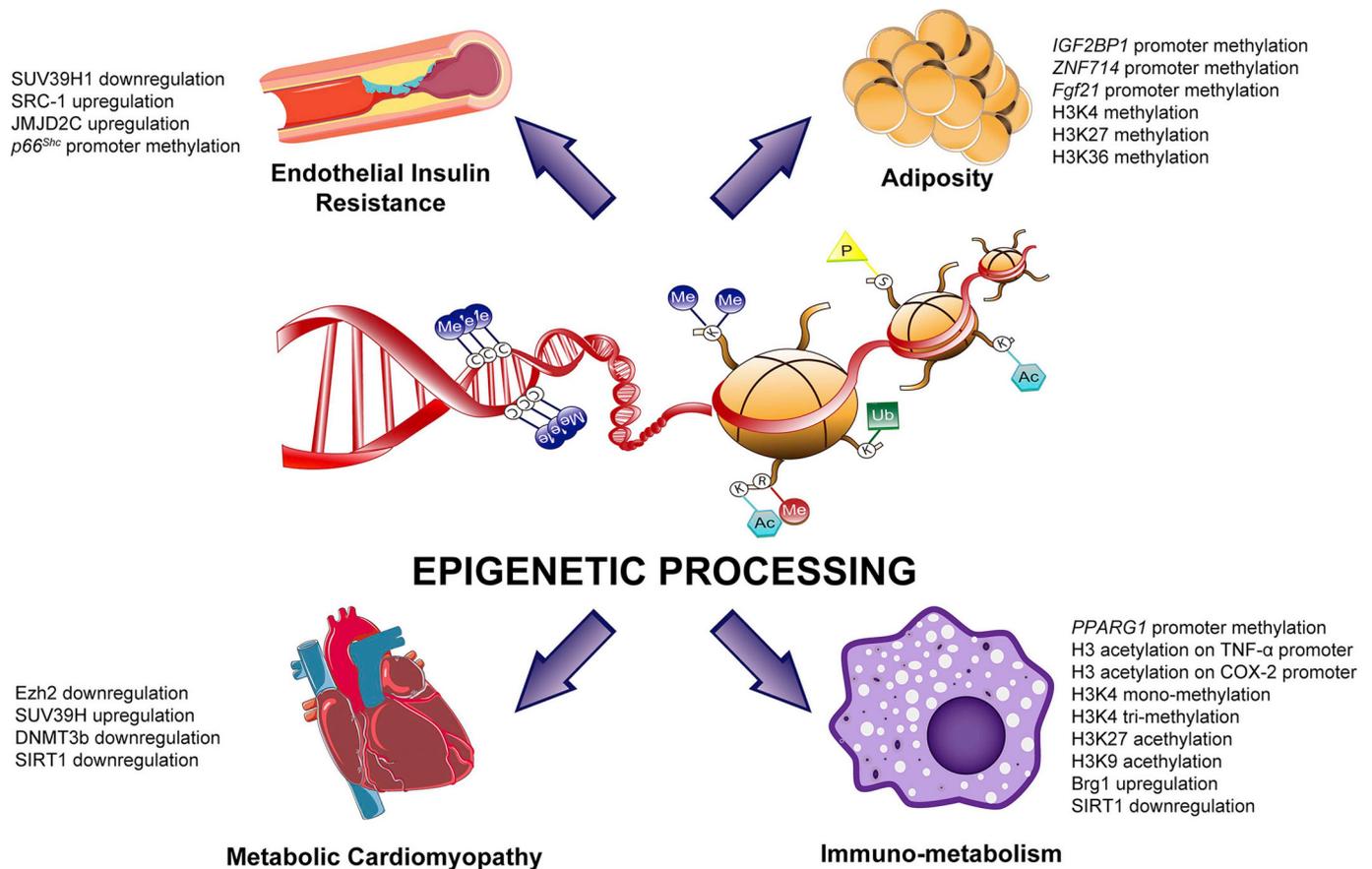
Fig. 1. Epigenetic processing and development of cardiometabolic traits.
H3, histone 3; K, lysine residue.

answered when dealing with epigenetic modifications is whether these changes play a causal role or they just associate with cardiometabolic features. A recent study in cultured human adipocytes showed that DNA methyltransferase 3a (DNMT3a) was both necessary and sufficient to mediate IR by regulating the expression of *Fgf21*. Furthermore, adipose-specific *Dnmt3a* knock-out mice were protected against diet-induced IR without accompanying changes in adiposity [35]. Plastic chromatin changes, namely methylation of histone 3 at lysine 4 (H3K4) and lysine 27 (H3K27) residues, are also strongly involved in adipogenesis [36]. PTIP, a protein that associates with H3K4 methyltransferases MLL3/MLL4 and histone H3K27 demethylase UTX, is required for PPARγ-induced adipogenesis [37]. In another study, the H3K27 methyltransferase PRC2 was found to promote adipogenesis by repressing Wnt signalling [38]. Depletion of histone H3K36 methylation in pre-adipocytes was also shown to inhibit adipogenesis by repressing C/EBPα and other PPARγ targets [39]. Hence, site-specific histone methylation is an emerging mechanism regulating adipogenesis. Editing histone marks by selective targeting of methyl-writing and methyl-erasing enzymes may represent a future approach to prevent SAT and VAT accumulation and IR.

3.2. Endothelial insulin signalling and vascular dysfunction

An increasing body of evidence indicates that loss of insulin signalling in the vascular endothelium plays a key role in the pathogenesis of cardiometabolic disturbances [40]. $ApoE^{-/-}$ mice with endothelium-specific IR show defective nitric oxide (NO)-dependent vasorelaxation and atherosclerotic lesions [41]. Even more interestingly, mice with endothelium-specific suppression of NF-κB (*E-DNIκB*) are protected against IR in other insulin-sensitive organs, namely adipose tissue and skeletal muscle. *E-DNIκB* showed reduced adipose tissue

inflammation as well as increased blood flow and mitochondrial content in skeletal muscle [42]. Of clinical relevance, insulin response and subsequent eNOS activation are blunted in freshly isolated endothelial cells from patients with T2D as compared to non-diabetic controls. Inhibition of protein kinase beta (PKCβ) with LY379196 improved insulin-mediated eNOS activation by suppressing NF-κB signalling in T2D patients [43]. Taken together, these findings suggest that endothelial IR may be an upstream event leading to systemic impairment of insulin sensitivity, thus overturning the so called "adipocentric paradigm" according to which adipocyte-derived inflammation is the first event triggering IR and obesity. We and others have recently demonstrated that epigenetic remodelling of pro-oxidant and pro-inflammatory genes participates to endothelial IR and vascular dysfunction. Specifically, we found that the mitochondrial adaptor p66^{Shc} is significantly upregulated in visceral fat arteries isolated from obese patients, and correlates with oxidative stress, endothelial dysfunction and IR, as assessed by HOMA-IR [44]. Unbiased gene profiling and chromatin immunoprecipitation experiments showed that a complex network of chromatin remodelers, namely the methyltransferase SUV39H1, the demethylase JMJD2C and the acetyltransferase SRC-1, regulates p66^{Shc} transcription by inducing both demethylation and acetylation of H3K9. Selective targeting of SUV39H1, JMJD2C and SRC-1 restored endothelial NO levels and rescued obesity-induced endothelial dysfunction in genetically-obese mice [44]. Consistent with these findings, we also reported that *in vivo* gene silencing of p66^{Shc} restored endothelial insulin response by affecting the IRS-1/Akt/eNOS and NF-kB pathways [45]. Collectively, our results show that epigenetic editing of p66^{Shc} promoter may contribute to the pathogenesis of endothelial IR and increased vascular risk in the context of obesity and T2D. Although potentially reversible, epigenetic modifications are rather stable and long-lasting despite corrections of the underlying risk factors. El-Osta

et al. were among the first to show that transient high glucose causes persistent epigenetic changes and altered gene expression during subsequent normoglycemia in human endothelial cells [46]. Specifically, hyperglycemic spikes lead to the activation of the methyltransferase SETD7, which induces a mono-methylation of H3K4 on the promoter of genes implicated on endothelial dysfunction and vascular inflammation [46,47]. More recently, epigenomic profiling revealed persistent DNA methylation changes despite intensive glycemic control in the DCCT/EDIC type 1 diabetes cohort, thus supporting the existence of a metabolic memory [48]. Along the same line, we showed that intensive glycemic control was not able to revert *p66^{Shc}*-related epigenetic changes in peripheral blood monocytes from T2D patients, thus explaining persistent endothelial dysfunction and oxidative stress [49]. Emerging evidence indicates that advanced glycation end products (AGEs) may contribute to affect chromatin accessibility, thus leading to persistent epigenetic signatures in the vascular endothelium, despite normalization of glucose levels [50].

3.3. Inflammation and immuno-metabolism

Burgeoning evidence supports the notion that epigenetics significantly impact inflammatory routes in patients with obesity and diabetes. Epigenetic modulation of inflammation may occur at several levels, although the most prominent effects are observed in macrophages, liver, immune and vascular cells. Increased levels of saturated fatty acids, a hallmark of obesity, lead to upregulation of the DNA methyltransferase DNMT3b in macrophages, thus fostering M1 polarization and adipose tissue inflammation. Targeting DNMT3b decreased inflammation and restored insulin sensitivity in adipocytes [51]. Along the same line, inhibition of DNA methylation by myeloid deletion of DNMT1 prevented obesity-induced macrophage polarization, inflammation and insulin resistance by epigenetic regulation of the PPARγ1 promoter [52]. Acetylation of H3 is enhanced in monocytes from patients with T1D and T2D and accounts for increased transcription of *TNF-α* and *COX-2* genes [53]. A further study employing unbiased transcriptomics revealed a strong demethylation of *TNF-α* promoter in leukocytes, which was associated with TNF-α upregulation [54]. We recently reported that mono-methylation of H3K4 (H3K4me1) - a specific epigenetic signal induced by the methyltransferase SETD7 - is enhanced in monocytes from T2D patients and correlates with NF-kB transcriptional activity and NF-kB-dependent genes *VCAM-1, ICAM-1* and *MCP-1* [47]. Moreover, *SETD7* gene expression in monocytes inversely correlated with flow-mediated dilation of the brachial artery, a measure of endothelial function, and urinary levels of 8-iso-PGF$_{2\alpha}$, a reliable *in vivo* marker of oxidative stress [47]. These findings suggest that SETD7 acts as an important epigenetic modulator of both monocyte and vascular inflammation, thus taking central stage on the cardiometabolic arena. In obesity, inflammation also plagues metabolically active tissues such as liver and adipose tissue. Upregulation of Brahma-related gene (Brg1) in hepatocytes exposed to saturated fatty acids enables histone acetylation and chromatin accessibility near the promoter of *IL-1, IL-6* and *MCP-1*. Interestingly, depletion of Brg1/Brm attenuated the release of proinflammatory mediators in the liver and significantly ameliorated steatohepatitis in obese mice [55]. Fat-specific depletion of the deacetylase SIRT1 causes macrophage recruitment to the adipose tissue, whereas its overexpression prevents macrophage accumulation and fat inflammation in diet-induced obese mice. Moreover, SIRT1 expression in human subcutaneous fat was inversely related to adipose tissue macrophage infiltration [56].

The pivotal role of innate immune cells in adipose tissue inflammation suggests that the immune system is not only confined to fight pathogens, but it plays a central role in the pathophysiology of cardiometabolic disturbances, being at the crossroad between metabolism and inflammation [57,58]. Several types of lymphocytes have shown their ability to enable trafficking of T cells and macrophages to visceral adipose tissue. Moreover, obesity is associated with an increased frequency of type 1 helper (Th1) CD4$^+$ and CD8$^+$ T cells and active depletion of regulatory T cells (Tregs) [59]. Changes in methylation status of *Tbet, IL-4, IFN*γ and Forkhead box P3 (*Foxp3*) gene loci are crucial for the polarization of CD4$^+$ cells towards the Th1, Th2 or Th17 phenotypes or to Tregs [60]. Histone modifications also contribute to derail transcriptional programs in immune cells. Differentiation of monocyte into macrophage is driven by distinct epigenetic signatures involving H3K4me1, H3K4me3, and H3K27ac, both at promoter and enhancer regions [61]. In addition, H3K4me3 and demethylation of H3K27 are necessary to turn on inflammatory cytokine production by M1 macrophages, and for M2 polarization, respectively [62]. Moreover, histone deacetylase 3 (HDAC3) controls the regulation of inflammatory genes in macrophages, while histone deacetylase 2 (HDAC2) contributes to the resolution of inflammation by suppressing IL-6 [57]. HDAC4 expression was reported to be reduced in PBMCs from obese individuals, and inversely correlated with the expression of the proinflammatory chemokine CCL5 [63]. Acetylation of H3 at the promoter of *TNFα* and *COX2* genes was enhanced in monocytes isolated from T1D and T2D subjects, while H3K4 mono-methylation contributes to monocyte dysfunction in T2D patients by inducing NF-kBp65 transcription and pro-inflammatory genes such as *VCAM-1, ICAM-1* and *MCP-1* [47,64,65]. Moreover, the H3 deacetylase SIRT1 is downregulated in the adipose tissue of obese individuals, leading to enhanced macrophage recruitment via increased chemoattractant and cytokine production [56].

3.4. Metabolic cardiomyopathy

A consistent proportion of patients with obesity and T2D develop a specific cardiomyopathy phenotype, known as metabolic cardiomyopathy (MC), which occurs independently from myocardial ischemia or arterial hypertension [66,67]. MC is an emerging cause of heart failure with preserved ejection fraction (HFpEF) in the cardiometabolic patient [68]. Over 80% of patients affected by HFpEF are either overweight or obese [69]. Obese and T2D patients with HFpEF display impaired left ventricular filling, worse exercise capacity, pathological remodelling of left and right ventricle, increased risk of atrial fibrillation, and impaired pulmonary vasodilation. Since prevalence of obesity and T2D is further escalating worldwide, the impact of MC on morbidity and mortality is expected to increase exponentially over the next decades [70]. The impairment of myocardial dysfunction in cardiometabolic states is mainly due to changes in energy substrate utilization, mitochondrial dysfunction, oxidative stress, and intracellular accumulation of triglycerides and lipotoxic by-products [71]. HDAC, namely sirtuins, play a key role in epigenetic remodelling. In diabetic rats, pharmacological activation of SIRT1 by resveratrol was able to rescue cardiac dysfunction by preventing cardiomyocyte apoptosis and endoplasmic reticulum stress. Indeed, SIRT1-dependent H3 deacetylation was found to modulate key pathways orchestrating myocardial damage such as PERK/eIF2α, ATF6/CHOP, and IRE1α/JNK [72]. Along the same line, we have recently shown that diabetes-induced SIRT1 and DNMT3b downregulation fosters H3 acetylation and DNA demethylation on *p66^{Shc}* promoter, thus leading to its upregulation and ROS-induced myocardial damage [73]. A recent study in obese mice reported that cardiac deregulation of mitochondrial aldehyde dehydrogenase (ALDH2) orchestrates a SUV39H-SIRT1 epigenetic loop leading to altered transcriptional programs involved in defective autophagic response and myocardial metabolism [74]. Members of the HDAC family are also heavily implicated in the development of key features of MC, such as LV hypertrophy and fibrosis. HDAC orchestrate network of transcription factors, chromatin-remodelling complexes, and specific histone modifiers to regulate the activity of pro-hypertrophic genes, namely the methyltransferase enhancer of zeste homolog 2 (Ezh2) [75]. Although several studies have suggested the importance of epigenetic remodelling in the pathogenesis of MC, our comprehension of how epigenetic regulation is fine-tuned in different cardiac cells types
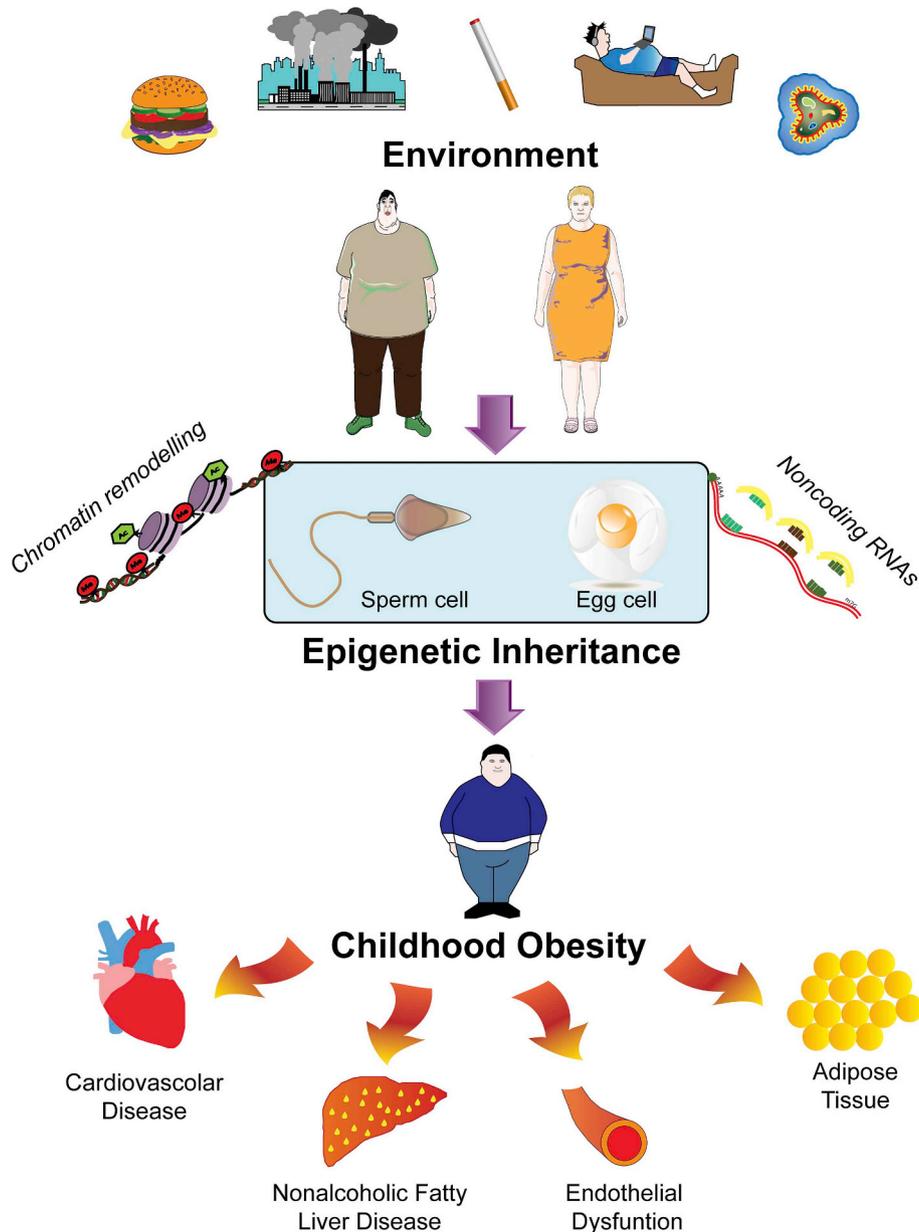
Fig. 2. Role of epigenetic inheritance in childhood obesity.
Environmental factors induce epigenetic changes, which are transmitted to the offspring, thus leading to pro-inflammatory transcriptional programs and cardiometabolic features.

(myocytes, fibroblasts, immune cells) or the contribution of epigenetic networks to energy substrate utilization and lipid metabolism remains elusive.

4. Epigenetic inheritance and childhood obesity

Ample evidence indicates that epigenetic information can be transmitted to the offspring, and may contribute to early development of cardiometabolic traits among the young generations (Fig. 2) [76,77]. Individuals conceived during the Dutch Hunger Winter (1944–1945) showed, 6 decades later, hypomethylation of insulin-like growth factor type 2 (*IGF-2*) promoter, a gene critically involved in the regulation of glucose homeostasis, cardiovascular function, and lipid metabolism [78]. Early paternal smoking was also found associated with a greater body mass index in sons a phenomenon likely mediated by transgenerational epigenetic inheritance [79]. Overall, these data suggest that early-life environmental conditions can induce long-lasting epigenetic

changes in humans. Inheritance of adverse epigenetic patterns, namely *IGF-2* promoter hypomethylation, may significantly contribute to the growing prevalence of cardiometabolic disorders in childhood. According to the *World Health Organization* (WHO), prevalence of obesity in children has increased worldwide from 32 million in 1990 to around 42 million in 2016 [80]. Most importantly, it is estimated that the prevalence of childhood obesity will increase globally to 70 million by 2025 [80]. One out of 4 obese children shows a detrimental cluster of CV risk factors which leads to a 10-fold increase in the risk of CVD as compared to non-obese children [81,82]. A great proportion of obese children display endothelial dysfunction, arterial stiffness, macrophage polarization and adipose tissue inflammation [83]. These changes associate with deregulation of several hormonal axes, including adipocytokines (i.e. leptin, resistin), upregulation of inflammatory cytokines interleukin-6, TNF-α, and high levels of oxidative stress [84]. Epigenetics has shown to modulate such inflammatory transcriptional programs during childhood. Promoter methylation of *TNF-α*, pyruvate

Table 1
Main chromatin modifying agents for the treatment of cardiometabolic disorders.

Compound	Epigenetic mechanism	Species	Main effects
Vorinostat	HDAC inhibitor	Mice, rabbit	Promotes the autophagic flux, prevents eNOS uncoupling, NF-kB activation and reduces oxidative stress [86–88]
Trichostatin A	HDACs inhibitor	Human cells, rodents	Prevents ischemia-induced left ventricular remodelling while promoting angiogenic response and cardiomyocyte survival [89]
Sodium butyrate	HDACs inhibitor	Human cells, rodents	Suppression of inflammatory cytokines in experimental models of myocardial infarction and atherosclerosis [90]
Resveratrol	SIRT1 activator	Human, rodent	Improves endothelial function, insulin sensitivity and cardiac dysfunction in obesity and T2D [91]
Metformin	SIRT1 activator	Human, rodent	Modulates the expression of genes implicated in insulin signalling and pancreatic beta cell homeostasis [22]
GLP-1	SIRT1 activator	Human, rodent	Improves insulin sensitivity and pancreatic beta cell function [22]
Curcumin	HATs inhibitor	Human, rodent	Prevents vascular dysfunction and left ventricular hypertrophy in experimental models of diabetes. In T2D patients, ameliorated proteinuria, reduced pro-fibrotic cytokines and improved microangiopathy [92]
Folates	DNA methylation	Human	Improve endothelium-dependent flow-mediated dilatation of the brachial artery in T2D patients [93]
Apicidin	HDACs inhibitor	Human cells, rodents	Decreases myocardial hypertrophy after 1-week pressure overload induced by thoracic aortic constriction [95]
Valproic acid	HDACs inhibitor	Rodents	Attenuates hypertrophic and hypertensive responses by modulating ROS-generating and pro-inflammatory pathways [96]
PPAR-γ agonists	HAT/HDAC recruitment	Human	Improve vascular function in T2D patients [97]
Apabetalone	Inhibitor of bromodomain and BET proteins	Human, mice	Modulates reverse cholesterol transport, vascular inflammation, coagulation, and complement activation in mice and humans [97]. It has been associated with a reduction of cardiovascular events in patients with coronary artery disease [98]

GLP-1, glucagon-like peptide 1; PPARγ, peroxisome proliferator-activated receptor gamma.

dehydrogenase kinase 4 (*PDK4*) and leptin (*LEP*) is reduced in obese as compared to lean children, while methylation of peroxisome proliferator-activated receptor gamma coactivator 1-alpha (*PGC-1α*) and proopiomelanocortin (*POMC*) genes is enhanced [85,86]. Hence, current evidence clearly indicates that our life style habits may influence not only our epigenome but those of our descendants with profound consequences toward "cardiometabolic transcriptional programs" and early CVD.

5. Chromatin modifying therapies

Epigenetic changes are amenable to pharmacological intervention. Vorinostat (suberoylanilide hydroxamic acid), a histone deacetylase inhibitor, has shown to prevent eNOS uncoupling, NF-kB signalling and oxidative stress in experimental diabetes [87]. Vorinostat also promotes the autophagic flux, a process which is defective in cardiometabolic states [88,89]. Trichostatin A (TSA), a class I and II HDACs inhibitor, prevents ischemia-induced left ventricular remodelling by repressing *TNF-α* transcription while promoting angiogenic response and cardiomyocyte survival by enhancing Akt-1 phosphorylation [90]. The HDAC inhibitor sodium butyrate was shown to blunt NF-kB signalling and inflammatory molecules, namely TNF-α, IL-6, VCAM-1 and ICAM-1 in experimental models of myocardial infarction and atherosclerosis, thus suggesting the potential of this compound to suppress low-grade inflammation and vascular disease in obesity and T2D [91]. Chronic treatment with the SIRT1 activator resveratrol improves endothelial function, insulin sensitivity and myocardial dysfunction in obesity and T2D patients [92]. Metformin and glucagon-like peptide 1 (GLP-1), widely-used anti-diabetic medications, have also shown to modulate SIRT1 activity, thus affecting histone acetylation and transcription of genes implicated in insulin signalling and pancreatic beta cell homeostasis [22]. Curcumin, a natural phenol responsible for the yellow color of turmeric, has shown to prevent vascular dysfunction and left ventricular hypertrophy in experimental models of diabetes. In T2D patients, chronic supplementation with curcumin (1–2 months) ameliorated proteinuria, reduced pro-fibrotic cytokines (i.e. TGF-β and IL-8) and improved microangiopathy [93]. Several other compounds including folates, apicidin, PPARγ agonists and valproic acid have shown the ability to revert chromatin modifications in cardiometabolic states (Table 1) [94–97]. Recent evidence indicates that Apabetalone (RVX-208) - an epigenetic regulator targeting bromodomain and extra-terminal (BET) proteins - is able of modulating reverse cholesterol transport, vascular inflammation, coagulation, and complement [98]. Pooled analysis of short-term studies demonstrated fewer cardiovascular events among patients treated with apabetalone, than among those treated with placebo [99]. Given the strong involvement of inflammation and coagulation defects in cardiometabolic disturbances, this compound may represent a concrete option to alleviate the burden of cardiovascular disease in this setting.

6. Conclusions

Evidence discussed here suggests that epigenetic processing plays a central role the pathogenesis of cardiometabolic disorders. The technological accomplishments made in recent years have led to the construction of epigenomic maps enabling the early detection of inflammatory processes in patients with obesity and T2D. Hence, a careful analysis of the individual epigenetic landscape may furnish novel targets to prevent adipose tissue inflammation, immune-metabolic processes and atherosclerotic vascular disease. The understanding of chromatin architecture and metabolism has led to the design of specific molecules able to modulate chromatin accessibility by enhancing or repressing epigenetic marks on DNA/histone complexes. Noteworthy, some of these drugs have been already approved for the treatment of several conditions including cancer, neurological and cardiovascular disease. An important aspect to be addressed in the

future is how to achieve tissue-specific modulation of chromatin re-modelers in the adipose tissue, vascular endothelium or immune cells. This is a relevant issue since systemic inhibition or activation of HDACs or HATs may lead to an array of adverse effects [100]. Taken together, epigenetic information could advance individualized risk assessment and personalized therapeutic approaches in patients with cardiometabolic disturbances.

Conflicts of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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