Epigenetic Network in Immunometabolic Disease

Geiger, Martin ; Gorica, Era ; Mohammed, Shafeeq Ahmed ; Mongelli, Alessia ; Mengozi, Alessandro ; Delfine, Valentina ; Ruschitzka, Frank ; Costantino, Sarah ; Paneni, Francesco

DOI: https://doi.org/10.1002/adbi.202300211

ADVANCED BIOLOGY
www.advanced-bio.com

Epigenetic Network in Immunometabolic Disease

Martin Geiger, Era Gorica, Shafeeq Ahmed Mohammed, Alessia Mongelli, Alessandro Mengozi, Valentina Delfine, Frank Ruschitzka, Sarah Costantino, and Francesco Paneni**

Although a large amount of data consistently shows that genes affect immunometabolic characteristics and outcomes, epigenetic mechanisms are also heavily implicated. Epigenetic changes, including DNA methylation, histone modification, and noncoding RNA, determine gene activity by altering the accessibility of chromatin to transcription factors. Various factors influence these alterations, including genetics, lifestyle, and environmental cues. Moreover, acquired epigenetic signals can be transmitted across generations, thus contributing to early disease traits in the offspring. A closer investigation is critical in this aspect as it can help to understand the underlying molecular mechanisms further and gain insights into potential therapeutic targets for preventing and treating diseases arising from immuno-metabolic dysregulation. In this review, the role of chromatin alterations in the transcriptional modulation of genes involved in insulin resistance, systemic inflammation, macrophage polarization, endothelial dysfunction, metabolic cardiomyopathy, and nonalcoholic fatty liver disease (NAFLD), is discussed. An overview of emerging chromatin-modifying drugs and the importance of the individual epigenetic profile for personalized therapeutic approaches in patients with immuno-metabolic disorders is also presented.

1. Introduction

Immunometabolic disease represents a growing public health concern and can lead to significant economic impacts, including increased medical costs, decreased productivity, and increased disability.[1] The direct costs of treating these diseases can be substantial, as well as the indirect costs associated with lost productivity and impaired quality of life. The economic burden is expected to increase in the coming years due to the growing prevalence of global population aging. A key feature of metabolic diseases is the clustering of metabolic dysfunction and inflammation, recently described as "meta-inflammation." The latter has been reported to play a pivotal role in the pathophysiology and progression of obesity, type 2 diabetes, and nonalcoholic fatty liver disease.[2] Diet, lifestyle, and exposure to toxins can all influence gene expression, thus leading to altered gene expression and disease phenotypes. For example, epigenetic modifications may lead to changes in metabolic pathways, directly impacting energy production and expenditure in different organs.[3] Furthermore, epigenetic signals have been shown to derail transcriptional programs underlying immune regulation with subsequent changes in innate and adaptive immune response in adipose tissue and the liver. Understanding how environmental cues alter the cellular epigenome is vital to prevent gene dysregulation and immuno-metabolic alterations, such as macrophage polarization, adipose tissue inflammation, insulin resistance, and lipotoxic damage. The review will address recent advances in understanding gene-environment interactions and targeting approaches to reset the epigenome in cardiometabolic disorders.

1.1. Epigenetic Mechanisms

Epigenetics refers to changes in gene expression that impact gene activity without changing the DNA sequence. Prominently, epigenetics leads to incorporation of inheritable but reversible phenomenon that regulates the expression of various genes. For instance, DNA methylation patterns can remain relatively stable over an individual's lifetime, particularly in somatic cells. But other epigenetic changes, like histone modifications, can be modified in response to various signals, allowing for rapid adjustments in gene expression.[4,5] The term "epigenetic" was first proposed by Conrad Waddington in the early 1940s to describe the

M. Geiger, E. Gorica, S. A. Mohammed, A. Mongelli, A. Mengozi, V. Delfine, F. Ruschitzka, S. Costantino, F. Paneni
Center for Translational and Experimental Cardiology
University Hospital Zürich and University of Zürich
Wagistrasse 12, Schlieren, Zurich 8952, Switzerland
E-mail: martinandreas.geiger@uzh.ch; francesco.paneni@uzh.ch
S. Costantino, F. Paneni
University Heart Center
University Hospital Zurich and University of Zürich
Wagistrasse 12, Schlieren, Zurich 8952, Switzerland
F. Paneni
Department of Research and Education
University Hospital Zurich and University of Zürich
Wagistrasse 12, Schlieren, Zurich 8952, Switzerland

The ORCID identification number(s) for the author(s) of this article can be found under https://doi.org/10.1002/adbi.202300211

DOI: 10.1002/adbi.202300211

molecular and biological mechanisms that transform a genetic trait into a visualized phenotype.[4,5] Epigenetic is currently the hottest and most rapidly developing field in the scientific world, with the advancement of novel technologies that can detect chromatin states at multiple dimensions.[6] Epigenetic research aims to unveil the effect of environment, social conditions, and nutrition on an individual's gene expression profile. In multicellular organisms, a single genotype may result in various phenotypes because of the ability of epigenetic markers to appear during development and be transmitted to the offspring.[7] Remarkably, epigenetic modifications are crucial for tightly regulating specific cell and tissue gene expression profiles. Dysregulation of epigenetic changes may result in numerous human disorders such as cardiovascular disease (CVD), immunemetabolic disorders, cancer, and neurological diseases.

Eukaryotic DNA consists of a wealth of information needed for the growth and development of a multicellular organism. Such information is stored both genetically in the DNA sequence and epigenetically through DNA methylation, post-translational histone modifications, and noncoding RNA´s.[8,9] Epigenetic modifications that affect chromatin accessibility and gene expression can be classified as follows: i) DNA methylation, ii) Histone modifications, and iii) noncoding RNAs. The duration and the reversibility of these modifications vary depending on different factors, such are specific types of epigenetic change, individual's genetic background, the lifestyle (diet, weight, BMI, physical activity), the environmental factor, as well as medication-mediated effects. For the latter one, further studies must elucidate the lasting effects of these epidrugs.[8,10]

1.2. Overview of Epigenetic Modifications

1.2.1. DNA Methylation

DNA methylation is one of the best characterized and well-studied pretranscriptional modification, that is achieved by addition of methyl groups to cytosine residues of the dinucleotide sequence (CpG) leading to stability of gene expression and maintains genome integrity. Importantly, CpG dinucleotides are unevenly distributed and nearly 80% of CpGs are methylated in normal healthy cells.[10] DNA methylation patterns are crucial during the postconceptional period. Especially during gametogenesis, a rapid demethylation of the entire parental DNA occurs followed by a de novo methylation and results in tissue-specific DNA methylation patterns which regulate the cellular differentiation in the developing cell.[11] DNA methyltransferases (DNMTs) are highly conserved enzymes that play a pivotal role in DNA methylation. They catalyze the addition of methyl groups to cytosine and forms 5-methylcytosine (5-mC). DNMTs are classified into two categories: i) de novo DNA methyltransferases (DNMT3A & DNMT3B), prominent during embryonic development, and such methyl marks are then faithfully maintained during the development by ii) maintenance DNA methyltransferase (DNMT1) that has specific function toward hemi methylated DNA.[12] Compelling reviews and studies strongly suggest that changes in DNA methylation states can regulate the biological processes causing immune metabolic diseases, such as atherosclerosis, hypertension, and inflammation.[13—15] Studies have found the mice with hypomethylated DNA showed an increase in the expression of inflammatory markers. Moreover, hypomethylation of DNA strongly correlates with the formation of aortic fatty streaks.[16] Studies investigated the DNA methylation in atherosclerosis-prone ApoE-null mice, found that changes in DNA methylation, in both peripheral blood leukocytes and the aorta, contribute to the development of vascular lesions.[17,18] Along the same line, patients with heart failure show differential methylation in genes related to angiogenesis, myocyte apoptosis, fibrosis, and altered contractility as compared with nondiseased heart tissue.[19]

1.2.2. Histone Modifications

In eukaryotic cells, DNA is condensed into chromatin. The nucleosomes are the main unit of chromatin where DNA is wrapped around four different histones (H2A, H2B, H3, & H4).[20] Remodeling of nucleosomes affects the architecture of DNA and its accessibility to replication and transcription factors. Over the course of life, histones are prone to different modifications such as methylation, acetylation, phosphorylation, sumoylation, ubiquitination, ADP-ribosylation, deamination, and proline isomerization..[20,21] Histone modifications usually lead to two outcomes (**Table 1**); i) active or open chromatin where DNA is accessible for replication and transcription and ii) inactive or closed chromatin in which DNA is inaccessible for replication and transcription. Histone modifications are usually performed by three class of enzymes. i) Writers, that add chemical group to the histone tails and lead to either active or inactive transcription based on the site of the modification. ii) Erasers, that remove chemical group from the histone tails, also lead to either active or inactive transcription. iii) Readers, that specifically reads the acetyl group present on histone tails, bind to it, and usually activate the gene transcription.[22,23]

Histone Methylation (Writers/Erasers): Histone methylation and demethylation is a crucial and reversible modification performed by histone methyltransferases and demethylases thus effecting the chromatin state and gene transcription.[24–26]

Histone methylation such as mono (me1), di (me2), and tri methylation (me3) specifically occurred on lysine (Lys or K), arginine (Arg or R) residues, and rarely on histidine (His or H). In Histone 3, lysine amino acids such as (4, 9, 26, 27, 36, 56, and 79) whereas arginine amino acids like (2, 8, and 17) can be methylated. And Histone 4, lysine amino acids (5, 12, and 20) and arginine amino acid 3 can be methylated.[25,27] Importantly, histone methylation occurred on different amino acids has a contrasting transcriptional activity. Histone methylation on histone H3K4, R8, R17, K26, K36, K79, H4R3, and K12 leads to active chromatin state and thus activate gene transcription. In contrast, histone methylation on H3K9, K27, K56, H4K5, and K20 leads to a closed chromatin state and thus inhibits the gene transcription.[27,28] In humans, there are two domains of proteins specifically carrying out lysine methylation; SET domain (SU(var)3-9, Enhancer of zeste and Trithorax domain and the 7Bs (seven beta strand) domain. On the other hand, histone demethylation is executed by two class of proteins: LSD1 and Jumonji C-domain containing family.[29]

Table 1. Key epigenetic regulators in CVD and immunometabolic diseases.

Epigenetic modification marks	Enzyme activity	Pathological effect	References
H3K4me, H3K9me	EZH2, JMJD3	Atherosclerotic SMCS, immune cells (macrophages)	[25,30]
H4R3me2	PRMT5	Cardiac hypertrophy	[31]
H3K79me3	DOT1L	Dilated cardiomyopathy	[25,32]
H3K4me	SMYD3	Cardiacdevelopment	[33]
H3K27me3	EZH2	Congenital Heart defects, atherosclerosis at an early age	[34]
H3K9me3	SUV39H1	Myocardial InfarctionIschemic/Reperfusion injury	[35]

Table 2. Different types of HDACs.

HDACs categories	Localization	Function	Cofactor	Role in the Context of IMD or CVD
Class I (1-3 & 8)	Nucleus	Deacetylation of nuclear proteins	Zinc dependent	**HDAC 1** levels positive correlate with the expression of TNF-a, IL-17, and IL-6. HDAC I has an enhancing effect on T-cell mediated immune response.[40–42] **HDAC 2** is involved in homeostasis of an inflammatory response in chronic inflammatory diseases. Additionally, it is also involved in the development of heart failure and cardiac hypertrophy.[43–46] **HDAC 3** promotes monocyte migration to inflammatory sites and favors cytokine production by macrophages.[47,48]
Class IIa (4,5,7 & 9)	Shuttled between nucleus and cytoplasm	Possess no intrinsic activity, act as a scaffold for other corepressor proteins	Zinc dependent	**HDAC 4** involved in the regulation of neointimal hyperplasia & vascular calcification.[1] HDAC 5 known to be involved in human osteoclasts and associated with the pathogenesis of bone loss in Rheumatoid arthritis.[49] HDAC 7 knockout showed severed hemorrhage and dilated blood vessels.[50] HDAC 9 may act as an epigenetic switch in regulating T-cell mediated in inflammation in the context of cardiac hypertrophy.[51]
Class IIb (6 & 10)	Cytoplasm	Deacetylation of cytosolic proteins	Zinc dependent	**HDAC 6** involved in pulmonary arterial hypertension.[52,53] **HDAC 10** shown to enhance 1L-1b expression and NF-kB in HDAC 10 knockdown alleviating the atherosclerosis in mice model.
Class III (Sirtuin family)	Nucleus, cytosol and mitochondria	Deacetylation of proteins	NAD+ dependent	Numerous reports on Sirtuin family involved in regulating CV-homeostasis (mediating the function of ECs, regulating angiogenic properties, senescence & apoptosis).[42]
Class IV HDACs (11)	Nucleus	Deacetylation of nuclear proteins	Zinc dependent	HDAC 11 involved in obesity and metabolic syndrome, specifically, HDAC 11 suppresses metabolic inflammation by inhibiting IL-10 secretion.[54]

The effect of histone methylation on a target gene depends on the cell type and site of the modification. Different histone methylation signatures and their role in immunometabolic disorders and CVD are listed in Table 1.

Histone Acetylation (Writers/Erasers): Histone acetylation is another crucial epigenetic modification that defines the chromatin state. It critically regulates gene transcription in the cell cycle, differentiation, and metabolism.[36] Histone acetylation is an addition of an acetyl group to lysine motifs modulated by histone acetyltransferases (HATs) and usually leads to gene activation. HATs use acetyl CoA as a cofactor and catalyze acetyl transfer to the lysine side chain. By doing so, it neutralizes the lysine's positive charge, weakening the interactions between histones and DNA and thus open and active chromatin state.[37] Conversely, histone deacetylases (HDACs) remove acetyl groups from histone tails thus resulting in gene inactivation.[37]

HATs are classified into three main categories; 1) Gcn5-related *N*-acetyltransferase (GNAT family); 2) CBP/p300 (CREB-binding protein (CBP) and its close relative to p300) & 3) MYST family (MOZ, Ybf2/Sas3, Sas2, & Tip60). HATs exist as either nuclear modifier (Type A). Cytoplasmic modifiers of newly synthesized histones (Type B).[38] Whereas HDACs divided into four categories (**Table 2**).[39]

1.2.3. RNA-Based Mechanisms

Noncoding RNAs have post-transcriptional action not affecting the chromatin architecture per se and are classified according

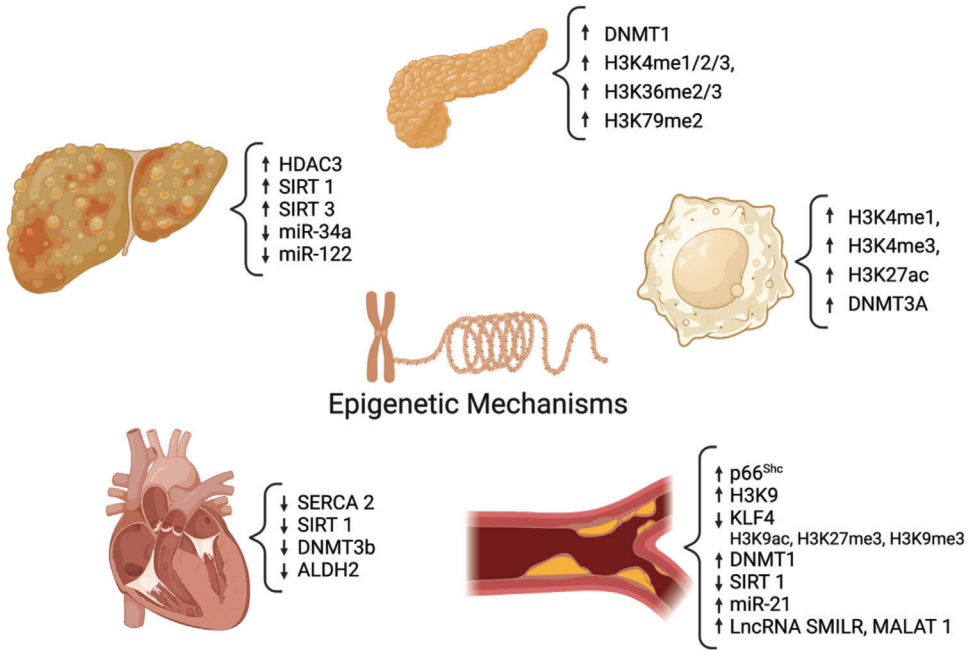


Figure 1. Illustration of Epigenetic Mechanisms in Immunometabolic Disease, highlighting genetic factors, the impact of chronic hyperglycemia, DNA methylation patterns, and histone modifications in the context of T2DM and related metabolic complications. Created with BioRender.com.

to their size. The three main classes are the small noncoding RNAs (ncRNA´s), long noncoding RNAs (lncRNA´s), and circular RNAs. The small noncoding RNAs group includes micro RNAs (miRNAs) and small interfering RNAs (siRNAs). MiRNAs regulate gene expression by binding to messenger RNAs (mRNAs) and either inhibiting or promoting their translation. They are usually about 22 nucleotides in length. siRNAs can also regulate gene expression by inducing the degradation of target mRNAs.[55] Long noncoding RNAs (lncRNAs) belong to transcripts that are longer than 200 nucleotides and do not code for proteins. They can regulate gene expression by acting as transcriptional regulators, recruiting chromatin-modifying proteins, or functioning as miRNA sponges.[56] As far as circular RNAs (circRNAs) concerns, they are formed by the joining of two exons, or by the circularization of an entire exon, and can act as miRNA sponges or as scaffolds for protein complexes. They are typically between 100 and 1000 nucleotides in length.[57]

2. The Interplay between Epigenetics and Immunometabolic Disorders

2.1. Epigenetic Influence

As depicted in **Figure 1**, the epigenetic mechanisms underlying immunometabolic disease are complex and the different modifications, like histone methylation, play a pivotal role in the regulation of immunometabolic disorders and CVD. Studies have shown that parental lifestyle and environmental exposures can influence the epigenetic profile of their offspring, which can, in turn, increase the risk of cardiovascular damage. For example, maternal smoking during pregnancy has been linked to an increased risk of cardiovascular damage in the offspring.[58–60] Similar was observed in maternal obesity.[61] This phenomenon was described in the historical "Dutch famine" cohort, which identified individuals born exposed to food restriction during World War II.[62] Compared to an unexposed population group born full-term before or after the famine. The famine-exposed offspring had higher rates of coronary heart disease and associated risk factors, such as obesity, glucose intolerance, and dyslipidemia in adulthood.[63]

Moreover, additional studies comparing same-sex siblings showed less DNA methylation of the imprinted IGF2 gene compared with their unexposed. The IGF2 gene plays a central role in glucose and lipid metabolism, regulating growth by regulating cellular activity and as an anabolic hormone capable of handling metabolic pathways.[64] In the Pima Indian population analysis, diabetes during pregnancy was associated with a mean BMI of 2.6 kg m^{-2} higher for the offspring exposed to diabetes during pregnancy.[61] In another study, the risk of being overweight was doubled in the offspring of women with diet-treated gestational diabetes or type 1 diabetes. Another interesting result from the same study identified that the risk of metabolic syndrome in the offspring increased with an increasing maternal fasting blood glucose or 2 h blood glucose during an oral glucose tolerance test in pregnancy.[65]

2.2. Endothelial Dysfunction

Loss of insulin signaling in the vascular endothelium has been shown to play a key role in the pathogenesis of cardiometabolic disorders.[66] ApoE deficient mice, with the inactivation of the insulin receptor in cells, showed decreased bioavailability of the signaling radical nitric oxide (NO) and consequently atherosclerotic lesions.[67] The expression of vascular adhesion molecules decreased in endothelium-specific suppression of NF-κB mice,

resulting in suppression of macrophage infiltration into adipose tissue, being this, one of the mechanisms underlying protection from obesity-induced insulin resistance (IR).[68] In human studies, endothelial cells from patients with T2DM show disarray of endothelial insulin signaling, through the activity of PKCβ and NFκB, with subsequent impairment of NO availability.[69] These findings provide evidence of altered endothelial NO synthase activation, consequently reducing insulin action, and increasing inflammatory activation in the endothelium of patients with diabetes mellitus. Recently, we demonstrated the epigenetic role of proinflammatory genes in endothelial IR and vascular dysfunction. We studied the mitochondrial adaptor p66^{Shc}, a protein involved in the mitochondrial complex system regulating endogenous production of free radicals and apoptosis. We observed a significant upregulation of p66^{Shc} in visceral fat arteries isolated from obese patients, correlated with oxidative stress, endothelial dysfunction, and IR.[70] We encountered a complex network of chromatin remodelers like the methyltransferase SUV39H1, the demethylase JMJD2C and the acetyltransferase SRC-1 inducing demethylation and acetylation of H3K9, regulating the p66^{Shc} transcription.[70] Many researchers have also dedicated themselves to evaluating the epigenetic changes of the endothelial cells related to the type of flow within the artery.[71–74] Blood flow alone generates shear stress (SS) in the vessel wall. Laminar, unidirectional SS presents itself in vessels with normal vascular function. In regions of disturbed blood flow, with oscillatory shear stress (cyclic stretch), the EC exhibit altered gene expression.[75] These alterations are finally characterized by an imbalance of vasodilator and vasoconstrictor factors originating from the endothelium itself, resulting in progressive pathophysiological changes.[76] The effects of shear stress on specific CpG sites were observed in human umbilical vein endothelial cell (HUVEC).[77,78] Examination of cell morphology and cytosolic calcium flux revealed that laminar shear stress upregulated KLF4 transcription, which was associated with increased methylation of the promoter region. In contrast, cyclic stretching decreased the expression of KLF4 and was accompanied by a decrease in methylation.[74] KLF4 regulates the expression of genes related to endothelial cell activation, proliferation, and survival, as well as genes that are related to inflammation, cell adhesion, and cytoskeletal remodeling, responsible to maintain an anti-inflammatory, quiescent EC state in unidirectional flow conditions.[79] Dunn et al. demonstrated that blood flow epigenetically controls endothelial gene expression by regulating DNA methylation patterns via a DNMT-dependent mechanism.[72] The genes in the arteries exposed to different flow regimes displayed different methylation profiles across different CpG sites, and the changes in methylation were induced by changes in the intensity and duration of the flow. The changes in gene expression and methylation correlated with each other. In a recent effort to identify flow-sensitive genes in arterial endothelium in vivo, endothelial RNA was obtained directly from mouse carotid arteries after partial carotid ligation. DNMT1 expression was ≈2.4-fold higher in the artery that was partially ligated and exposed to disturbed flow than in the contralateral exposed to normal flow. In vivo validation was performed in EC culture with unidirectional laminar shear stress exposure. Inhibition of DNMT1 by 5-aza-2′-deoxycytidine or by DNMT1 small interfering RNA prevented disturbed flow-induced monocyte adhesion, demonstrating the functional importance of DNMT1 in endothelial inflammation.[72] Chromatin condensation has also an important role in ECs flow adaptation. Examining immunostaining of H3K9ac, H3K27me3, and H3K9me3 showed the impact of SS in histone 3 methylation and acetylation. EC exposed to SS (atheroprotective) have histones which are more acetylated and less methylated, suggesting a more decondensed chromatin structure in this hemodynamic environment.[80] The chromatin remodeling in HUVEC´s resulted in increased expression of genes important to the endothelial inflammatory response, such as TNFα, ICAM-1, and MCP-1.[71] SS-induced histone H3 serine phosphorylation and lysine acetylation.[71] Another example of flow disturbance relation with epigenetics manifestations could be observed in close proximity to branch openings compared with areas of undisturbed flow. The effects of both wall-adjacent branches, as well as out-of-wall branches were compared with areas of undisturbed flow. Findings suggest that the presence of open branches causes an increase in the local velocity of the flow, with the magnitude of the increase depending on the size and the location of the branch opening. Histone deacetylase 3 (HDAC3) expression was increased in close proximity to the branch openings.[81] The mechanism behind this expression increase is thought to be due to the activation of KLF2. Upon activation, KLF2 binds to the promoter of the HDAC3 gene and causes an increase in expression. HDAC3 had a negative effect on vascular homeostasis, leading to reduced vascular smooth muscle relaxation.[82] NcRNAs also have a role in controlling molecular events associated with vascular remodeling.[83] In conjunction, ncRNAs can regulate the synthesis and trafficking of cytokines and chemokines, which modulate the responses of endothelial cells and vascular smooth muscle cells to various stimuli.[84] Dysregulated miRNA expression has been implicated in the pathogenesis of atherosclerosis, hypertension, and other cardiovascular diseases.[85] For example, miR-21 was first identified to be significantly increased in rat carotid arteries following balloon injury.[86] miR-21 expression has also been shown to be upregulated in diabetic vasculature decreasing nitric oxide production when overexpressed in endothelial progenitor cells. The participation of miR-21 in arterial flow type has also been observed.[87] Oscillatory SS-induced miR-21 inhibited the translation, but not transcription of PPARα, which, in turn, reduced the inhibition of the transcription factor activator protein-1 pathway by PPARα. Positive feedback was observed increasing the transcription of miR-21 and inflammation in ECs.[88] miR-21 has also been demonstrated to attenuate EC apoptosis and NO production in the PI3K/Akt pathway modulating the atheroprotective effects of SS.[89] Understanding the cell type-specific functions and precise targets is important for potential clinical application.[90] Adipocytes, endothelial cells, and macrophages, for example, may each contain unique epigenetic information that is translated into particular transcriptional processes related to cell development. The epigenetic landscape of individual cells has been demonstrated to vary as a result of micro- and macroenvironmental influences.[91]

Studies about OxLDL-induced endothelial cell proliferation approach DNA methylation associated with inflammation and plaque growth in atherosclerosis.[92] It is present in several genes involved in inflammation and human atherosclerotic lesions.

LncRNA smooth muscle-induced lncRNA (SMILR) as well as metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) have been reported to be overexpressed in

atherosclerotic patients.[93,94] SMILR is a critical mediator of vascular smooth muscle cell (SMC) proliferation via direct regulation of mitotic progression. Increased SMILR levels were detected in unstable compared with stable human atherosclerotic plaques.[95] MALAT1 expression in human atherosclerotic plaque was downregulated in comparison to healthy vessel and moreover decreased in symptomatic versus asymptomatic patients.[96] MiR-21 has been found to target and reduce the expression of sirtuin 1 (SIRT1), a transcriptional corepressor that can modulate intracellular responses to oxidative stress and inflammatory signals.[97] Downregulation of SIRT1 by miR-21 has been suggested to mediate a proinflammatory phenotype in human vascular smooth muscle cells and thus contribute to vascular inflammation and atherosclerosis.[98]

2.3. Systemic Inflammation

Pathogenic infection and tissue injury usually course with inflammation. Epigenetic dysregulation can be used to explain inflammation to the onset of several diseases.[99] The inflammatory signaling results in changes in the epigenetics of an individual modulating the expression of proinflammatory cytokines, interleukins, and tumor suppressor genes.[100]

DNA methylation has a key role in the regulation of inflammatory genes. Recently, a DNA methylation signature could be applied to understand the influence of low-grade inflammation in existing or novel epigenome-wide association studies.[101] The association between C-Reactive protein (CRP) DNA methylation signatures and clinically relevant phenotypes were evaluated, where CRP DNA methylation was positively associated with several inflammation markers including IL1RA, IL6, and TNF receptor.[101] Methylation levels of TNFexon 1 showed a significant correlation with specific fatty acids in a gender-specific manner suggesting that one way that fatty acids interact with the inflammation is through altered methylation profiles of cytokine genes.[102] Another DNA methylation example related to inflammation is observed in Helicobacter pylori infection. Helicobacter pylori infection of epithelial cells is associated with the activation of several intracellular pathways. These pathways include the MAPK/ERK, PI3K/Akt, and NF-κB pathways and are activated by H. pylori through the binding of its flagellin to the Toll-like receptor 5 (TLR5).[103]

The disruption of immune cell transcriptional pathways is also facilitated by histone alterations. H3K4me1, H3K4me3, and H3K27ac are unique epigenetic markers that trigger the differentiation of monocytes into macrophages.[104] Macrophages play an important role in tissue remodeling and angiogenesis. Inflammatory responses to bacterial or viral infection are mediated by macrophages called M1. The macrophage M1 produces proinflammatory cytokines, such as TNF. It is well known that M1 macrophages produce NO by expressing induced NO synthase and are crucial to clearing bacterial, viral, and fungal infections. In contrast, alternatively activated macrophages or M2 macrophages contribute to parasite infection, tissue remodeling, angiogenesis, and tumor progression.[105] The histone H3 Lys 27 (H3K27) demethylase JMJD3 is a transcription factor that is also involved in the regulation of inflammatory responses. It is induced by macrophages exposed to bacterial products and inflammatory cytokines, such as TNF-α, IL-1β, and IL-6. JMJD3 is thought to play a role in the regulation of the inflammatory response by modulating the expression of genes involved in inflammation, such as those encoding proinflammatory cytokines, chemokines, and adhesion molecules. JMJD3 is involved in the regulation of macrophage polarization, with its expression are higher in M1-polarized macrophages compared to M2-polarized macrophages.[106] HDAC3 controls the regulation of inflammatory genes in macrophages, while histone deacetylase 2 (HDAC2) contributes to the resolution of inflammation.[107] In monocytes isolated from T1DM and T2DM patients, acetylation of H3 at the promoter of TNF and COX2 genes was increased, whereas H3K4 mono-methylation contributes to monocyte dysfunction in T2DM patients by inducing transcription of NF-kBp65 and proinflammatory genes like VCAM-1, ICAM-1, and MCP-1.[108,109] A critical role is also played by inflammation in increasing fatty acid accumulation.[110] The accumulation of body fat, or adiposity, is a condition that is influenced by a range of circumstances. Environmental factors, diet, and sedentary behavior can interfere with hormone signaling pathways and alter metabolism, thus, contributing to adipose tissue accumulation in the body.[111] In recent years, various epigenetic modifications have been implicated in the development of different metabolic diseases and also of adiposity and related metabolic disorders.[112] The growing studies in the field have hypothesized that this condition is companied with changes in DNA methylation patterns. In particular, this contributes to alterations in genes that are involved in metabolic pathways related to obesity and its diseases.[113] For instance, in obese patients, DNA methylation changes have been observed in genes involved in glucose metabolism, insulin signaling, and adipogenesis.[114] Some in vitro and in vivo models have shown that DNMT3A impairs insulin tolerance via DNA methylation in the Fg21 gene, while carnitine palmitoyltransferase 1A (CPT1A) gene DNA methylation changes were associated with obesity and T2DM.[115,116] The specific mechanisms by which adiposity leads to changes in DNA methylation are not fully understood, but may involve both, alterations in the availability of methyl donors and modifications in the DNMT enzyme activity. Histone modifications are also known to be associated with this condition. Due to histone changes are affected genes that are involved in lipid metabolism and adipocyte differentiation.[117] PPARγ is the master regulator of adipocyte differentiation. Histone modifications play a crucial role in the regulation of the expression of this gene. Hence, acetylation and methylation lead to either increased or decreased expression respectively, contributing so to the governance of adipogenesis.[118] Similarly, Sterol regulatory element-binding protein 1 (SREBP-1c) and Fatty acid binding protein 4 (FABP4) which are both involved in lipid metabolism and fatty acid transportation, are strongly regulated by histone and noncoding RNA alterations. For instance, SREBP-1c is dependent by the acetyltransferase activity of coactivators p300 and CREB-binding protein (CBP). On the other hand, a recent study showed the FABP4 gene is strongly regulated by the lncRNA MIR31HG.[119–121] Changes in the status of histones, DNA methylation, or RNA-based mechanism of key genes involved in adiposity can significantly contribute to the development and maintenance of this trait.

2.4. Type 2 Diabetes Mellitus

T2DM is a chronic metabolic disorder which is associated with high blood glucose levels. The contribution of genetic and environmental factors, such as diet, lack of physical activity, smoking, stress, BMI, waist circumference as well as aging are associated and play a crucial role in the occurrence and development of T2DM. Maternal malnutrition has been linked to altered epigenetic modifications and increased susceptibility to T2DM development in children.[122] Chronic hyperglycemia occurs in T2DM as a result of impaired insulin secretion from pancreatic β-cells and insulin resistance in target tissues.[123] The duration of exposure to elevated glucose levels affects insulin secretion differently. Both in vivo and in vitro, hyperglycemia stimulates insulin secretion while long-term hyperglycemia impairs it.[124,125] An individual's response to chronic hyperglycemia can be rated on a continuum. Desensitization occurs first, followed by exhaustion and finally glucotoxicity, which is irreversible.[126] High lipid levels have also been reported to impair β-cell function. Human pancreatic islets exposed to high palmitate levels for 48 h showed decreased glucose-stimulated insulin secretion and altered global gene expression and DNA methylation patterns.[127]

Initial studies analyzed DNA methylation of candidate genes for T2DM, such as encoding insulin (INS), encoding hepatocyte nuclear factor 1-alpha (HNF1A), and encoding zinc transporter 8 (SLC30A8).[128] DNA methylation in the context of T2DM is believed to be a key factor in the disrupted glucoregulation associated with the disease. In particular an association between increased INS gene methylation and reduced insulin secretion, ultimately leading to T2DM.[129] Overnutrition of rat insulin-1 (Ins1) cells and Zucker diabetic fatty rats were used to determine the effects of overnutrition on DNA methylation at the promoter of the insulin-1 gene. A high glucose concentration seemed to increase Dnmt1 mRNA expression levels and activity. By increasing DNA methylation at five CpG sites within the Ins1 promoter and suppressing Ins1 mRNA expression, glucose concentration, and time were positively correlated, conversely metformin, the first line of T2DM treatment, has been shown to significantly suppress insulin promoter DNA methylation and upregulate Ins1 mRNA expression.[130]

Hepatocyte nuclear factor 1α (HNF1α), also known as the Maturity-onset diabetes of the young (MODY) type 3 gene, is a gene associated with the regulation of glucose homeostasis and insulin production and is the pathogenic gene for MODY3. Common types of HNF1α mutations cause MODY3. Other mutations are not associated with MODY3 but increase the risk of T2DM significantly. Hyperglycemia in MODY3 is caused by single-gene abnormalities. T2DM, in contrast to MODY, has genetic and environmental causes.[131]

To maintain cellular function, zinc levels are regulated in the body. Diabetes may be caused by dysregulation of zinc metabolism. Insulin synthesis, storage, and secretion are facilitated by zinc, which acts as a second messenger in insulin signaling pathways and glucose homeostasis. Pancreatic islets have the highest zinc concentration. Cell granules accumulate zinc through ZnT8, a zinc transporter expressed primarily in pancreatic α and β cells. ZnT8 gene (SLC30A8) polymorphisms are associated with type 2 diabetes mellitus (T2DM), and some mutations may protect against it.[132,133]

H3K4me1/2/3, H3K36me2/3, and H3K79me2 are correlated with transcriptional activation and play critical roles in the specific promoters and enhancers of the islet and pathogenesis of diabetes.[134] Diabetic nephropathy is associated with dysregulation of H3K4me1/2/3.[135]Transient hyperglycemia endothelial cells were found to have increased H3K4me1 level at the proximal promoter of p65 as well as sustained activation of the NF-κB subunit p65.[136]

2.5. Nonalcoholic Fatty Liver Disease

NAFLD is a disease in which extra fat is accumulated in liver cells without being caused by alcohol consumption.[137] Nonalcoholic steatohepatitis (NASH) is a subgroup of NAFLD that causes hepatocellular injury and inflammation, which may progress to irreversible cirrhosis and hepatocellular carcinoma.[138] The pathogenesis of NAFLD considers the "two-hit" theory, to explain the NAFLD presentation (steatosis, NASH, and cirrhosis).[139] The first hit consists of a "trigger" event, such as an increase in the rate of lipogenesis, an increase in the rate of fatty acid uptake, or an accumulation of toxic lipids. This initial event leads to the accumulation of the lipids in the hepatocytes, resulting in the development of simple steatosis. The second hit is a result of various predisposing factors, such as obesity, diabetes, hyperlipidemia, and oxidative stress, which culminate in the activation of proinflammatory cytokines and the recruitment of immune cells to the liver.[140] Studies suggest that the progression of NASH to cirrhosis is driven by oxidative stress, mitochondrial dysfunction, endoplasmic reticulum stress, and dysregulation of the innate immune system.[141–143] Oxidative stress results in the production of reactive oxygen species such as superoxide and hydrogen peroxide, which damage the hepatocytes, thus exacerbating the lipid accumulation and causing inflammation. Mitochondrial dysfunction leads to decreased fatty acid oxidation, resulting in an accumulation of lipids in the hepatocytes, followed by inflammation and further damage.[144] Endoplasmic reticulum (ER) stress is an accumulation of unfolded or misfolded proteins in the ER, which leads to the activation of proinflammatory pathways and the development of fibrosis.[145] The methyl-group donors from foods, such as folate, betaine, and choline, are required for S-Adenosyl methionine synthesis (SAM). SAM is the methyl donor of the DNA methylation reaction catalyzed by DNA methyltransferases. Tryndyak et al. showed that diets depleted of methyl donors decreased the level of hepatic SAM and caused CpG island demethylation of 164 genes in mouse livers.[146] These genes were shown to be involved in DNA damage/repair, lipid and glucose metabolism, and fibrogenesis. A recent study showed a predisposition of offspring to NAFLD induced by maternal hypercholesterolemia.[147] Mice were offered a high-fat and high-cholesterol Western diet (WD) during pregnancy and the lactation period. Their offspring were fed with chow diet after birth. Offspring exposed to this high-cholesterol environment showed insulin resistance and hepatic steatosis at 4 months of age. Increased methylation of CpG sites in the ApoB gene promoter region in the livers of male mice born to WD-fed mice was observed. Human studies have also shown that an unfavorable environment during pregnancy and lactation has long-term effects on the development of

NAFLD-related clinical disorders.[148] DNA methylation profiles in liver biopsy samples from patients with NAFLD were compared to healthy controls.[149] There were significant differences when it came to the level of global DNA methylation in the liver of overweight participants with NAFLD. As hepatic inflammation grade and disease progression increased, hepatic global DNA methylation level decreased. Furthermore, Murphy et al., showed that NAFLD patients with mild disease can be distinguished from those with advanced NAFLD based on their DNA methylation profiles.[150] HDACs are considered to play an important role in the development of NAFLD. A liver-specific deletion of HDAC3 leads to advanced fibrotic NAFLD and hepatocellular carcinoma. Inflammation-induced obesity and fatty liver disease were improved by liver-specific deletion of SIRT1, whereas overexpression of SIRT1 was beneficial in preventing IR and steatohepatitis. As a result of suppressing protein tyrosine phosphatase 1B (PTP1B) at the chromatin level, SIRT1 enhances insulin response under IR conditions. Increased expression of the SIRT1-binding macroH2A1.1 metabolite, a variant of histone H2A, protects hepatocytes from lipid accumulation.[151] During oxidative stress, SIRT3 is required to maintain mitochondrial integrity. SIRT3 knockout mice were documented to exhibit NASH, and disruption of SIRT3 function in mice correlated with metabolic syndrome and NAFLD-like abnormalities.[152]Circulating miRNAs have been identified as promising noninvasive biomarkers of NAFLD. Overexpression of miR-34a results in hepatocellular apoptosis. A major target of miR-34a is SIRT1.[153] Silencing of miR-34a restores the expression of SIRT1 and PPARα, resulting in activation of AMPK and the activation of various PPARα target genes, suggesting a fundamental role of miR-34a in the deregulation of lipid metabolism associated with NAFLD.[154] The most abundant miRNA in the liver is miR-122. It is highly expressed in the liver and is involved in the regulation of cholesterol and lipid metabolism. The predicted targets of miR-122 include genes regulating cholesterol and lipid metabolism, such as HMGCR, NPC1, ABCA1, and LDLR.[155] MiR-122 is involved in several steps during the evolution of NAFLD. Mice deficient for miR-122 results in steatohepatitis. Csak et al. showed that decreased hepatocyte expression of miR-122 has a causal role in increased HIF-1α, vimentin and MAP3K3 mRNA expression in steatohepatitis and fibrosis.[156]

2.6. Metabolic Cardiomyopathy

The term "metabolic cardiomyopathy" (MC) has been used more frequently in recent years and occurs in patients with obesity and T2DM unrelated to hypertension, valve disease, or myocardial ischemia.[157,158] MC is characterized by heart failure with preserved ejection fraction in obese patients with IR and diabetes.[159] A state of chronic metabolic inflammation promotes the structural and functional changes found in MC resulting from metabolic processes involving systemic inflammatory cytokines, circulating metabolic substrates, and immune dysregulation.[160] In terms of molecular mechanisms, there is often an insufficient differentiation between diabetic cardiomyopathy, obesity-related cardiomyopathy, and MC.[161] DNA methylation is increased in the promoter region of the sarcoplasmic reticulum Ca2+-ATPase (SERCA2a) in diabetic hyperglycemia. SERCA2a is responsible for the myocardium relaxation. Downregulation of SERCA2 attends myocardium relaxation and diastolic dysfunction.[162] IR is significantly increased by DNA methylation. It decreases the heart's cardiac contractility causing myocardial remodeling and cardiac hypertrophy.[163–165] HDAC1, SIRT1 plays a significant role in the prevention and treatment of cardiac dysfunction. SIRT1 activated by Resveratrol prevent cardiomyocyte apoptosis and endoplasmic reticulum stress. SIRT1-dependent H3 deacetylation is pivotal in the response to myocardial injury and involves PERK/eIF2α, ATF6/CHOP, and IRE1α/JNK.[166] We have recently shown that diabetes-induced SIRT1 and DNMT3b downregulation fosters H3 acetylation and DNA demethylation on the p66Shc promoter, leading to myocardial damage.[167] A recent study in obese mice could show that cardiac deregulation of mitochondrial aldehyde dehydrogenase (ALDH2) orchestrates a SUV39H-SIRT1 epigenetic loop leading to altered transcriptional programs involved in myocardial metabolism.[168]

2.7. Epidrugs in Immunometabolic Diseases

Generally, immunometabolic diseases are characterized by insulin resistance and chronic inflammation and usually result from the interaction between the immune system and metabolic pathways.[1] Based on the individuals and the specific disease, their treatment involves a combination of lifestyle adjustments (diet and exercise) and medical treatments (hypoglycemic and anti-inflammatory drugs).[169] As broadly described in the previous sections, these diseases, are recently associated with epigenetic alterations. It is necessary to explore novel therapies that aim to reverse epigenetic modifications (**Figure 2**). Currently, no drugs are specifically designed to target epigenetic changes in metabolic diseases, however, some existing ones were been found to have an impact on epigenetic regulation.[170,171] Some drugs that have shown to have positive effects in this setting are either tested in clinical trials or are still in the exploratory phase.[172] Still, further research is needed to fully elucidate their potential in the treatment of immunometabolic diseases.

2.8. Already Used Drugs Capable to Reverse Epigenetic Modifications in Immunometabolic Diseases

T2DM is a complex metabolic disorder that arises from the interplay of genetic, environmental, and lifestyle factors and is characterized by epigenetic modifications that contribute to the development and progression of the disease.[173] Recent advances in the field of epigenetics have expanded our understanding of the underlying mechanisms of T2DM and its associated complications. Metformin, a commonly used drug for T2DM, has demonstrated therapeutic potential beyond glycemic control, including its efficacy in treating diabetes-related complications such as liver disease, cardiovascular conditions, and obesity.[174] This biguanide has also been found to impact DNA methylation and histone modification, which may contribute to its ability to reduce oxidative stress and improve epigenetic modifications in liver cells.[175,176] In T2DM it alters cell energy metabolism by reducing hepatic glucose production through AMPK-dependent

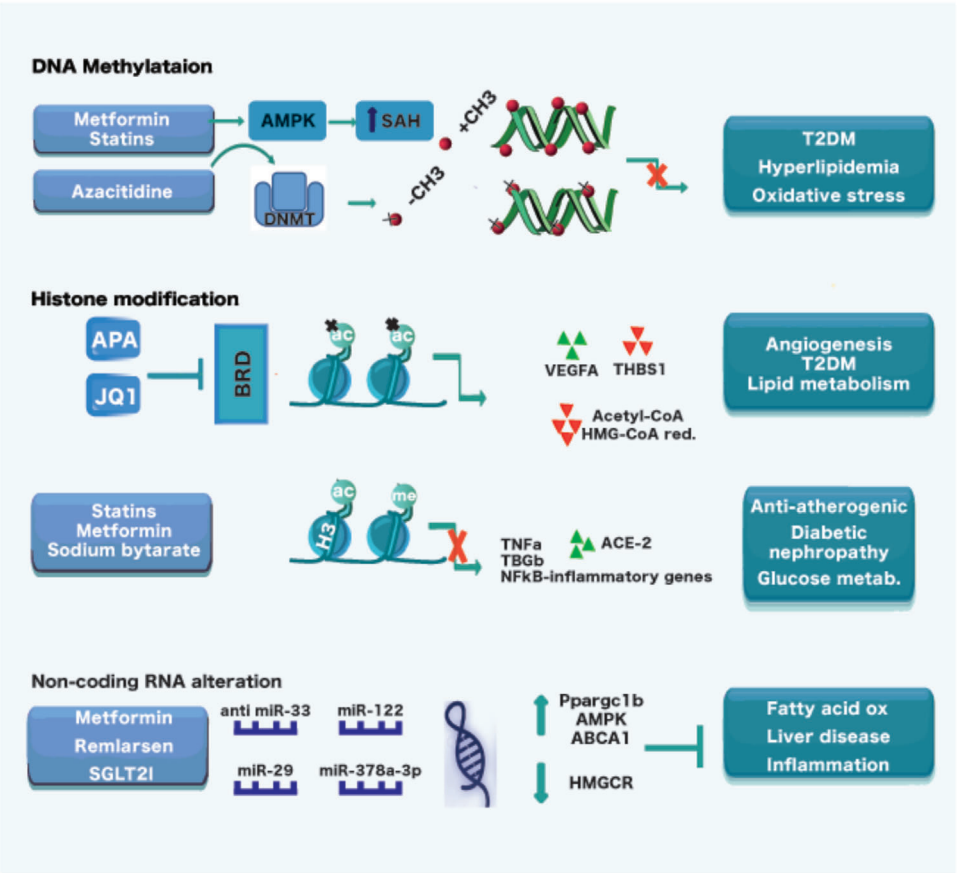


Figure 2. Epigenetic modifications, regulated by specific enzymes and proteins, can be selectively influenced by epidrugs. Existing drugs such as metformin and statins, as well as emerging agents like APA and JQ1, hold significant potential for-fine-tuning gene expression, therefore, paving the way for addressing metabolic disorders.

or independent pathways. Modulation of the AMPK activity itself influences epigenetic processes. Through this pathway, histone modifications are present. For example, HAT expression, HMT inhibition, and histone ubiquitination occur.[177] Studies have shown that AMPK activation by metformin can enhance activity of some HATs and decrease of others. The biguanide indirectly contributes to the phosphorylation of HATs p300 and the CREB-binding protein through AMPK pathway modulation. In mouse embryonic fibroblasts, metformin-AMPK activation increased HAT1 activity through phosphorylation.[178,179] The involved epigenetic mechanisms due to metformin contribute to either an increase or decrease in gene expression. The drug can interact with epigenetic-modifying enzymes such as SIRT1 by increasing its activity through NAD+ generation.[180] This was observed in an increase of the NAD+/NADH ratio in myotubes due to AMPK activation but also increasing SIRT1 mRNA and protein levels in peripheral blood mononuclear cells.[181,182] HDACs of class II inhibition, HATs phosphorylation, and additional phosphorylation of gene residues are other typical epigenetic modifications caused by metformin.[183,184] This drug can also cause hypo- and hypermethylation of DNA at the promoters of different genes. The AMPK modulation still contributes to this additional epigenetic change due to metformin.[185] At the insulin gene promoter in a β cell line exposed to high glucose levels, a reduction in DNA methylation was observed after metformin treatment.[186] In addition to these modifications, metformin can also induce miRNA alterations. Santovito and colleagues reported at least 25 miRNAs were altered in diabetes, whereas metformin treatment could help in the restoration of let-7a and let-7f, both found downregulated in diabetes.[187] Metformin exhibits pleiotropic effects on lipid metabolism, potentially mediated by its ability to modulate DNA methylation.[188] Additionally, it may mitigate oxidative stress and promote angiogenesis in diabetic vascular disease via its regulatory effects on miR-34a.[188,189] Sodium-glucose co-transporter-2 inhibitors (SGLT2I) are another antidiabetic class which contributes to reversing epigenetic changes not only in diabetes but also in cardiac and/or renal diseases. Modulation of miRNAs like miR199a-3p and miR30e-5p helps in mitochondrial fatty acid oxidation, therefore, having an impact on cardiac disorders. In a mouse model of myocardial infarction SGLT2I were found to attenuate myocardial oxidative stress and fibrosis.[190,191] Additionally, clinical data highlight the potential therapeutic benefit of SGLT2I Dapagliflozin in diabetic cardiomyopathy.[192] Recent studies have suggested that statins, drugs commonly used to lower cholesterol and prevent cardiovascular disease, may have additional effects on gene expression through epigenetic mechanisms. Specifically, statins have been found to alter gene expression patterns by affecting

DNA methylation and histone modification, which are known to play a role in the development of atherosclerosis, insulin signaling, and cell-cycle progression.[193,194] Additionally, emerging evidence suggests that statins may act as inhibitors of histone deacetylases (HDACs) and DNA methyltransferases (DNMTs), as well as agents that modify miRNAs. These novel findings suggest that statins have potential therapeutic applications beyond their traditional use as cholesterol-lowering agents.[195,196] T Through the alterations of DNA methylation patterns, statins may cause a hypo- or hypermethylation in DNA at specific promoter genes. A recent study conducted on diabetic patients undergoing statin treatment showed that these drugs have epigenetic effects that can modulate gene expression. Specifically, the study found that statins were able to cause methylation at four out of five identified CpGs associated with glycemic traits, type 2 diabetes, and blood lipids. These CpGs were located in genes implicated in insulin signaling, suggesting that the epigenetic effects of statins may contribute to their therapeutic benefits beyond their known cholesterol-lowering effects.[197] Additionally, they are attributed to antiatherogenic properties. In a rabbit model of atherosclerosis, it was observed that atorvastatin modulates the epigenetic up-regulation of ACE2 through histone H3 acetylation.[196,198] A growing body of evidence suggests that statins can be suitable for the treatment of metabolic disorders, such as obesity and metabolic syndrome due to their ability to modulate the expression of proinflammatory genes.[199,200] However, the exact mechanisms by which statins exert their epigenetic effects and how they may be optimized for therapeutic use require further investigation. Nonsteroidal anti-inflammatory drugs (NSAIDs) are a class of drugs that reduce inflammation by inhibiting the activity of cyclooxygenase. NSAIDs, like other anti-inflammatory agents such as JAK inhibitors, may act at the epigenetic level altering the epigenome and regulating gene expression involved in inflammation, oxidative stress, and apoptosis. Also, they can alter DNA methylation patterns in various tissues.[201–203] Although the evidence is consistent, additional investigations are required to better elucidate the exact mechanism of action of these drugs and their real role in attenuating metabolic diseases through epigenetic alterations.

2.9. New Drugs for Altering Epigenetic Modifications in Immunometabolic Disease

Epigenetic modifications play a crucial role in the development and progression of immunometabolic diseases. The growing understanding of the epigenetic changes that occur in these diseases has led to the need for the development of new drugs that specifically target these changes in immunometabolic diseases.[204] Epidrugs can easily contribute to this causing epigenetic changes by targeting at least one of the three main epigenetic mechanisms. This alters the activity of specific genes that contribute to pathological changes occurring in metabolic disorders.[26] Worth noting that while these drugs have been shown to have epigenetic effects in laboratory and/or animal studies, further investigation is needed to determine their exact mechanisms of action and clinical efficacy in humans.

Sirtuin activators (Sirt activators) are involved in regulating various cellular processes, including gene expression, metabolism, and aging. Some of these activators have been shown to have epigenetic effects, meaning they can modify the activity of certain genes without changing the underlying DNA sequence.[205] Early investigations in this class of drugs showed they are successful in improving the glucose and lipid metabolism in metabolic diseases, such as T2DM and obesity.[206–208]

Epidrugs targeting microRNAs have emerged as a promising new approach for treating metabolic diseases by modulating gene expression and regulating metabolic pathways. Preclinical studies have shown that microRNA-targeted epidrugs have therapeutic potential for improving glucose and lipid metabolism, and reducing inflammation in metabolic diseases.[209] For instance, Remlarsen was found promising results for the treatment of fibrotic disorders and osteoarthritis via miR-29 mimicking.[210,211] While, MRX34, a liposomal miR-34a mimic, is currently being developed for the treatment of liver diseases.[212] On the other hand, miR-33 antagonists are under investigation for the treatment of lipid disorders, including hyperlipidemia and atherosclerosis.[213]

Additional epigenetic modulators are also being studied for potential effects in the treatment of fatty liver disease (FLD) as it is associated and attributed to obesity and metabolic syndrome.[214] In animal models of FLD, HDAC inhibitors have been shown to have an impact in this setting as HDAC1 can limit adipogenesis.[215] Recent insights on a novel HDAC inhibitor, Givinostat, have promoted it as an epidrug with a high potential use in immunometabolic disorders. It is known to have anti-inflammatory properties. Additionally, clinical trials evidence has shown this epidrug can be effective in the treatment of systemic juvenile idiopathic arthritis.[216]

Bromodomain and extra terminal motif (BET) proteins inhibitors (BETi) are a new class of drugs that target specific epigenetic modifications to regulate gene expression. Inhibitors of BET proteins lead to changes in gene expression and cellular behavior by blocking the interaction between BET proteins and histones.[217] BET proteins are involved in many cellular processes, including cell division, differentiation, and survival, therefore, by disrupting the activity of these proteins, BETi have been shown to have anti-inflammatory, antiproliferative, and proangiogenic effects.[172,218] JQ1 is a small inhibitory molecule of bromodomain and extra-terminal proteins, specifically BRD4.[219] Although this drug is in the very early stages of research, it has shown to have a potential in regulating glucose and lipid metabolism.[220–222]

Apabetalone (APA) is another recently-developed drug that falls under BETi class. This newly discovered drug binds to specific acetylated histone proteins and leads to gene expression changes. Specifically, it targets BRD2, BRD3, and BRD4.[172] By inhibiting these proteins, APA contributes to various cellular processes, making this molecule to be considered as a potential treatment for a range of diseases; inflammatory, metabolic, and immunometabolic ones.[223] BET inhibitors, like APA, target specific bromodomains within BET proteins that bind to specific acetylated histone proteins, leading to changes in gene expression and cellular processes.[172] Apabetalone has been investigated in clinical trials for the treatment of various diseases, including cardiovascular diseases, vascular inflammatory conditions, and diabetes.[223–225] Based on the current evidence, this class is still in the early stages of development. Further research

is needed to thoroughly understand their mechanisms of action and/or determine their safety and efficacy.

3. Conclusion

The evidence presented in this review shows that epigenetics plays a crucial role in the pathophysiology of immunometabolic diseases. A better understanding of the affected organs and their inter-relations is of fundamental importance for a better approach and prevention of adipose tissue inflammation and immunometabolic processes. Some of the presented drugs have already been approved for treating cardiovascular disease and cancer. The challenge still lies in achieving tissue-specific modulation of chromatin remodelers since the activation or inhibition of these factors systemically has resulted in several side effects.

In the evolving landscape od epigenetics and its application to immunometabolic disorders, several pressing challenges are faced. There is an unmet need for advanced tissue-specific epigenomic profiling methods, addressing ethical and regulatory considerations, and at the same time ensuring the long-term safety and effectiveness of epigenetic interventions. Effectively addressing these challenges is paramount for unlocking the full potential of epigenetics in preventing and treating this spectrum of diseases, ultimately enhancing the quality of life for those impacted by these conditions.

In other words, epigenetic information accessed may lead to a more specific and personalized treatment for each tissue affected.

Acknowledgements

Open access funding provided by Universitat Zurich.

Conflict of Interest

F.R. has not received personal payments by pharmaceutical companies or device manufacturers in the last 3 years (remuneration for the time spent in activities, such as participation as a steering committee member of clinical trials and member of the Pfizer Research Award selection committee in Switzerland, were made directly to the University of Zurich).

Keywords

DNA methylations, epi-drugs, histone modifications, immune dysfunctions, signaling pathways

Received: June 8, 2023
Revised: September 8, 2023
Published online: October 4, 2023

[1] G. S. Hotamisligil, *Immunity* **2017**, *47*, 406.
[2] M. Blüher, *Nat. Rev. Endocrinol.* **2019**, *15*, 288.
[3] J. G. Ryall, T. Cliff, S. Dalton, V. Sartorelli, *Cell Stem. Cell* **2015**, *17*, 651.
[4] S. A. Tammen, S. Friso, S. W. Choi, *Mol. Aspects Med.* **2013**, *34*, 753.
[5] I. Lacal, R. Ventura, *Front. Mol. Neurosci.* **2018**, *11*, 292.
[6] Y. Li, *Methods* **2021**, *187*, 104.
[7] Z. A. Kaminsky, T. Tang, S.-C. Wang, C. Ptak, G. H. T. Oh, A. H. C. Wong, L. A. Feldcamp, C. Virtanen, J. Halfvarson, C. Tysk, A. F. McRae, P. M. Visscher, G. W. Montgomery, I. I. Gottesman, N. G. Martin, A. Petronis, *Nat. Genet.* **2009**, *41*, 240.
[8] G. L. Semenza, *Hum. Mutat.* **1994**, *3*, 180.
[9] J. Loscalzo, D. E. Handy, *Pulm. Circ.* **2014**, *4*, 169.
[10] S. C. Wu, Y. Zhang, *Nat. Rev. Mol. Cell Biol.* **2010**, *11*, 607.
[11] D. Prasher, S. C. Greenway, R. B. Singh, *Biochem. Cell. Biol. Biochim. Biol. Cell.* **2020**, *98*, 12.
[12] M. Okano, D. W. Bell, D. A. Haber, E. Li, *Cell* **1999**, *99*, 247.
[13] A. Baccarelli, M. Rienstra, E. J. Benjamin, *Circ. Cardiovasc. Genet.* **2010**, *3*, 567.
[14] S. Friso, F. Pizzolo, S.-W. Choi, P. Guarini, A. Castagna, V. Ravagnani, A. Carletto, P. Pattini, R. Corrocher, O. Olivieri, *Atherosclerosis* **2008**, *199*, 323.
[15] M. P. Turunen, E. Aavik, S. Ylä-Herttuala, *Biochim. Biophys. Acta* **2009**, *1790*, 886.
[16] K. W. Makar, C. B. Wilson, *J. Immunol.* **2004**, *173*, 4402.
[17] M. Movassagh, M. K. Choy, M. Goddard, M. R. Bennett, T. A. Down, R. S. Y. Foo, *PLoS One* **2010**, *5*, e8564.
[18] G. Lund, L. Andersson, M. Lauria, M. Lindholm, M. F. Fraga, A. Villar-Garea, E. Ballestar, M. Esteller, S. Zaina, *J. Biol. Chem.* **2004**, *279*, 29147.
[19] J. Zhong, G. Agha, A. A. Baccarelli, *Circ. Res.* **2016**, *118*, 119.
[20] W. Zhang, M. Song, J. Qu, G. H. Liu, *Circ. Res.* **2018**, *123*, 773.
[21] T. Zhang, S. Cooper, N. Brockdorff, *EMBO Rep.* **2015**, *16*, 1467.
[22] K. Hyun, J. Jeon, K. Park, J. Kim, *Exp. Mol. Med.* **2017**, *49*, e324.
[23] B. E. Collins, C. B. Greer, B. C. Coleman, J. D. Sweatt, *Epigenet. Chromatin* **2019**, *12*, 7.
[24] S. Costantino, S. A. Mohammed, S. Ambrosini, F. Paneni, *Atherosclerosis* **2019**, *281*, 150.
[25] Y. Yang, Y. Luan, R. X. Yuan, Y. Luan, *Front. Cardiovasc. Med.* **2021**, *8*, 710053.
[26] E. Gorica, S. A. Mohammed, S. Ambrosini, V. Calderone, S. Costantino, F. Paneni, *Front. Cardiovasc. Med.* **2022**, *9*, 923014.
[27] D. Douillet, C. C. Sze, C. Ryan, A. Piunti, A. P. Shah, M. Ugarenko, S. A. Marshall, E. J. Rendleman, D. Zha, K. A. Helmin, Z. Zhao, K. Cao, M. A. Morgan, B. D. Singer, E. T. Bartom, E. R. Smith, A. Shilatifard, *Nat. Genet.* **2020**, *52*, 615.
[28] S. Zhou, S. Feng, W. Qin, X. Wang, Y. Tang, S. Yuan, *Stem. Cell. Rev. Rep.* **2021**, *17*, 562.
[29] L. Y. Huang, D. W. Hsu, C. J. Pears, *Nucl. Acids Res.* **2021**, *49*, 3781.
[30] K. M. Bernt, N. Zhu, A. U. Sinha, S. Vempati, J. Faber, A. V. Krivtsov, Z. Feng, N. Punt, A. Daigle, L. Bullinger, R. M. Pollock, V. M. Richon, A. L. Kung, S. A. Armstrong, *Cancer Cell* **2011**, *20*, 66.
[31] T. H. Beacon, W. Xu, J. R. Davie, *Gene* **2020**, *742*, 144593.
[32] E. M. Stein, G. Garcia-Manero, D. A. Rizzieri, R. Tibes, J. G. Berdeja, M. R. Savona, M. Jongen-Lavrenic, J. K. Altman, B. Thomson, S. J. Blakemore, S. R. Daigle, N. J. Waters, A. B. Suttle, A. Clawson, R. Pollock, A. Krivtsov, S. A. Armstrong, J. DiMartino, E. Hedrick, B. Löwenberg, M. S. Tallman, *Blood* **2018**, *131*, 2661.
[33] T. Fujii, T. S. ichiro, K. Yamaguchi, S. Watanabe, Y. Furukawa, *PLoS One* **2011**, *6*, e23491.
[34] J. Wang, P. Li, X. Xu, B. Zhang, J. Zhang, *Front. Immunol.* **2020**, *11*, 907.
[35] G. Yang, X. Zhang, X. Weng, P. Liang, X. Dai, S. Zeng, H. Xu, H. Huan, M. Fang, Y. Li, D. Xu, Y. Xu, *Basic Res. Cardiol.* **2017**, *112*, 22.
[36] J. Gräff, L. H. Tsai, *Nat. Rev. Neurosci.* **2013**, *14*, 97.
[37] A. J. Bannister, T. Kouzarides, *Cell Res.* **2011**, *21*, 381.
[38] M. S. Fallah, D. Szarics, C. M. Robson, J. H. Eubanks, *Front. Genet.* **2020**, *11*, 613098.
[39] H. T. Lee, S. Oh, D. H. Ro, H. Yoo, Y. W. Kwon, *J. Lipid. Atheroscler.* **2020**, *9*, 419.
[40] M. D. Cantley, D. R. Haynes, *Inflammopharmacology* **2013**, *21*, 301.

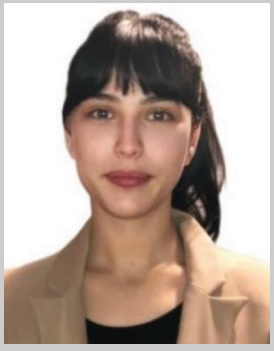
[41] L. Göschl, T. Preglej, N. Boucheron, V. Saferding, L. Müller, A. Platzer, K. Hirahara, H.-Y. Shih, J. Backlund, P. Matthias, B. Niederreiter, A. Hladik, M. Kugler, G. A. Gualdoni, C. Scheinecker, S. Knapp, C. Seiser, R. Holmdahl, K. Tillmann, R. Plasenzotti, B. Podesser, D. Aletaha, J. S. Smolen, T. Karonitsch, G. Steiner, W. Ellmeier, M. Bonelli, *J. Autoimmun.* **2020**, *108*, 102379.
[42] S. Kulthinee, N. Yano, S. Zhuang, L. Wang, T. C. Zhao, *Pathophysiol. Off. J. Int. Soc. Pathophysiol.* **2022**, *29*, 471.
[43] W. Liao, A. Y. H. Lim, W. S. D. Tan, J. Abisheganaden, W. S. F. Wong, *Br. J. Pharmacol.* **2020**, *177*, 3662.
[44] P. J. Barnes, *Annu. Rev. Physiol.* **2009**, *71*, 451.
[45] H. J. Kee, G. H. Eom, H. Joung, S. Shin, J.-R. Kim, Y. K. Cho, N. Choe, B.-W. Sim, D. Jo, M. H. Jeong, K. K. Kim, J.-S. Seo, H. Kook, *Circ. Res.* **2008**, *103*, 1259.
[46] H. J. Kee, H. Kook, *J. Mol. Cell. Cardiol.* **2009**, *47*, 770.
[47] X. Chen, I. Barozzi, A. Termanini, E. Prosperini, A. Recchiuti, J. Dalli, F. Mietton, G. Matteoli, S. Hiebert, G. Natoli, *Proc. Natl. Acad. Sci. USA* **2012**, *109*, E2865.
[48] M. Haberland, R. L. Montgomery, E. N. Olson, *Nat. Rev. Genet.* **2009**, *10*, 32.
[49] T. Crotti, M. D. Smith, R. Hirsch, S. Soukoulis, H. Weedon, M. Capone, M. J. Ahern, D. Haynes, *J. Periodontal. Res.* **2003**, *38*, 380.
[50] S. Chang, B. D. Young, S. Li, X. Qi, J. A. Richardson, E. N. Olson, *Cell* **2006**, *126*, 321.
[51] S. Lu, H. Li, K. Li, X. D. Fan, *Biochem. Biophys. Res. Commun.* **2018**, *503*, 1322.
[52] D. H. Kwon, J. Ryu, Y. K. Kim, H. Kook, *Int. J. Mol. Sci.* **2020**, *21*, 3246.
[53] J. Weisell, P. Ohukainen, J. Näpänkangas, S. Ohlmeier, U. Bergmann, T. Peltonen, P. Taskinen, H. Ruskoaho, J. Rysä, *BMC Cardiovasc. Disord.* **2019**, *19*, 306.
[54] C. Yanginlar, C. Logie, *Biochim. Biophys. Acta Gene Regul. Mech.* **2018**, *1861*, 54.
[55] J. K. W. Lam, M. Y. T. Chow, Y. Zhang, S. W. S. Leung, *Mol. Ther. Nucl. Acids* **2015**, *4*, e252.
[56] F. P. Marchese, I. Raimondi, M. Huarte, *Genome Biol.* **2017**, *18*, 206.
[57] R. Chen, S. K. Wang, J. A. Belk, L. Amaya, Z. Li, A. Cardenas, B. T. Abe, C. K. Chen, P. A. Wender, H. Y. Chang, *Nat. Biotechnol.* **2023**, *41*, 262.
[58] A. A. Mamun, M. J. O'Callaghan, G. M. Williams, J. M. Najman, *PLoS One* **2012**, *7*, e41106.
[59] N. Leybovitz-Haleluya, T. Wainstock, D. Landau, E. Sheiner, *Reprod. Toxicol.* **2018**, *78*, 69.
[60] L. Högberg, S. Cnattingius, C. Lundholm, B. M. D'Onofrio, N. Långström, A. N. Iliadou, *J. Hypertens.* **2012**, *30*, 693.
[61] P. Agarwal, T. S. Morriseau, S. M. Kereliuk, C. A. Doucette, B. A. Wicklow, V. W. Dolinsky, *Crit. Rev. Clin. Lab. Sci.* **2018**, *55*, 71.
[62] L. H. Lumey, A. C. J. Ravelli, L. G. Wiessing, J. G. Koppe, P. E. Treffers, Z. A. Stein, *Paediatr. Perinat. Epidemiol.* **1993**, *7*, 354.
[63] T. Roseboom, S. de Rooij, R. Painter, *Early Hum. Dev.* **2006**, *82*, 485.
[64] M. F. Lopez, L. Zheng, J. Miao, R. Gali, G. Gorski, J. N. Hirschhorn, *Am. J. Physiol. Endocrinol. Metab.* **2018**, *315*, E735.
[65] T. D. Clausen, E. R. Mathiesen, T. Hansen, O. Pedersen, D. M. Jensen, J. Lauenborg, L. Schmidt, P. Damm, *J. Clin. Endocrinol. Metab.* **2009**, *94*, 2464.
[66] F. Paneni, *World J. Diabetes* **2015**, *6*, 326.
[67] M. C. Gage, N. Y. Yuldasheva, H. Viswambharan, P. Sukumar, R. M. Cubbon, S. Galloway, H. Imrie, A. Skromna, J. Smith, C. L. Jackson, M. T. Kearney, S. B. Wheatcroft, *Atherosclerosis* **2013**, *230*, 131.
[68] Y. Hasegawa, T. Saito, T. Ogihara, Y. Ishigaki, T. Yamada, J. Imai, K. Uno, J. Gao, K. Kaneko, T. Shimosawa, T. Asano, T. Fujita, Y. Oka, H. Katagiri, *Circulation* **2012**, *125*, 1122.
[69] C. E. Tabit, S. M. Shenouda, M. Holbrook, J. L. Fetterman, S. Kiani, A. A. Frame, M. A. Kluge, A. Held, M. M. Dohadwala, N. Gokce, M. G. Farb, J. Rosenzweig, N. Ruderman, J. A. Vita, N. M. Hamburg, *Circulation* **2013**, *127*, 86.
[70] S. Costantino, F. Paneni, A. Virdis, S. Hussain, S. A. Mohammed, G. Capretti, A. Akhmedov, K. Dalgaard, S. Chiandotto, J. A. Pospisilik, T. Jenuwein, M. Giorgio, M. Volpe, S. Taddei, T. F. Lüscher, F. Cosentino, *Eur. Heart J.* **2019**, *40*, 383.
[71] B. Illi, S. Nanni, A. Scopece, A. Farsetti, P. Biglioli, M. C. Capogrossi, C. Gaetano, *Circ. Res.* **2003**, *93*, 155.
[72] J. Dunn, H. Qiu, S. Kim, D. Jjingo, R. Hoffman, C. W. Kim, I. Jang, D. J. Son, D. Kim, C. Pan, Y. Fan, I. K. Jordan, H. Jo, *J. Clin. Invest.* **2014**, *124*, 3187.
[73] J. Zhou, Y. S. Li, K. C. Wang, S. Chien, *Cell Mol. Bioeng.* **2014**, *7*, 218.
[74] Y. Z. Jiang, J. M. Jiménez, K. Ou, M. E. McCormick, L. D. Zhang, P. F. Davies, *Circ. Res.* **2014**, *115*, 32.
[75] J. J. Chiu, S. Chien, *Physiol. Rev.* **2011**, *91*, 327.
[76] K. H. Ku, N. Subramaniam, P. A. Marsden, *Hypertension* **2019**, *74*, 467.
[77] N. Arslan, S. Isik, O. Uykan, *Acta Bioeng. Biomech.* **2010**, *12*, 3.
[78] M. Inglebert, L. Locatelli, D. Tsvirkun, P. Sinha, J. A. Maier, C. Misbah, L. Bureau, *Biomicrofluidics* **2020**, *14*, 024115.
[79] G. Villarreal, Y. Zhang, H. B. Larman, J. Gracia-Sancho, A. Koo, G. García-Cardeña, *Biochem. Biophys. Res. Commun.* **2010**, *391*, 984.
[80] B. E. Danielsson, K. V. Tieu, S. T. Spagnol, K. K. Vu, J. I. Cabe, T. B. Raisch, K. N. Dahl, D. E. Conway, *Mol. Biol. Cell* **2022**, *33*, ar101.
[81] A. Zampetaki, L. Zeng, A. Margariti, Q. Xiao, H. Li, Z. Zhang, A. E. Pepe, G. Wang, O. Habi, E. deFalco, G. Cockerill, J. C. Mason, Y. Hu, Q. Xu, *Circulation* **2010**, *121*, 132.
[82] D.-Y. Lee, C.-I. Lee, T.-E. Lin, S. H. Lim, J. Zhou, Y.-C. Tseng, S. Chien, J.-J. Chiu, *Proc. Natl. Acad. Sci. USA* **2012**, *109*, 1967.
[83] R. Islam, C. Lai, *Epigenomes* **2019**, *3*, 20.
[84] Y. Fang, D. Wu, K. G. Birukov, in *Comprehensive Physiology*, (Ed: R. Terjung), Wiley, New York **2019**, pp. 873–904. https://onlinelibrary.wiley.com/doi/10.1002/cphy.c180020.
[85] S. Ultimo, G. Zauli, A. M. Martelli, M. Vitale, J. A. McCubrey, S. Capitani, L. M. Neri, *OncoTargets Ther.* **2018**, *9*, 17238.
[86] R. Ji, Y. Cheng, J. Yue, J. Yang, X. Liu, H. Chen, D. B. Dean, C. Zhang, *Circ. Res.* **2007**, *100*, 1579.
[87] P. F. Davies, *Nat. Clin. Pract. Cardiovasc. Med.* **2009**, *6*, 16.
[88] J. Zhou, K.-C. Wang, W. Wu, S. Subramaniam, J. Y.-J. Shyy, J.-J. Chiu, J. Y.-S. Li, S. Chien, *Proc. Natl. Acad. Sci. USA* **2011**, *108*, 10355.
[89] M. Weber, M. B. Baker, J. P. Moore, C. D. Searles, *Biochem. Biophys. Res. Commun.* **2010**, *393*, 643.
[90] I. Cantone, A. G. Fisher, *Nat. Struct. Mol. Biol.* **2013**, *20*, 282.
[91] A. Baccarelli, S. Ghosh, *Curr. Opin. Clin. Nutr. Metab. Care* **2012**, *15*, 323.
[92] S. Mitra, M. Khaidakov, J. Lu, S. Ayyadevara, J. Szwedo, X. W. Wang, C. Chen, S. Khaidakov, S. R. Kasula, A. Stone, I. Pogribny, J. L. Mehta, *Am. J. Physiol. Heart Circ. Physiol.* **2011**, *301*, H506.
[93] A. D. Mahmoud, M. D. Ballantyne, V. Miscianinov, K. Pinel, J. Hung, J. P. Scanlon, J. Iyinikkel, J. Kaczynski, A. S. Tavares, A. C. Bradshaw, N. L. Mills, D. E. Newby, A. Caporali, G. W. Gould, S. J. George, I. Ulitsky, J. C. Sluimer, J. Rodor, A. H. Baker, *Circ. Res.* **2019**, *125*, 535.
[94] K. M. Michalik, X. You, Y. Manavski, A. Doddaballapur, M. Zörnig, T. Braun, D. John, Y. Ponomareva, W. Chen, S. Uchida, R. A. Boon, S. Dimmeler, *Circ. Res.* **2014**, *114*, 1389.
[95] T. Josefs, R. A. Boon, *Curr. Atheroscler. Rep.* **2020**, *22*, 55.
[96] S. Cremer, K. M. Michalik, A. Fischer, L. Pfisterer, N. Jaé, C. Winter, R. A. Boon, M. Muhly-Reinholz, D. John, S. Uchida, C. Weber, W. Poller, S. Günther, T. Braun, D. Y. Li, L. Maegdefessel, L. Perisic Matic, U. Hedin, O. Soehnlein, A. Zeiher, S. Dimmeler, *Circulation* **2019**, *139*, 1320.
[97] Z. Chen, T. P. Shentu, L. Wen, D. A. Johnson, J. Y. J. Shyy, *Antioxid. Redox. Signal.* **2013**, *19*, 1522.

[98] G. Santulli, in *microRNA: Basic Science*, (Ed: G. Santulli), Springer International Publishing, Cham **2015**, pp. 53–77, http://link.springer.com/10.1007/978-3-319-22380-3_4.
[99] A. Mantovani, P. Allavena, A. Sica, F. Balkwill, *Nature* **2008**, *454*, 436.
[100] S. Y. X. Tan, J. Zhang, W. W. Tee, *Front. Cell. Dev. Biol.* **2022**, *10*, 931493.
[101] M. Wielscher, P. R. Mandaviya, B. Kuehnel, R. Joehanes, R. Mustafa, O. Robinson, Y. Zhang, B. Bodinier, E. Walton, P. P. Mishra, P. Schlosser, R. Wilson, P.-C. Tsai, S. Palaniswamy, R. E. Marioni, G. Fiorito, G. Cugliari, V. Karhunen, M. Ghanbari, B. M. Psaty, M. Loh, J. C. Bis, B. Lehne, N. Sotoodehnia, I. J. Deary, M. Chadeau-Hyam, J. A. Brody, A. Cardona, E. Selvin, A. K. Smith, et al., *Nat. Commun.* **2022**, *13*, 2408.
[102] B. Hussey, R. P. Steel, B. Gyimah, J. C. Reynolds, I. M. Taylor, M. R. Lindley, S. Mastana, *Mol. Genet. Genomic Med.* **2021**, *9*, e1679.
[103] M. A. Valenzuela, *World J. Gastroenterol.* **2015**, *21*, 12742.
[104] T.-H. Pham, C. Benner, M. Lichtinger, L. Schwarzfischer, Y. Hu, R. Andreesen, W. Chen, M. Rehli, *Blood* **2012**, *119*, e161.
[105] L. ChÃ¡vez-GalÃ¡n, M. L. Olleros, D. Vesin, I. Garcia, *Front. Immunol.* **2015**, *26*, 263.
[106] D. Das, N. Karthik, R. Taneja, *Front. Cell. Dev. Biol.* **2021**, *9*, 756458.
[107] S. Raghuraman, I. Donkin, S. Versteyhe, R. Barrès, D. Simar, *Trends Endocrinol. Metab.* **2016**, *27*, 782.
[108] F. Miao, I. G. Gonzalo, L. Lanting, R. Natarajan, *J. Biol. Chem.* **2004**, *279*, 18091.
[109] Y. Li, M. A. Reddy, F. Miao, N. Shanmugam, J.-K. Yee, D. Hawkins, B. Ren, R. Natarajan, *J. Biol. Chem.* **2008**, *283*, 26771.
[110] L. Liu, M. Mei, S. Yang, Q. Li, *Mediators Inflamm.* **2014**, *2014*, 418185.
[111] A. Fernández-Sánchez, E. Madrigal-Santillán, M. Bautista, J. Esquivel-Soto, Á. Morales-González, C. Esquivel-Chirino, I. Durante-Montiel, G. Sánchez-Rivera, C. Valadez-Vega, J. A. Morales-González, *Int. J. Mol. Sci.* **2011**, *12*, 3117.
[112] K. Rohde, M. Keller, L. la Cour Poulsen, M. Blüher, P. Kovacs, Y. Böttcher, *Metabolism* **2019**, *92*, 37.
[113] M. Samblas, F. I. Milagro, A. Martínez, *Epigenetics* **2019**, *14*, 421.
[114] A. M. Mahmoud, *Int. J. Mol. Sci.* **2022**, *23*, 1341.
[115] M. R. Irvin, D. Zhi, R. Joehanes, M. Mendelson, S. Aslibekyan, S. A. Claas, K. S. Thibeault, N. Patel, K. Day, L. W. Jones, L. Liang, B. H. Chen, C. Yao, H. K. Tiwari, J. M. Ordovas, D. Levy, D. Absher, D. K. Arnett, *Circulation* **2014**, *130*, 565.
[116] D. You, E. Nilsson, D. E. Tenen, A. Lyubetskaya, J. C. Lo, R. Jiang, J. Deng, B. A. Dawes, A. Vaag, C. Ling, E. D. Rosen, S. Kang, *Elife* **2017**, *6*, e30766.
[117] K. Papsdorf, A. Brunet, *Trends Cell. Biol.* **2019**, *29*, 97.
[118] R. Stienstra, C. Duval, M. Müller, K. S. PPARs, *PPAR Res.* **2007**, *2007*, 95974.
[119] C. Crewe, Y. Zhu, V. A. Paschoal, N. Joffin, A. L. Ghaben, R. Gordillo, D. Y. Oh, G. Liang, J. D. Horton, P. E. Scherer, *JCI Insight* **2019**, *5*, 29397.
[120] V. Giandomenico, M. Simonsson, E. Grönroos, J. Ericsson, *Mol. Cell. Biol.* **2003**, *23*, 2587.
[121] Y. Huang, C. Jin, Y. Zheng, X. Li, S. Zhang, Y. Zhang, L. Jia, W. Li, *Sci. Rep.* **2017**, *7*, 8080.
[122] A. Vaiserman, O. Lushchak, *Int. J. Genomics* **2019**, *2019*, 3821409.
[123] M. E. Cerf, *Front. Endocrinol.* **2013**, *4*, 37.
[124] J. D. Brunzell, R. P. Robertson, R. L. Lerner, W. R. Hazzard, J. W. Ensinck, E. L. Bierman, D. Porte, *J. Clin. Endocrinol. Metab.* **1976**, *42*, 222.
[125] D. L. Eizirik, G. S. Korbutt, C. Hellerström, *J. Clin. Invest.* **1992**, *90*, 1263.
[126] R. P. Robertson, J. Harmon, P. O. Tran, Y. Tanaka, H. Takahashi, *Diabetes* **2003**, *52*, 581.
[127] E. Hall, P. Volkov, T. Dayeh, K. Bacos, T. Rönn, M. D. Nitert, C. Ling, *BMC Med.* **2014**, *12*, 103.
[128] G. H. Genetic, *Curr. Diabetes Rev.* **2017**, *13*, 132.
[129] S. A. H. Ahmed, S. A. Ansari, E. P. K. Mensah-Brown, E. BS, *Clin. Epigenet.* **2020**, *12*, 104.
[130] K. Ishikawa, S. Tsunekawa, M. Ikeniwa, T. Izumoto, A. Iida, H. Ogata, E. Uenishi, Y. Seino, N. Ozaki, Y. Sugimura, Y. Hamada, A. Kuroda, K. Shinjo, Y. Kondo, Y. Oiso, *PLoS One* **2015**, *10*, e0115350.
[131] J. Stanik, P. Dusatkova, O. Cinek, L. Valentinova, M. Huckova, M. Skopkova, L. Dusatkova, D. Stanikova, M. Pura, I. Klimes, J. Lebl, D. Gasperikova, S. Pruhova, *Diabetologia* **2014**, *57*, 480.
[132] S. A. Myers, A. Nield, M. Myers, *J. Nutr. Metab.* **2012**, *2012*, 1737121.
[133] G. A. Rutter, F. Chimienti, *Diabetologia* **2015**, *58*, 31.
[134] W. Zheng, J. Guo, Z. S. Liu, *Clin, Epigenet.* **2021**, *13*, 87.
[135] M. Kato, R. Natarajan, *Nat. Rev. Nephrol.* **2014**, *10*, 517.
[136] M. Wegner, D. Neddermann, M. Piorunska-Stolzmann, P. P. Jagodzinski, *Diabetes Res. Clin. Pract.* **2014**, *105*, 164.
[137] L. A. Adams, J. F. Lymp, J. St Sauver, S. O. Sanderson, K. D. Lindor, A. Feldstein, P. Angulo, *Gastroenterology* **2005**, *129*, 113.
[138] E. Dhamija, S. Paul, S. Kedia, *Indian J. Med. Res.* **2019**, *149*, 9.
[139] J. Yu, S. Marsh, J. Hu, W. Feng, C. Wu, *Gastroenterol. Res. Pract.* **2016**, *2016*, 2862173.
[140] E. Buzzetti, M. Pinzani, E. A. Tsochatzis, *Metabolism* **2016**, *65*, 1038.
[141] S. Hwang, Y. He, X. Xiang, W. Seo, S.-J. Kim, J. Ma, T. Ren, S. H. Park, Z. Zhou, D. Feng, G. Kunos, B. Gao, *Hepatology* **2020**, *72*, 412.
[142] T. Mahata, A. S. Sengar, M. Basak, K. Das, A. Pramanick, S. K. Verma, P. K. Singh, S. Biswas, S. Sarkar, S. Saha, S. Chatterjee, M. Das, A. Stewart, B. Maity, *Redox Biol.* **2021**, *46*, 102105.
[143] D. Das, A. Paul, A. Lahiri, M. Adak, S. K. Maity, A. Sarkar, S. Paul, P. Chakrabarti, *Redox Biol.* **2021**, *45*, 102043.
[144] M. Wajner, A. U. Amaral, *Biosci. Rep.* **2016**, *36*, e00281.
[145] C. Nedeva, *Biomolecules* **2021**, *11*, 1011.
[146] V. P. Tryndyak, T. Han, L. Muskhelishvili, J. C. Fuscoe, S. A. Ross, F. A. Beland, I. P. Pogribny, *Mol. Nutr. Food Res.* **2011**, *55*, 411.
[147] H. C. Chen, Y. Z. Chen, C. H. Wang, F. J. Lin, *J. Nutr. Biochem.* **2020**, *77*, 108319.
[148] M. Gaggini, M. Morelli, E. Buzzigoli, R. DeFronzo, E. Bugianesi, A. Gastaldelli, *Nutrients* **2013**, *5*, 1544.
[149] Z. Lai, J. Chen, C. Ding, K. Wong, X. Chen, L. Pu, Q. Huang, X. Chen, Z. Cheng, Y. Liu, X. Tan, H. Zhu, L. Wang, *Obes. Silver Spring Md.* **2020**, *28*, 197.
[150] S. K. Murphy, H. Yang, C. A. Moylan, H. Pang, A. Dellinger, M. F. Abdelmalek, M. E. Garrett, A. Ashley–Koch, A. Suzuki, H. L. Tillmann, M. A. Hauser, A. M. Diehl, *Gastroenterology* **2013**, *145*, 1076.
[151] R. Nogueiras, K. M. Habegger, N. Chaudhary, B. Finan, A. S. Banks, M. O. Dietrich, T. L. Horvath, D. A. Sinclair, P. T. Pfluger, M. H. Tschöp, *Physiol. Rev.* **2012**, *92*, 1479.
[152] F. Nassir, J. Ibdah, *Int. J. Mol. Sci.* **2014**, *15*, 8713.
[153] M. Yamakuchi, M. Ferlito, C. J. Lowenstein, *Proc. Natl. Acad. Sci. USA* **2008**, *105*, 13421.
[154] Y. Dang, D. Luo, M. Rong, G. Chen, *PLoS One* **2013**, *8*, e61054.
[155] L. Goedeke, A. Wagschal, C. Fernández-Hernando, A. M. Näär, *Biochim. Biophys. Acta* **2016**, *1861*, 2047.
[156] T. Csak, S. Bala, D. Lippai, A. Satishchandran, D. Catalano, K. Kodys, G. Szabo, *Liver Int.* **2015**, *35*, 532.
[157] K. Nishida, K. Otsu, *Cardiovasc. Res.* **2017**, *113*, 389.
[158] S. Costantino, A. Akhmedov, G. Melina, S. A. Mohammed, A. Othman, S. Ambrosini, W. J. Wijnen, L. Sada, G. M. Ciavarella, L. Liberale, F. C. Tanner, C. M. Matter, T. Hornemann, M. Volpe, F. Mechta-Grigoriou, G. G. Camici, R. Sinatra, T. F. Lüscher, F. Paneni, *Eur. Heart J.* **2019**, *40*, 997.

[159] A. Dei Cas, S. S. Khan, J. Butler, R. J. Mentz, R. O. Bonow, A. Avogaro, D. Tschoepe, W. Doehner, S. J. Greene, M. Senni, M. Gheorghiade, G. C. Fonarow, *JACC Heart Fail.* **2015**, *3*, 136.
[160] G. G. Schiattarella, D. Rodolico, J. A. Hill, *Cardiovasc. Res.* **2021**, *117*, 423.
[161] S. Mishra, D. A. Kass, *Nat. Rev. Cardiol.* **2021**, *18*, 400.
[162] Y. H. Kao, Y. C. Chen, C. C. Cheng, T. I. Lee, Y. J. Chen, S. A. Chen, *Crit. Care Med.* **2010**, *38*, 217.
[163] J. S. Dobrin, D. Lebeche, *Expert Rev. Cardiovasc. Ther.* **2010**, *8*, 373.
[164] E. R. Chemaly, L. Hadri, S. Zhang, M. Kim, E. Kohlbrenner, J. Sheng, L. Liang, J. Chen, P. K-Raman, R. J. Hajjar, D. Lebeche, *J. Mol. Cell. Cardiol.* **2011**, *51*, 144.
[165] P. Bobbert, A. Jenke, T. Bobbert, U. Kühl, U. Rauch, D. Lassner, C. Scheibenbogen, W. Poller, H.-P. Schultheiss, C. Skurk, *Eur. J. Heart Fail.* **2012**, *14*, 1265.
[166] R. Guo, W. Liu, B. Liu, B. Zhang, W. Li, Y. Xu, *Int. J. Cardiol.* **2015**, *191*, 36.
[167] S. Costantino, F. Paneni, K. Mitchell, S. A. Mohammed, S. Hussain, C. Gkolfos, L. Berrino, M. Volpe, C. Schwarzwald, T. F. Lüscher, F. Cosentino, *Int. J. Cardiol.* **2018**, *268*, 179.
[168] S. Wang, C. Wang, S. Turdi, K. L. Richmond, Y. Zhang, J. Ren, *Int. J. Obes.* **2018**, *42*, 1073.
[169] R. A. DeFronzo, D. Tripathy, *Diabetes Care* **2009**, *32*, S157.
[170] Y. Miao, N. E. Ajami, T.-S. Huang, F.-M. Lin, C.-H. Lou, Y.-T. Wang, S. Li, J. Kang, H. Munkacsi, M. R. Maurya, S. Gupta, S. Chien, S. Subramaniam, Z. Chen, *Nat. Commun.* **2018**, *9*, 292.
[171] S. Jiang, A. M. Teague, J. B. Tryggestad, M. E. Jensen, S. D. Chernausek, *Sci. Rep.* **2020**, *10*, 8314.
[172] S. A. Mohammed, M. Albiero, S. Ambrosini, E. Gorica, G. Karsai, C. M. Caravaggi, S. Masi, G. G. Camici, F. A. Wenzl, V. Calderone, P. Madeddu, S. Sciarretta, C. M. Matter, G. Spinetti, T. F. Lüscher, F. Ruschitzka, S. Costantino, G. P. Fadini, F. Paneni, *Antioxid. Redox. Signal.* **2022**, *36*, 667.
[173] A. Kuroda, T. A. Rauch, I. Todorov, H. T. Ku, I. H. Al-Abdullah, F. Kandeel, Y. Mullen, G. P. Pfeifer, K. Ferreri, *PLoS One* **2009**, *4*, e6953.
[174] Z. Lv, Y. Guo, *Front. Endocrinol.* **2020**, *11*, 191.
[175] Y. Zhang, H. Wang, H. Xiao, *Int. J. Mol. Sci.* **2021**, *22*, 5016.
[176] S. C. Bridgeman, G. C. Ellison, P. E. Melton, P. Newsholme, C. D. S. Mamotte, *Diabetes Obes. Metab.* **2018**, *20*, 1553.
[177] B. Gongol, I. Sari, T. Bryant, G. Rosete, T. Marin, *Int. J. Mol. Sci.* **2018**, *19*, 3238.
[178] T. L. Marin, B. Gongol, F. Zhang, M. Martin, D. A. Johnson, H. Xiao, Y. Wang, S. Subramaniam, S. Chien, J. Y.-J. Shyy, *Sci. Signal.* **2017**, *10*, eaaf7478.
[179] J. Y. Lim, M. A. Oh, W. H. Kim, H. Y. Sohn, S. I. Park, *J. Cell. Physiol.* **2012**, *227*, 1081.
[180] V. N. Anisimov, *Cell Cycle Georget Tex.* **2013**, *12*, 3483.
[181] S. Vigili de Kreutzenberg, G. Ceolotto, A. Cattelan, E. Pagnin, M. Mazzucato, P. Garagnani, V. Borelli, M. G. Bacalini, C. Franceschi, G. P. Fadini, A. Avogaro, *Nutr. Metab. Cardiovasc. Dis.* **2015**, *25*, 686.
[182] C. Cantó, Z. Gerhart-Hines, J. N. Feige, M. Lagouge, L. Noriega, J. C. Milne, P. J. Elliott, P. Puigserver, J. Auwerx, *Nature* **2009**, *458*, 1056.
[183] Q. Xu, C. Yang, Y. Du, Y. Chen, H. Liu, M. Deng, H. Zhang, L. Zhang, T. Liu, Q. Liu, L. Wang, Z. Lou, H. Pei, *Nucl. Acids Res.* **2014**, *42*, 5594.
[184] D. Bungard, B. J. Fuerth, P.-Y. Zeng, B. Faubert, N. L. Maas, B. Viollet, D. Carling, C. B. Thompson, R. G. Jones, S. L. Berger, *Science* **2010**, *329*, 1201.
[185] P. Banerjee, H. Surendran, D. R. Chowdhury, K. Prabhakar, R. Pal, *J. Mol. Med. Berl. Ger.* **2016**, *94*, 1397.
[186] S. Khan, G. Jena, *Chem. Biol. Interact.* **2016**, *254*, 124.
[187] D. Santovito, V. De Nardis, P. Marcantonio, C. Mandolini, C. Paganelli, E. Vitale, F. Buttitta, M. Bucci, A. Mezzetti, A. Consoli, F. Cipollone, *J. Clin. Endocrinol. Metab.* **2014**, *99*, E1681.
[188] D. G. Hardie, F. A. Ross, S. A. Hawley, *Nat. Rev. Mol. Cell Biol.* **2012**, *13*, 251.
[189] G. Arunachalam, A. P. Lakshmanan, S. M. Samuel, C. R. Triggle, H. Ding, *J. Pharmacol. Exp. Ther.* **2016**, *356*, 314.
[190] C. Li, J. Zhang, M. Xue, X. Li, F. Han, X. Liu, L. Xu, Y. Lu, Y. Cheng, T. Li, X. Yu, B. Sun, L. Chen, *Cardiovasc. Diabetol.* **2019**, *18*, 15.
[191] H. el Azzouzi, S. Leptidis, E. Dirkx, J. Hoeks, B. van Bree, K. Brand, E. A. McClellan, E. Poels, J. C. Sluimer, M. M. G. van den Hoogenhof, A.-S. Armand, X. Yin, S. Langley, M. Bourajjaj, S. Olieslagers, J. Krishnan, M. Vooijs, H. Kurihara, A. Stubbs, Y. M. Pinto, W. Krek, M. Mayr, P. A. D. C. Martins, P. Schrauwen, L. J. De Windt, *Cell Metab.* **2013**, *18*, 341.
[192] M. Arow, M. Waldman, D. Yadin, V. Nudelman, A. Shainberg, N. G. Abraham, D. Freimark, R. Kornowski, D. Aravot, E. Hochhauser, M. Arad, *Cardiovasc. Diabetol.* **2020**, *19*, 7.
[193] N. Mohammadzadeh, F. Montecucco, F. Carbone, S. Xu, K. Al-Rasadi, A. Sahebkar, *Eur. J. Clin. Invest.* **2020**, *50*, e13388.
[194] S. Xu, J. Pelisek, Z. G. Jin, *Trends Endocrinol. Metab.* **2018**, *29*, 739.
[195] S. Bridgeman, W. Northrop, G. Ellison, T. Sabapathy, P. E. Melton, P. Newsholme, C. D. S. Mamotte, *Cancers* **2019**, *11*, 516.
[196] J. E. Feig, Y. Shang, N. Rotllan, Y. Vengrenyuk, C. Wu, R. Shamir, I. P. Torra, C. Fernandez-Hernando, E. A. Fisher, M. J. Garabedian, *PLoS One* **2011**, *6*, e28534.
[197] C. Ochoa-Rosales, E. Portilla-Fernandez, J. Nano, R. Wilson, B. Lehne, P. P. Mishra, X. Gao, M. Ghanbari, O. L. Rueda-Ochoa, D. Juvinao-Quintero, M. Loh, W. Zhang, J. S. Kooner, H. J. Grabe, S. B. Felix, B. Schöttker, Y. Zhang, C. Gieger, M. Müller-Nurasyid, M. Heier, A. Peters, T. Lehtimäki, A. Teumer, H. Brenner, M. Waldenberger, M. A. Ikram, J. B. J. van Meurs, O. H. Franco, T. Voortman, J. Chambers, et al., *Diabetes Care* **2020**, *43*, 875.
[198] K. Tikoo, G. Patel, S. Kumar, P. A. Karpe, M. Sanghavi, V. Malek, K. Srinivasan, *Biochem. Pharmacol.* **2015**, *93*, 343.
[199] K. Koushki, S. K. Shahbaz, K. Mashayekhi, M. Sadeghi, Z. D. Zayeri, M. Y. Taba, M. Banach, K. Al-Rasadi, T. P. Johnston, A. Sahebkar, *Clin. Rev. Allergy Immunol.* **2021**, *60*, 175.
[200] B. D. Xiu, G. Griffin, A. H. Lichtman, *Curr. Opin. Lipidol.* **2011**, *22*, 165.
[201] L. E. Wilson, S. Kim, Z. Xu, S. Harlid, D. P. Sandler, J. A. Taylor, *PLoS One* **2015**, *10*, e0138920.
[202] R. Wu, L. Wang, R. Yin, R. Hudlikar, S. Li, H.-C. D. Kuo, R. Peter, D. Sargsyan, Y. Guo, X. Liu, A. Kong, *Mol. Carcinog.* **2020**, *59*, 227.
[203] J. G. C. Peeters, A. Boltjes, R. C. Scholman, S. J. Vervoort, P. J. Coffer, M. Mokry, S. J. Vastert, F. van Wijk, J. van Loosdregt, *Rheumatol. Oxf. Engl.* **2023**, *62*, 2887.
[204] S. Ambrosini, E. Gorica, S. A. Mohammed, S. Costantino, F. Ruschitzka, F. Paneni, *Curr. Opin. Cardiol.* **2022**, *37*, 219.
[205] F. J. Alcaín, J. M. Villalba, *Expert Opin. Ther. Pat.* **2009**, *19*, 403.
[206] J. Olholm, S. K. Paulsen, K. B. Cullberg, B. Richelsen, S. B. Pedersen, *Int. J. Obes* **2010**, *34*, 1546.
[207] D. J. Lomb, G. Laurent, M. C. Haigis, *Biochim. Biophys. Acta* **2010**, *1804*, 1652.
[208] X. Li, *Acta Biochim. Biophys. Sin.* **2013**, *45*, 51.
[209] C. Fernández-Hernando, C. M. Ramírez, L. Goedeke, Y. Suárez, *Arterioscler. Thromb. Vasc. Biol.* **2013**, *33*, 178.
[210] C. L. Gallant-Behm, J. Piper, J. M. Lynch, A. G. Seto, S. J. Hong, T. A. Mustoe, C. Maari, L. A. Pestano, C. M. Dalby, A. L. Jackson, P. Rubin, W. S. Marshall, *J. Invest. Dermatol.* **2019**, *139*, 1073.
[211] F. Motta, A. Pederzani, M. C. Carena, A. Ceribelli, P. B. Wordsworth, M. De Santis, C. Selmi, M. Vecellio, *Curr. Rheumatol. Rep.* **2021**, *23*, 59.

[212] D. S. Hong, Y.-K. Kang, M. Borad, J. Sachdev, S. Ejadi, H. Y. Lim, A. J. Brenner, K. Park, J.-L. Lee, T.-Y. Kim, S. Shin, C. R. Becerra, G. Falchook, J. Stoudemire, D. Martin, K. Kelnar, H. Peltier, V. Bonato, A. G. Bader, S. Smith, S. Kim, V. O'Neill, M. S. Beg, *Br. J. Cancer* **2020**, *122*, 1630.
[213] K. J. Rayner, F. J. Sheedy, C. C. Esau, F. N. Hussain, R. E. Temel, S. Parathath, J. M. van Gils, A. J. Rayner, A. N. Chang, Y. Suarez, C. Fernandez-Hernando, E. A. Fisher, K. J. Moore, *J. Clin. Invest.* **2011**, *121*, 2921.
[214] H. Yki-Järvinen, *Lancet Diabetes Endocrinol.* **2014**, *2*, 901.
[215] H. L. Kammoun, H. Chabanon, I. Hainault, S. Luquet, C. Magnan, T. Koike, P. Ferré, F. Foufelle, *J. Clin. Invest.* **2009**, *119*, 1201.
[216] J. Vojinovic, N. Damjanov, *Mol. Med.* **2011**, *17*, 397.
[217] K. L. Cheung, C. Kim, M. M. Zhou, *Front. Mol. Biosci.* **2021**, *8*, 728777.
[218] T. Ullmann, S. Luckhardt, M. Wolf, M. J. Parnham, E. Resch, *Int. J. Mol. Sci.* **2021**, *22*, 3022.
[219] C. Tonini, M. Colardo, B. Colella, S. Di Bartolomeo, F. Berardinelli, G. Caretti, V. Pallottini, M. Segatto, *Int. J. Mol. Sci.* **2020**, *21*, 1297.
[220] E. Leng, Y. Xiao, Z. Mo, Y. Li, Y. Zhang, X. Deng, M. Zhou, C. Zhou, Z. He, J. He, L. Xiao, J. Li, W. Li, *BMC Complement Altern. Med.* **2018**, *18*, 122.
[221] S. R. Nagarajan, M. Paul-Heng, J. R. Krycer, D. J. Fazakerley, A. F. Sharland, A. J. Hoy, *Am. J. Physiol. Endocrinol. Metab.* **2019**, *316*, E578.
[222] F. Sun, Q. Zhu, T. Li, M. Saeed, Z. Xu, F. Zhong, R. Song, M. Huai, M. Zheng, C. Xie, L. X, H. Yu, *Adv. Sci.* **2021**, *8*, 2002746.
[223] L. M. Tsujikawa, L. Fu, S. Das, C. Halliday, B. D. Rakai, S. C. Stotz, C. D. Sarsons, D. Gilham, E. Daze, S. Wasiak, D. Studer, K. D. Rinker, M. Sweeney, J. O. Johansson, N. C. W. Wong, E. Kulikowski, *Clin. Epigenet.* **2019**, *11*, 102.
[224] S. Wasiak, K. E. Dzobo, B. D. Rakai, Y. Kaiser, M. Versloot, M. Bahjat, S. C. Stotz, L. Fu, M. Sweeney, J. O. Johansson, N. C. W. Wong, E. S. G. Stroes, J. Kroon, E. Kulikowski, *Clin. Epigenet.* **2020**, *12*, 166.
[225] K. K. Ray, S. J. Nicholls, K. A. Buhr, H. N. Ginsberg, J. O. Johansson, K. Kalantar-Zadeh, E. Kulikowski, P. P. Toth, N. Wong, M. Sweeney, G. G. Schwartz, *JAMA, J. Am. Med. Assoc.* **2020**, *323*, 1565.

Martin Geiger is a postdoctoral fellow in the field of atherosclerosis. He holds a medical degree from Pontifical University of Campinas, Brazil and a Ph.D. in Science from the State University of Campinas, Brazil. He participates, as visiting fellow in various projects, at the Center for Translational and Experimental Cardiology (CTEC) at the University Hospital Zurich and the University of Zurich. In recent years, in addition to the field of assistance in medicine, he has become interested in basic research. He is author of 11 peer-reviewed articles.



Era Gorica is a postdoctoral fellow in the field of cardiovascular epigenetics. She holds a Pharmacy degree from Albanian University in Tirana and a Ph.D. in Science of Drug and Bioactive Substances from the University of Pisa, Italy. The Fellow is an alumni of University of Zurich for her last semester of Ph.D. performed there and currently works at the Center for Translational and Experimental Cardiology (CTEC) at the University Hospital Zurich and the University of Zurich. She is author of 14 peer-reviewed articles and has an h-index 10.

Francesco Paneni is professor of Cardiology at the University of Zurich and Head of the Cardiometabolic Division at the Department of Cardiology, Zurich University Hospital. He is also Director of the Center for Translational and Experimental Cardiology (CTEC) at the Zurich University Hospital and Group Leader of the Cardiovascular Epigenetics lab within CTEC. Worked as research fellow at Mount Sinai Medical Centre and trained as a post-doctoral fellow at the Institute of Cardiovascular Physiology, University of Zurich and the Center for Molecular Medicine at the Karolinska Institute. He is author of 160 peer-reviewed articles.

