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Role of Epigenetics and Metabolomics in Predicting Endothelial Dysfunction in Type 2 Diabetes

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Type 2 diabetes (T2D) is a worldwide health problem and cardiovascular disease (CVD) is a leading cause of morbidity and mortality in T2D patients, making the prevention of CVD onset a major priority. It is therefore crucial to optimize diagnosis and treatment to reduce this burden. Endothelial dysfunction is one of the most important prognostic factors for CVD progression, thus novel approaches to identify the early phase of endothelial dysfunction may lead to specific preventive measures to reduce the occurrence of CVD. Nowadays, multiomics approaches have provided unprecedented opportunities to stratify T2D patients into endotypes, improve therapeutic treatment and outcome and amend the survival prediction. Among omics strategies, epigenetics and metabolomics are gaining increasing interest. Recently, a dynamic correlation between metabolic pathways and gene expression through chromatin remodeling, such as DNA methylation, has emerged, indicating new perspectives on the regulatory networks impacting cellular processes. Thus, a better understanding of epigenetic-metabolite relationships can provide insight into the physiological processes altered early in the endothelium that ultimately head to disease development. Here, recent studies on epigenetics and metabolomics related to CVD prevention potentially useful to identify disease biomarkers, as well as new therapies hopefully targeting the early phase of endothelial dysfunction are highlighted.

1. Introduction

1.1. Type 2 Diabetes and the Role of Endothelial Dysfunction in Cardiovascular Disease

Type 2 Diabetes (T2D) is a chronic metabolic disorder characterized by persistent hyperglycemia and associated with increased prevalence of cardiovascular disease (CVD). Despite the tremendous efforts invested in the research of diabetes and related cardiovascular complications, the search for innovative therapies for disease prevention and treatment is far from finished. Improvement of risk prediction for T2D and CVD is critical to the identification of high-risk individuals who could benefit from preventive approaches.

Endothelial dysfunction is a critical early event in the pathogenesis of atherosclerosis, contributing to plaque initiation and progression. The endothelium represents the interface between blood and tissue, and it is affected by changes in blood composition and blood flow, therefore playing a crucial role in vascular homeostasis. It regulates vascular tone, permeability, the balance between coagulation and fibrinolysis, the inflammatory activity, and cell proliferation.

Many factors contribute to endothelial dysfunction in T2D, including aging, obesity, hyperlipidemia, hypertension, low-grade inflammation, insulin resistance, and hyperglycemia. These factors lead to the release of adipokines and cytokines in vascular endothelium and to the accumulation of glucose and glycated proteins in endothelial cells, inducing the impairment of insulin-stimulated vasodilatation and vascular inflammation.[1] Hyperglycaemia causes several cellular events thus increasing the production of reactive oxygen species that following interaction with Nitric oxide (NO) form peroxynitrite[2,3] Peroxynitrites may oxidize the nitric oxide synthase (NOS) and co-factor tetrahydrobiopterin (BH4) leading to a process called NOS uncoupling, in which the enzyme preferentially increases superoxide anion production over NO production. Additionally, mitochondrial production of superoxide anion also increases intracellular production of advanced glycation end products (AGEs)[4] that negatively affect cellular function both by altering protein function and by

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activating AGEs receptor (RAGE). AGEs increase the production of oxygen-derived free radicals, and RAGE activation increases intracellular enzymatic superoxide production[5]

In addition, superoxide anion activates protein kinase C (PKC), or vice versa, activation of PKC may contribute to superoxide generation through the regulation and activation of membrane-associated NAD(P)H-dependent oxidase.[6]

Furthermore, diabetes is also characterized by high circulating levels of free fatty acids due to their increased release from adipose tissue and diminished uptake by skeletal muscle[7] Free fatty acids may impair endothelial function through activation of PKC and reduction of Insulin receptor substrate 1 (IRS1) – associated Phosphoinositide 3-kinase (PI3K), that reduce the NO production. Insulin signaling via the mitogen-activated protein kinase pathway remains intact.

Hyperinsulinemia can induce PI3K and Akt-dependent signaling pathways impairment, whereas over activates Mitogen-Activated Protein Kinases (MAPK-pathways), creating an imbalance between PI3K and MAPK-dependent functions of insulin. MAPK activation is associated with increased endothelin (ET-1) production and a greater level of inflammation and thrombosis[8,9] MAP-kinase signaling increases also the expression of adhesion molecules like VCAM-1 and E-selectin.[1]

Chronic inflammation in diabetes is mainly based on the increased plasma concentrations of C-reactive protein (CRP), fibrinogen, IL-6, IL-1, and Tumor Necrosis Factorα[10] These inflammatory cytokines enhance vascular permeability and leukocyte adhesion to the endothelium, facilitating thrombus formation by the increase of procoagulant activity and the impairment of fibrinolysis via stimulation of plasminogen activator inhibitor-1 (PAI-1).

In addition, nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) is a key factor in vascular inflammation; it induces gene expression of several cytokines which increase adhesion of monocytes, neutrophils, and macrophages to the endothelium resulting in cell damage. On the other hand, NF-κB is also a regulator of genes involved in cell proliferation and cell survival. Once activated, NF-κB translocates from the cytoplasm to the nucleus to regulate the expression of genes such as vascular adhesion molecule-1 Vascular adhesion molecule-1 (VCAM-1), E-selectin, Intercellular adhesion molecule-1 (ICAM-1), IL-1, IL-6, IL-8, Monocyte Chemoattractant Protein-1 (MCP-1), PAI-1, and NOS. Vascular inflammation and endothelial dysfunction play an important role in the pathogenesis of T2D through a bidirectional relationship between hyperinsulinemia and low-grade chronic inflammation. Therefore, taking into account all these occurrences, innovative attempts to avoid endothelial dysfunction are of extreme clinical relevance. Indeed, nowadays there is an urgent need to prevent disease onset and progression by identifying endothelial dysfunction at a very early phase[11]

1.2. Omics Approach to Identify Early Endothelial Dysfunction

In the latest years, advanced phenotyping of cardiovascular diseases has evolved with the application of unbiased methods to phenotype disease. The emergence of omics technologies, allowing a large simultaneous analysis of genes, transcripts, proteins, and metabolites, has generated tons of data with the final identification of pathways and potential biomarkers related to specific diseases[12]

In the context of T2D and cardiovascular complications, a global profiling of genome, transcriptome, miRNA-ome, DNA methylome, and metabolome combining different omics strategies could help in defining early endothelial dysfunction, investigating pathophysiological mechanisms and identifying new potential predictive biomarkers[13,14,15,16] Indeed, golden standard techniques to assess early endothelial dysfunction are currently unavailable[17] Furthermore, genetic variants associated with diabetes and cardiovascular complications are constantly growing, making personalized medicine highly promising for disease prevention and treatment.

Epigenetics, defined as heritable changes in gene function without any changes in the DNA sequence, seems to contribute to development of T2D and related complications. Hence it is feasible to translate current epigenetics knowledge into the clinic to decrease disease prevalence and to develop innovative therapies.

Furthermore, among omics technologies, metabolomics besides the comprehension of physiologic pathways aims to develop diagnostic biomarkers that could serve as tools for clinical practice, diagnosis, prognosis, and predictors of therapeutic response. Application of metabolomics approaches to complex metabolic disorders such as diabetes, is of relevance since alterations of metabolic processes are expected to be directly related to relevant disease endpoints. In addition, emphasis has been placed on a patient-centered approach for treatment of T2D, creating the need for having indicators for future response for individual therapies.

Here we discuss how epigenetics and metabolomics may speed up early identification of endothelial dysfunction and prompt new interventions to prevent/slow down CVD.

2. Epigenetics and Endothelial Dysfunction in Type 2 Diabetes

Identifying people with a high risk of developing T2D and its complications is vital for disease prevention. It is also crucial that patients who have already been diagnosed with T2D receive optimal glucose-lowering treatment. Hence, there is a need for clinically useful biomarkers that predict T2D and related complications as well as response to therapy. Recent evidence suggests that targeting epigenetic mechanisms might be promising therapeutic strategies[18,19,20,21,22] and epigenetic editing might be one of them[23,24,25,26] Accumulating evidence suggest that the progression of diabetes and its vascular complications could be the result of a complex interaction between environmental and genetic factors, in which epigenetics plays a key role[27,28,29,30] Indeed, epigenetic changes that occur in response to environmental stimuli have been considered as a crucial aspect in etiology and inheritance of pathological phenotypes that cannot be explained by genetic mutations alone[31,32] Recently, epigenome-wide association studies (EWAS) expanded considerably increasing the knowledge of epigenetic mechanisms, thanks to the growing availability of DNA methylation arrays and high-throughput sequencing platforms, whose results are analyzed using bioinformatics tools capable of integrating multi-omics datasets. In addition, single-cell sequencing approaches and transposase-accessible chromatin-sequencing will further improve the EWAS

outcome by unveiling cell type-specific epigenetic[33] Epigenome-wide association studies in cohorts with diabetes are contributing to the discover of new epigenetic changes potentially involved in diabetic vascular complications[34,35,30] Therefore, epigenetic marks have been considered as possible biomarkers for early intervention in T2D, providing new insights on the pathogenesis of diabetic complications and useful tools for precision medicine[26] (**Table 1**). In particular, a deep investigation of epigenetic modifications related to diabetes-associated endothelial dysfunction might certainly represent a promising strategy for identifying individuals with higher susceptibility to developing cardiovascular complications. Moreover, a better knowledge of the epigenetic mechanisms might set the basis for new therapeutic targets and more appropriate therapies[36,37]

Several evidence demonstrated the key role of epigenetic regulation in different biological processes. For example, pluripotent stem cells which have the same genetic code differentiate towards different cell lines (i.e, fibroblasts, myocytes) through specific epigenetic rearrangements[38] Moreover, epigenetic profiles in twins could explain their predisposition to developing different diseases during the lifetime[39] Epigenetic changes are very complex and include DNA methylation, histone modifications, and noncoding RNAs (ncRNAs) which often cooperate to regulate gene expression[40]

2.1. DNA Methylation

DNA methylation is a key regulator of gene expression and one of the most well-characterized epigenetic modifications. It consists of the conversion of cytosine to 5-methylcytosine via the covalent transfer of a methyl group to the fifth carbon position of cytosine[41] It mainly occurs at promoter regions characterized by cytosines and guanines, called CpG islands[42,43] The methyl group responsible for DNA and histone methylation originates from S-adenosyl methionine[42] This epigenetic mark remains stable during cell division and regulates a wide range of cellular mechanisms including transcription and chromosomal stability, and plays a pivotal role in embryonic development, genomic imprinting, and X-chromosome inactivation[44] DNA methylation is established by DNA methyltransferases (DNMTs). DNMT1 is responsible for the maintenance of methylation, whereas DNMT3a and DNMT3b mediate de novo methylation of DNA[45] DNA methylation is a reversible modification that can be removed by the ten-eleven translocation enzymes (TETs), or by a reduced activity of DNMT1. In most cases, methylation of DNA leads to the repression of gene transcription[40] Aberrant DNA methylation has been found to be associated with various complex human diseases, in particular with metabolic disturbances such as obesity and T2D[46,47,48]

2.1.1. DNA Methylation in Candidate Genes

Experiments in primary human endothelial cells showed that hyperglycemia reduces DNA methylation at the promoter of the mitochondrial adaptor p66Shc, a key protein involved in cytochrome c oxidation and accumulation of free radicals[49] The reduction of methylation at p66Shc promoter induces gene up-regulation, contributing to mitochondrial oxidative stress that reduces the Nitric oxide (NO) availability. These epigenetic networks were found to be active also in individuals for whom intensive glycaemic control was not able to reverse the epigenetic mark[50] Of note, Liu et al. found that Monocyte Chemoattractant Protein-1 (MCP-1) promoter methylation status negatively correlates with serum MCP-1, blood glucose, and triglyceride levels, suggesting that hypomethylation of CpG sites can lead to MCP-1 overexpression and to the development of T2D-associated inflammation[51]

2.1.2. Genome-Wide DNA Methylation Studies

Several studies have investigated whether DNA methylation in blood cells is associated with the incidence of diseases and such markers might be developed and used for precision medicine in obesity and diabetes mellitus[52,53,47,54,55,56]

Blood-circulating epigenetic biomarkers might be clinically useful as they can be easily analyzed. Interestingly, a study showed an association between methylation in whole-blood samples at key genes involved in T2D such as ABCG1, PHOSPHO1, SOCS3, SREBF1 and TXNIP and future development of T2D[47] A similar association was found in a cohort from west Finland, following whole-blood methylation analysis of KLF14, FHL2 and GNPNAT1[52] Another study also showed that 15 novel methylation sites in whole blood, including in CPT1A, were associated with high incidence of T2D[54] Furthermore, DNA methylation of TXNIP, ABCG1 and SAMD12 is involved in T2D heritability in Mexican American families[57] Global methylation studies in CVD identified differential methylation of 84 genes involved in obesity, inflammation, and lipid and carbohydrate metabolism[58] Moreover, an increase of DNA methylation in the atherosclerotic aortas compared to healthy regions correlated with the expression of genes involved in vascular smooth muscle cells (VSMC) and endothelial cells (EC) functions[59] Recently, the influence of increased glucose levels on the overall DNA methylation pattern in human aortic endothelial cells (HAECs) was investigated[60] In particular, it was observed that heightened glucose levels disproportionately impact the methylation of genomic regions within genes associated with angiogenesis, endothelin signaling, and PI3K/AKT-mediated insulin signaling.

DNA methylation has been suggested as a potential biomarker of vascular complications in individuals with prediabetes, specifically hypomethylation of the SPARC gene in CD08+ T cells[61] DNA methylation has also been proposed as an indicator of age-related diseases. The two most recent measurements proposed are, Levine's phenotypic age estimator "DNAm PhenoAge" and GrimAge[62,63] Of note, GrimAge has been investigated in association with phenotypic alterations involved in T2D development, such as the higher Body mass index (BMI), elevated CRP levels, and increased PAI-1 activity in overweight and obese women[64] Moreover, it was recently investigated the association between DNA methylation-based epigenetic age measurements and incidence of T2D and prediabetes among individuals recruited in the Coronary Artery Risk Development in Young Adults (CARDIA) study and the results supported the potential use for GrimAge as a biomarker in diabetes[65] In particular, DNA methylation levels of the gene encoding for PAI-1 have been associated with T2D[26]

Table 1. Studies on Epigenetics and Endothelial Dysfunction in Type 2 Diabetes.

References	Epigenetic modification	Type of source	Summary points
Feinberg et al.[46]	DNA methylation	Blood	Differential methylation on genes such as MMP9, PRKG1, SORCS1, implicated in regulating body weight or diabetes. This study proposes an epigenetic approach to identify individuals susceptible to prevalent diseases.
Chambers et al.[47]	DNA methylation	Blood	Methylated indicators at five genomic sites (ABCG1, PHOSPHO1, SOCS3, SREBF1, TXNIP) demonstrated a correlation with the occurrence of T2D.
Volkmar et al.[48]	DNA methylation	Pancreatic islets	They discovered 276 CpG sites linked to the regulatory regions of 254 genes, exhibiting noteworthy variations in DNA methylation within diabetic islets. The functional characterization of the genes with abnormal methylation patterns emphasized the pathways associated with functionality of beta cells in pancreatic islets, both in individuals with T2D and nondiabetic donors.
Liu et al.[51]	DNA methylation	PBMC	The methylation state of CpG sites within the MCP-1 promoter region was examined in individuals with T2D. The results demonstrated a significant correlation between MCP-1 promoter methylation and serum MCP-1 levels, as well as HbA1c, fasting blood glucose, and triglyceride levels.
Bacos Et al.[52]	DNA methylation	Pancreatic islets and blood	The DNA methylation patterns detected in blood samples are indicative of age-related alterations in methylation within 83 genes that were initially identified in human islets. These genes, including KLF14, FHL2, ZNF518B, and FAM123C, exhibit associations with insulin secretion and T2D.
Dayeh et al.[53]	DNA methylation	Blood	Methylation of a locus within the ABCG1 gene in blood DNA demonstrated a positive correlation with a higher likelihood of developing T2D in the future. Conversely, methylation of a locus within the PHOSPHO1 gene in blood DNA exhibited a negative association with the risk of T2D.
Cardona et al.[54]	DNA methylation	Blood	15 new Methylation variable positions (MVPs) that strongly correlate with the onset of T2D were discovered, and three previously identified MVPs were verified (adjacent to TXNIP, ABCG1, and SREBF1).
Ouni et al.[55]	DNA methylation	Pancreatic Islets	The identified abnormally methylated genomic regions have been revealed as potential new biomarkers for early pancreatic islet abnormalities that occur prior to the onset of T2D.
Agardh et al.[56]	DNA methylation	Blood	Distinct DNA methylation variations in 349 CpG sites were found, which corresponded to 233 distinct genes, including TNF, CHI3L1 (YKL-40), CHN2, GIPR, GLRA1, GPX1, AHRR, and BCOR, in individuals with proliferative diabetic retinopathy (PDR) when compared to controls.
Kulkarni et al.[57]	DNA methylation	Blood	Fifty-three CpG sites exhibited a notable correlation with susceptibility to T2D, fasting blood sugar, and insulin insensitivity. The methylation levels of DNA at five CpG sites, which align with three extensively studied genes (TXNIP, ABCG1, and SAMD12), autonomously elucidated 7.8% of the inheritability of T2D.
Zaina et al.[59]	DNA methylation	Aorta	A distinctive DNA methylation pattern specific to atherosclerosis was found, which underscores the involvement of various genes and pathways in the condition. Notably, the observed increase in DNA methylation within the atherosclerotic lesions supports endeavors aimed at creating therapeutic interventions with DNA demethylating properties.
Lu et al.[126]	DNA methylation	Blood	Estimators based on DNA methylation are utilized to measure plasma proteins, including plasminogen activator inhibitor 1 and growth differentiation factor. The resultant predictor of lifespan, DNAm GrimAge (expressed in years), is a composite biomarker comprising seven DNAm surrogates and a DNAm-based estimate of smoking pack-years. By adjusting DNAm GrimAge for chronological age, we establish a novel measure of epigenetic age acceleration.
Kyeezu et al.[65]	DNA methylation	Blood	Epigenetic age, as determined by DNA methylation, has been proposed as a valuable biomarker for age-related conditions such as T2D. The latest advancements in this field, known as GrimAge measurements, have demonstrated initial potential. GrimAge measurements played a partial mediating role in the statistical relationship between cumulative obesity and the onset of diabetes or prediabetes.
Pepin et al.[60]	DNA methylation	HAECs	The methylation of genomic regions dependent on glucose affected 2199 genes, with an imbalanced distribution observed in genes linked to angiogenesis and nitric oxide (NO) signaling pathways. Through multiomics analysis, they identified distinct patterns of methylation and gene expression alterations in VEGF and NOS3, key regulators of angiogenesis and NO signaling, respectively.

(*Continued*)

Table 1. (Continued).

References	Epigenetic modification	Type of source	Summary points
Benincasa et al.[61]	DNA methylation	CD04+ and CD08+ T cells	In CD04+ T cells, hypermethylated differentially methylated regions (DMRs) outnumbered hypomethylated ones, while CD08+ T cells displayed the opposite pattern. Interestingly, DMRs that overlapped between Pre-Diab and T2D patients exhibited mostly hypermethylation in both T cell types. Notably, the gene SPARC showed the most significant hypomethylation in pre-Diab, and its methylation level gradually decreased in T2D patients. Additionally, SPARC demonstrated a positive correlation with clinical parameters.
El-Osta et al.[79]	H3K4me1	HAECs	Temporary elevation of blood glucose levels leads to an elevation of a distinct epigenetic modification, namely histone 3 lysine 4 monomethylation (H3K4me1), in the proximal promoter region of the p65 gene. This modification subsequently triggers the upregulation of p65 and the NF-κB-dependent genes MCP-1 and VCAM-1.
Paneni et al.[80]	H3K4me1	HAECs and PBMCs	Epigenetic alterations induced by Set7 play a role in the development of vascular dysfunction in individuals with T2D. Inhibiting this enzyme responsible for modifying chromatin structure could serve as an innovative therapeutic strategy to prevent atherosclerotic vascular disease in patients with T2D.
Villeneuve et al.[81]	H3K9me3	VSMC	There is aberrant regulation of Suv39h1 and H3K9me3 in diabetic mice, leading to the negative regulation of inflammatory genes such as IL-6, MCSF, and MCP-1.
Yu et al.[82]	H3K9me3	Cardiomyocytes	These findings provide evidence that high glucose conditions enhance the expression of inflammatory cytokines while diminishing histone-3 methylation levels at cytokine promoters. These results imply that manipulating histone 3 methylation and regulating inflammatory cytokine expression could serve as a valuable approach in preventing metabolic memory and cardiomyopathy in diabetic individuals.
Yunfei Liao[84]	H3K4m1, H3K9me2 and H3K9me3	Aortas and HAECs	Long-lasting alterations in H3K4me1, H3K9me2, and H3K9me3 occur at the proximal promoters of the Nox4 and eNOS genes in metabolic memory. It has been observed that a temporary exposure to high glucose leads to enduring modifications in H3K4me1, H3K9me2, and H3K9me3 marks at the Nox4 promoter. Furthermore, the upregulation of Nox4 and eNOS expression induced by glucose, along with endothelial dysfunction, is evident.
Floris et al.[85]	H3K27me3	HUVECs	Gestational diabetes is associated with decreased H3K27me3 levels.
Han et al.[86]	H3K4me2/3	EA.hy926	High glucose-induced upregulation of H3K4 di- and tri-methylation (H3K4me2/3) on the MCP-1 gene promoter.
Park et al.[91]	H3K4me3	Macrophages	The administration of LPS resulted in elevated levels of positive histone marks, specifically H4-Ac and H3K4me3. Genes, which are functionally linked to IFN/cytokine Jak-STAT signaling, exhibited a significant increase in H3K4me3, resulting in the opening of chromatin. The presence of a primed chromatin state, particularly with high H3K4me3 levels, can facilitate robust transcriptional responses to weaker signals.
Gupta et al.[97]	H3K4me1 and H3K9me1	3T3	These modifications were associated to genes which are known to play a role in diabetes (GAPVD1, MAPK6, CTBP1 AND NFAT) under hyperglycemic/ hyperinsulinemic condition.

2.2. Histones Modifications

Histone proteins contain a flexible N-terminal tail extending from the globular nucleosome that can be subject to post-translational modifications (PTMs) such as acetylation, methylation, phosphorylation, ubiquitination, and sumoylation[66] These modifications, driven by histone-modifying enzymes, can change the state of chromatin structure leading to genes activation or silencing[67] Histone PTMs may induce gene expression by favoring an open transcriptionally active chromatin structure (euchromatin). In contrast, some histone PTMs induce closed chromatin conformation and lead to gene repression, by preventing the accessibility of DNA for transcription machinery[68] Numerous proteins involved in chromatin remodeling are characterized by an evolutionary conserved 110 amino acids motif called bromodomain. Bromodomain proteins are critical, nonredundant players in the control of adipogenesis, energy metabolism, and inflammation[69] Histones are acetylated by histone acetyltransferases (HATs). HATs transfer an acetyl group from acetyl-coenzyme A to lysine residues at the ϵ-amino group in the N-terminal tail of histones[70] Histone acetylation is associated with gene transcriptional activation, whereas removal of an acetyl group from histone lysine residues by histone deacetylases (HDACs) reverses this effect leading to gene transcriptional repression[71] Recent studies have highlighted the role of the acetyltransferase p300 in establishing an early vascular senescent phenotype, playing a relevant role in diabetes-associated inflammation and oxidative stress, which drive endothelial dysfunction[72,73] Among the classes of HDACs there is the silent information regulator (SIR) genes (sirtuins) group, a highly conserved family of proteins with histone deacetylase activity and ADP-ribosyltransferase activity involved in histone modifications. Histone methylation is a reversible posttranslational modification driven by histone methyl transferases (HMTs) and erased

by histone demethylases (HDMTs)[74,75] HMTs transfer methyl groups from the methyl donor S-adenosyl methionine (SAM) to lysine or arginine residues of histone proteins[75] Lysines can be mono- (me1), di- (me2), or tri- (me3) methylated on their ϵ-amine groups, and arginines can be monomethylated, symmetrically dimethylated or asymmetrically dimethylated on their guanidino groups. Methylation of histone proteins may have different effects on gene expression. For example, methylations of H3R17, H4R3, and H3K4 are linked with transcriptional activation, whereas methylations of H3K9, H3K27, and H4K20 are considered as markers of transcriptional repression[76]

Recent studies have demonstrated a link between histone modifications and vascular complications of diabetes[43] In particular, it has been shown a key role of epigenetic modifications in vascular inflammation[77,78]

One of the most important inflammatory pathways is NF-κB signaling, able to induce the release of inflammatory factors such as cytokines. The methylation status of histones on the NF-κB p65 gene appears to play a key role in the regulation of inflammatory responses under diabetic conditions. In this regard, transient exposure of endothelial cells to high concentrations of glucose has been shown to induce the recruitment of the histone H3K4 methyltransferase SETD7 (also known as SET7 and SET7/9) and the lysine-specific demethylase 1 (LSD1) to the NF-κB p65 gene promoter, resulting in H3K4 hypermethylation and H3K9 hypomethylation, respectively[79] These alterations in histone methylation levels lead to the persistent upregulation of p65 as well as higher expression of NF-κB-regulated genes MCP-1 and Vascular cell adhesion protein-1 (VCAM-1)[79] Accordingly, studies have shown that an increased SETD7-mediated methylation of H3K4 at the NF-κB p65 promoter, in peripheral blood mononuclear cells (PBMCs) from patients with T2D, leads to higher expression of MCP-1, intercellular adhesion molecule-1 (ICAM-1), and cyclooxygenase-2 (COX-2)[80] Some studies showed that high-glucose-induced decrease of H3K9 methylation at the promoters of Interleukin-6 (IL-6), MCP-1, macrophage colony-stimulating factor-1 (MCSF1) and IL-12B is due to reduced levels of the enzyme Suppressor of Variegation 3–9 Homolog 1 (SUV39H1) and associated with a significant increase in the expression of these inflammatory genes[81,82]

A large body of evidence has revealed that the overproduction of reactive oxygene species (ROS) precedes the development of endothelial dysfunction and vascular inflammation in diabetes[83] Nicotinamide adenine dinucleotide phosphate oxidase 4 (Nox4) and Endothelial Nitric Oxide Synthase (eNOS), which are important enzymatic sources of ROS in diabetic vasculature, were found to be dysregulated by H3K4me1, H3K9me2, and H3K9me3 promoting endothelial dysfunction[84] Furthermore, the downregulation of the methyltransferase Enhancer of zeste homolog 2 (EZH2) regulating H3K27me3, has been found to be involved in endothelial dysfunction induced by gestational diabetes through the regulation by miR-101[85] Interestingly, Han and collaborators also demonstrated the ability of high glucose to increase H3K4me2 and H3K4me3 marks at the promoter of the MCP-1 gene in human umbilical vein cells[86]

Regulation of inflammatory genes expression can also be driven by histone acetylation. In particular, it has been shown treatment of THP-1 monocytes with high glucose decreases the association of specific HDACs with the promoters of inflammatory genes and enhances the recruitment of NF-κB and HATs CREB binding protein (CBP) and p300/CBP-associated factor (PCAF) to these promoters[87] Other epigenetic networks driven by SIRT1, also known as NAD-dependent deacetylase sirtuin-1, were found to be responsible for the vascular complications of diabetes. Specifically, SIRT1 overexpression prevents endothelial dysfunction by suppressing NF-κB activation and Poli ADP-ribosio polimerasi (PARP) cleavage while restoring hyperglycemia-induced dephosphorylation of liver kinase B1 (LKB1) and Adenosine Monophosphate (AMP) kinase (AMPK), two critical regulators of energy balance[88] Variants associated with autoimmune diseases, including T1D, occur often in enhancer regions, supporting the importance of enhancers in gene regulation of diseases[89,90] In the context of inflammation, Park et al. demonstrated that differential enhancer activations in response to lipopolysaccharides (LPS), TNF or type I interferons (IFNαI) induce transcriptional cascades that alter chromatin accessibility in monocytes. Moreover, the binding of coactivator histone acetyltransferases (CBP/p300) to enhancers positively regulate their associated gene expressions and it is generally coupled with a gain of H3K27ac modification[91,92] Challenge of monocytes with β-glucan leads to the enrichment of H3K4me1, H3K4me3, and increased DNase I accessibility across specific loci of monocytes. The deposition of H3K27ac marks is often paralleled by that of H3K4me1. Furthermore, studies have shown that innate immune cells exposed to certain stimuli activating inflammatory pathways (e.g., Candida albicans, its cell wall component b-glucan, BCG, or IFN-b) can respond faster to secondary stimulation[93]

This process of transcriptional memory has been associated with the establishment of an epigenetic signature that contributes to the chromatin remodeling[94,95] For instance, H3K4me1 at enhancers is an epigenetic mark that tends to be stable even after the stimulus has disappeared, contributing to maintain the epigenetic memory[96] A recent study showed that epigenetic changes leading to chronic proinflammatory genes expression in hyperglycemia are associated to a persistent, long-lasting H3K4me1 in proinflammatory genes[97] This evidence suggests that stimulus-specific prolonged stimulation affects cis-regulatory elements, providing an "epigenomic memory" of the exposure to environmental agents[96] The epigenetic mark H3K4me3 at the promoters of loci encoding proinflammatory genes also plays a central role in different experimental models of innate immune memory, such as β-glucan stimulation or the induction of trained immunity by oxidized low density lipoprotein (oxLDL) in human cells[98] and is involved in the activation of inflammatory chemokine by favoring the interaction between enhancer and promoter[99,100]

3. Metabolomics and Endothelial Dysfunction in Type 2 Diabetes

Metabolomics aims at the measurement of ideally all small molecules, named metabolites, in a biological sample that could lead to novel tools for clinical practice, diagnosis, prognosis, and predictors of disease and therapeutic response. The metabolome, which includes all intermediates and small molecules of cellular metabolism representing the final product of genome,

Table 2. Studies on Metabolomics and Endothelial Dysfunction in Type 2 Diabetes.

References	Metabolites	Type of source	Summary points
Filla et al.[105]	Vitamin B6, propanoate, butanoate	Mice aortic cells	48 metabolic pathways were found to be altered in diabetic samples. Vitamin B6, propanoate, and butanoate metabolism were altered in multiple points along the pathway, thus providing potential innovative biomarkers and novel insights into therapeutic targets.
Yuan et al.[106]	Amine	Human aortic endothelial cells	Variations in amine levels were found in human aortic endothelial cells exposed to acute and chronic hyperglycemia, thus suggesting a potential role of amine into the pathophysiology of diabetic complications
Danget al.[107]	Glycosphingolipid, in particular ceramides	Plasma from mice	The glycosphingolipid pathway was identified as a potential therapeutic target to prevent atherogenesis in hyperglycemic mice.
Mousa et al.[109]	Lipids such as dihydroceramides and glycophosphatidylinositol	Plasma from overweight or obese nondiabetic individuals	Some circulating lipids, such as dihydroceramides and glycophosphatidylinositol may represent novel biomarkers to identify individuals at high risk of diabetes before the disease onset.
Pipino et al.[112]	ɣ-glutamyl amino acids, ophthalmate, S-lactoyl-glutathione	Human umbilical vein endothelial cells	In endothelial cells carrying the SNP rs10911021 changes in several metabolites demonstrating an impairment of the γ-glutamyl cycle and methylglyoxal detoxification were found. This study suggests a possible glutamine supplementation in T2D patients carrying the SNP to prevent CVD.
Huang et al.[113]	l-methionine	Human umbilical vein endothelial cells	Increased levels of l-methionine able to inhibit the apoptosis of vascular endothelial cells were found following treatment with aspirin eugenol ester (AEE). This study highlights the anti-atherosclerotic effects of AEE potentially related to a reduction in vascular endothelial dysfunction mediated by ameliorating alterations in metabolism, reducing oxidative stress, and lowering the expression of adhesion molecules.

transcriptome, and proteome, has become a specialized tool for metabolic biomarker discovery and pathway analysis.

The metabolomics techniques mainly used are based on mass spectrometry (MS) and/or nuclear magnetic resonance (NMR) and can be targeted or untargeted. Targeted metabolomics is the study of specific metabolites by adding stable standards isotopically labeled to the samples before the extraction, while untargeted metabolomics is characterized by the measure of a large spectrum of metabolites through the comparison of different experimental conditions or groups of patients[101]

Together with other omics technologies, metabolomics can help understanding pathogenesis as well as the metabolic influence of diseases onset and progression[102] Moreover, metabolomics allows the identification of multiple biomarkers at the same time.

Some relevant findings highlighting the potential role of metabolomics in predicting endothelial dysfunction in Type 2 Diabetes are described below and summarized in **Table 2**.

Through metabolomics, changes in lipid metabolism and plasma amino acid were found associated with the risk of developing T2D, suggesting a potential role of such metabolites in the pathogenesis of diabetes and the possibility of targeting them for diabetes prevention[103] In addition, a different metabolomic profile comparing T2D individuals with and without microalbuminuria was found. In detail, patients with microalbuminuria exhibited lower levels of plasma histidine and higher levels of butenoylcarnitine together with lower hexose, glutamine, and tyrosine. This study highlighted the importance of some metabolites as a potential novel biomarker, that in combination with known kidney disease risk markers may help in predicting microalbuminuria development in T2D patients[104]

Changes in some metabolic pathways associated with diabetic vascular complications such as vitamin B6, propanoate, and butanoate were discovered in diabetic mice[105] In addition, some variations in amine levels were found in human aortic endothelial cells exposed to acute and chronic hyperglycemia[106] Also, the glycosphingolipid pathway was identified as a potential therapeutic target to prevent atherogenesis in hyperglycemic mice[107] Indeed sphingolipids, in particular the most widely studied ceramides, have been found to be a candidate in prediction of CVD together with the traditional risk factors[108] Some circulating lipids, such as dihydroceramides and glycophosphatidylinositol may represent novel biomarkers to identify individuals at high risk of diabetes before the disease onset[109]

It is well known that the metabolome can be influenced by genetic factors and by environmental factors such as lifestyle, diet, drugs, microbiome and physical activity[110]

Regarding the impact of genetic variations on metabolome, we recently analyzed metabolites from endothelial cells carrying the Single Nucleotide Polymorphism (SNP) rs10911021. This SNP was found associated with CVD specifically in T2D subjects[111] Interestingly, in endothelial cells carrying the SNP we found changes in several metabolites demonstrating an impairment of the γ-glutamyl cycle and methylglyoxal detoxification[112] This study suggests a possible glutamine supplementation in T2D patients carrying the SNP as a potential preventive CVD approach.

Metabolomics studies have been performed also to evaluate the impact of medications such as the study of aspirin eugenol

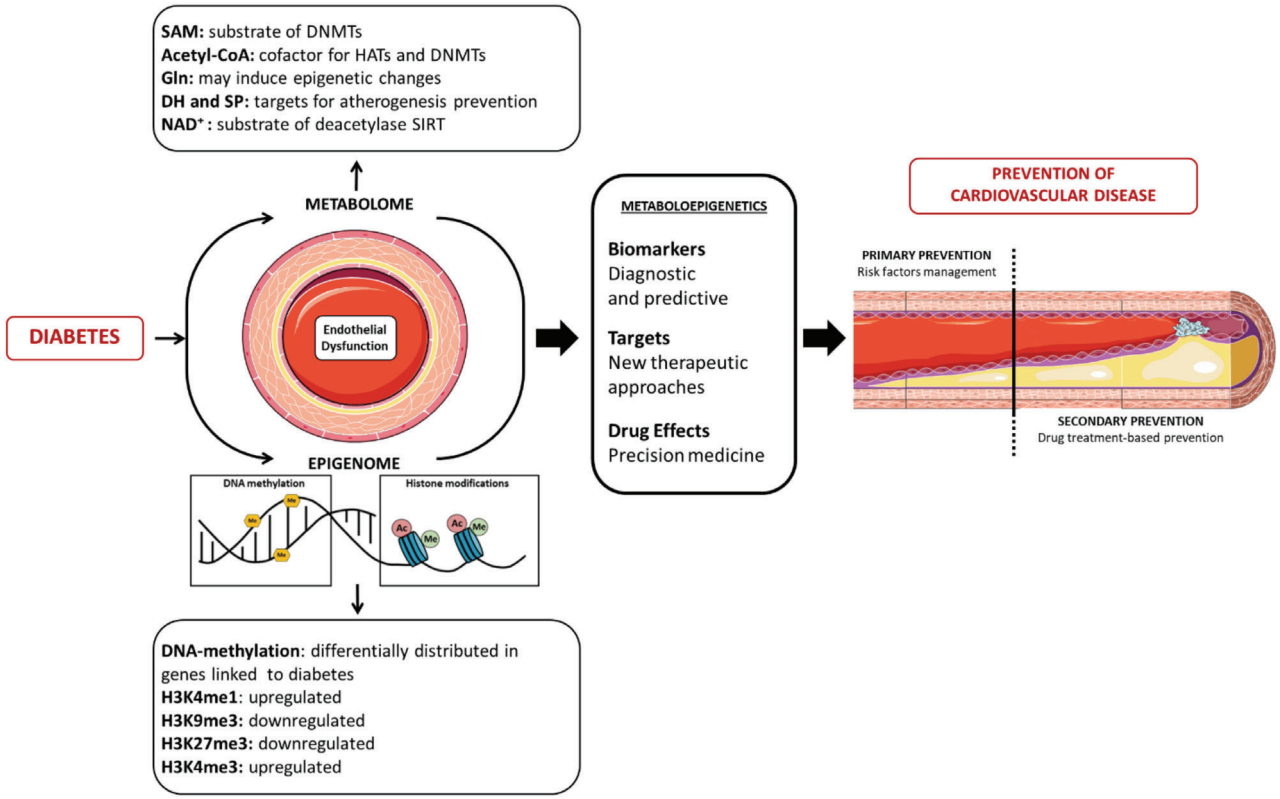

Figure 1. Epigenetics meets Metabolomics. A close connection between epigenetic modifications and dysfunctional metabolism may lead to early identification of endothelial dysfunction contributing to biomarkers discovery and novel therapeutic approaches in primary or secondary prevention of diabetes and its cardiovascular progression. Some metabolites associated with diabetic cardiovascular complications: NAD: nicotinamide adenin dinucleotide; SP:sphingolipids; DH:dihydroceramides; Gln: glutamine; Acyl-CoA: acetyl-Coenzime A; SAM: S-adenosylmethionine; and some chromatin modifying enzymes: DNMTs: DNA Methyltransferases, HATs: Histone acetyltransferase, SIRT: Sirtuin.

ester on vascular endothelial dysfunction in atherosclerotic rats and endothelial cells following hydrogen peroxide treatment. Increased levels of l-methionine able to inhibit the apoptosis of vascular endothelial cells, were found following treatment with aspirin eugenol ester[113]

Interestingly, metabolomics data obtained so far provide novel insight into the development of diabetes and atherosclerosis, although studies related to early endothelial dysfunction are still inconsistent[101] Since diabetes is a complex metabolic disorder based on the imbalance of thousands of metabolic pathways, metabolomics has emerged as a powerful tool to gain insight into innovative therapeutic targets and biomarkers discovery in diabetes and vascular complications.

Of note, by correlating biomarkers found in hyperglycemia condition with early endothelial dysfunction, together with integrated approaches combining other omics results, would allow developing methods for disease prevention. Therefore, further in dept studies, including multiomics approaches, and optimistically combining worldwide expertise, are needed to define new biomarkers and therapeutic targets at an early stage of the disease.

4. Epigenetics Meets Metabolomics

Within the last decade, the field of epigenetic regulation of gene function is moving fast. In addition, metabolomics, driven by technological progress, continues to gain momentum by opening promising avenues for disease diagnosis and therapies. Since endothelial dysfunction precedes and fosters atherosclerosis representing an early target, in this review, we summarize how epigenetics and metabolomics are leveraged to better describe disease progression and potentially identify novel therapeutic targets. The studies mentioned above have proven useful in the field of diabetes and cardiovascular complications leading to new insights into pathophysiology of the disease. More in detail, in the last years, researchers are studying how metabolites and metabolic networks impact gene regulation, focusing on recently discovered roles of metabolites in disease onset and progression and how this opens innovative therapeutic route. Many studies have demonstrated that the metabolic phenotype carries information on important biological changes and that some metabolic properties represent intermediate phenotypes connecting genetic and environmental factors to endpoints of complex disorders.

It has been shown that metabolites deriving from food sources can be considered as substrates for transcription factors and histone-modifying enzymes that then affect chromatin remodeling, inducing a more open or compact state of the genome which in turn regulate gene transcription[114,115] Metabolites can also affect the enzymes of chromatin-modifying machinery itself then defining the expression of genes influencing atherosclerosis and vascular complications of diabetes. Conversely, several evidences show that epigenetics could affect metabolism[115,116] Indeed,

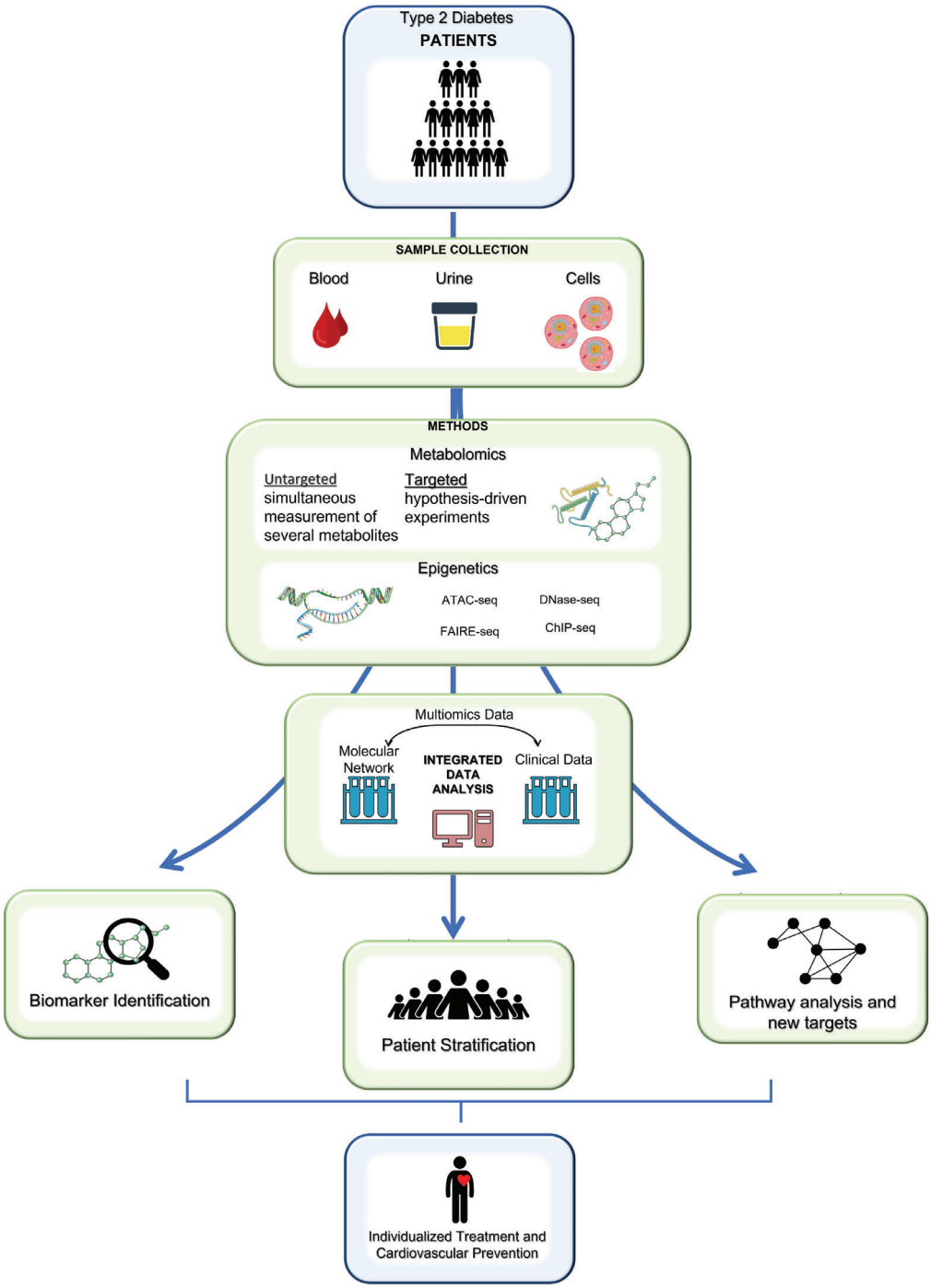

Figure 2. The workflow involving metabolomics and epigenetics for personalized medicine begins with the collection of biological samples from an individual, such as blood, urine, or tissue. These samples are then subjected to various analytical techniques to gather information about the individual's metabolome and epigenetic profile. Once data are obtained, they are subjected to a computational integrated analysis together with other information, such as clinical data. This comprehensive analysis helps in identifying specific metabolic and epigenetic patterns associated with certain diseases or treatment responses, leading to the development of targeted therapies or interventions.

epigenetics could represent a link between metabolic processes and gene expression, referred to as metaboloepigenetics[7]

The dysregulation of metabolites in diabetes is due to an impaired uptake of glucose from extracellular environment, reduced glycolysis, and mitochondrial dysfunction[117] This leads to an imbalance between the use of glucose by the cell which decreases, and the use of fatty acids which instead increases[118] Fatty acid oxidation increases the mitochondrial ratios of acetyl-CoA to CoA and nicotinamide adenine dinucleotide (NADH) to NAD+. As a consequence, there is a decreased acetyl-CoA

synthesis from pyruvate, mainly due to the inhibition of malate dehydrogenase, isocitrate dehydrogenase, and α-ketoglutarate dehydrogenase and increased use of acetyl-CoA for the synthesis of ketone bodies[119] Metabolites, including S-adenosylmethionine, acetyl-CoA, NADH, α-ketoglutarate (αKG), and ATP serve as cofactors for chromatin-modifying enzymes, such as methyltransferases and acetyltransferases responsible for chromatin remodeling. The fluctuation of nutrients, such as glucose, glutamine, and oxygen, may induce epigenetic changes in disease pathology.

More in detail, DNA and histone methylation requires a methyl donor group called S-adenosylmethionine (SAM), which is a substrate of DNMTs, deriving from the synthesis of methionine and ATP. The methyl group is transferred from activated SAM through a positive charge leading to the generation of a product called S-Adenosyl-L-homocysteine (SAH). The inhibition of SAH hydrolase can reduce cellular methylation reactions[120] Moreover, recent studies showed that the levels of methionine, derived from SAH hydrolysis, may influence methylation levels of histones[121] The process of demethylation, consisting of a methyl group removal from DNA or histone proteins, requires as cofactors αKG and flavin adenine dinucleotide (FAD)[122] Histone acetylation neutralizes the positive charges on histones, diminishing the interaction of the nucleosome with the DNA, which determines an open chromatin configuration and active transcription. Histone acetylation is catalyzed by HATs that use acetyl-CoA as a substrate. On the other end, Histone deacetylation generates a more compact chromatin configuration and is driven by the $NAD^{[+]}$-dependent sirtuin family of deacetylases[115]

On the basis of the above evidence, a deeper study of the close connection between epigenetic modifications and dysfunctional metabolism would provide a better understanding of the pathogenesis of diseases contributing to the discovery of new biomarkers and proper therapeutic approaches (**Figure 1**).

5. Conclusions

In the last years, epigenetic regulation is extensively studied to gain insight into the progression of diabetes and vascular complications. Several epigenetic alterations like DNA methylation and histone modifications, have been demonstrated as key players in the development of atherosclerosis. In addition, advanced techniques have been adopted to study the metabolic signature molecules. Through metabolomics, changes in some metabolic pathways were found associated with diabetic vascular complications, suggesting the possibility to prevent the disease. More important, biological changes found through metabolomics represent intermediate phenotypes connecting genetic and environmental factors. Therefore, integrative approaches including epigenetics and metabolomics, may have great importance in biomarkers research as well as drug discovery and innovative therapeutic applications.

The progresses of these innovative technologies are tremendous, and considering a future scenario, these research fields hold unlimited potential. The large volume of data obtained so far is complex and requires appropriate computational experience to understand disease progression and inflammatory signaling development, identify novel targets, and predicting how different therapeutics may influence the progression of disease. More studies are needed, possibly through worldwide collaborations[123,61,124,125] Furthermore, because of the cell-specific nature of epigenetic information, more human biopsies and samples could be useful. In this scenario, epigenomic and metabolomics, together with other omics technologies, would provide a valid tool to identify all biomolecular mechanisms underlying disease development and possibly categorize patients into endotypes based on common omics expression patterns. Therefore, improving the knowledge on the crucial connection between relevant metabolites and epigenetics may help to detect endothelial dysfunction at a very early stage. Overall, this will significantly boost the objective of precision medicine for tailoring the right therapeutic strategy for the right person at the right time (**Figure 2**).

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Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

N.D.P. wrote, reviewed, and edited the manuscript; I.C. wrote and reviewed the manuscript; D.M. wrote and reviewed the manuscript; M.P.A.B. wrote and reviewed the manuscript; A.P. reviewed the manuscript; C.P. conceptualized, wrote, reviewed, and edited the manuscript.

Keywords

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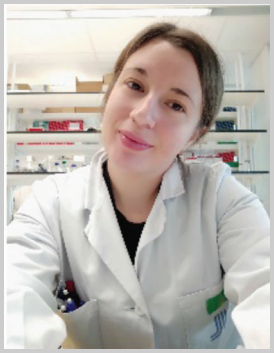
[1] S. Simsek, I. A. M. van den Oever, H. G. Raterman, M. T. Nurmohamed, *Mediators Inflammation* **2010**, *2010*, 792393.
[2] J. A. Beckman, A. B. Goldfine, Mary, B. Gordon, M. A. Creager, *Circulation* **2001**, *103*, 1618.
[3] P. Di Tomo, R. Canali, D. Ciavardelli, S. Di Silvestre, A. De Marco, A. Giardinelli, C. Pipino, N. Di Pietro, F. Virgili, A. Pandolfi, *Mol. Nutr. Food Res.* **2012**, *56*, 217.
[4] X. Ren, L. Ren, Q. Wei, H. Shao, L. Chen, N. Liu, *Cardiovasc. Diabetol.* **2017**, *16*, 28427390.
[5] M.-P. Wautier, O. Chappaey, S. Corda, D. M. Stern, A. M. Schmidt, J. L. Wautier, *Am J Physiol Endocrinol Metab.* **2001**, *280*, E685.
[6] F. Cosentino, M. Eto, P. De Paolis, B. van der Loo, M. Bachschmid, V. Ullrich, A. Kouroedov, C. Delli Gatti, H. Joch, M. Volpe, T. F. Lu?Scher, *Circulation* **2003**, *107*, 1017.

[7] Z. Wang, H. Long, C. Chang, M. Zhao, Q. Lu, *Cell. Mol. Life Sci.* **2018**, *75*, 3353.
[8] A. Pandolfi, A. Solini, G. Pellegrini, G. Mincione, S. Di Silvestre, P. Chiozzi, A. Giardinelli, M. C. Di Marcantonio, A. Piccirelli, F. Capani, A. Consoli, *Arterioscler Thromb Vasc. Biol.* **2005**, *25*, 2392.
[9] R. Muniyappa, H. Chen, M. Montagnani, A. Sherman, M. J. Quon, *Am J Physiol Endocrinol Metab.* **2020**, *319*, E629.
[10] R. Shurtz-Swirski, S. Sela, A. T. Herskovits, S. M. Shasha, G. Shapiro, L. Nasser, B. Kristal, *Diabetes Care* **2001**, *24*, 104.
[11] A. R. Leite, M. Borges-Canha, R. Cardoso, J. S. Neves, R. Castro-Ferreira, A. Leite-Moreira, *Angiology* **2020**, *71*, 397.
[12] Y. V. Sun, Y. J. Hu, in *Advances in Genetics*, Elsevier Ltd, New York **2016**, *93*.
[13] R. D. Simmons, S. Kumar, S. R. Thabet, S. Sur, H. Jo, *Wiley Interdiscip Rev. Syst. Biol. Med.* **2016**, *8*, 378.
[14] T. Maruhashi, Y. Higashi, *Antioxidants* **2021**, *10*, 1306.
[15] G. Benincasa, E. Coscioni, C. Napoli, *Biochem. Pharmacol.* **2022**, *202*, 115108.
[16] C. Napoli, G. Benincasa, C. Schiano, M. Salvatore, *Eur. Heart J. Cardiovasc Pharmacother* **2020**, *6*, 239.
[17] M. P. A. Baldassarre, C. Pipino, A. Pandolfi, A. Consoli, N. D. Pietro, G. Formoso, *Oxid Med Cell Longev* **2021**, 7887426.
[18] M. Daneshpajooh, K. Bacos, M. Bysani, A. Bagge, E. Ottosson Laakso, P. Vikman, L. Eliasson, H. Mulder, C. Ling, *Diabetologia* **2017**, *60*, 116.
[19] M. Daneshpajooh, L. Eliasson, K. Bacos, C. Ling, *Acta Diabetol* **2018**, *55*, 1231.
[20] A. Galmozzi, N. Mitro, A. Ferrari, E. Gers, F. Gilardi, C. Godio, G. Cermenati, A. Gualerzi, E. Donetti, D. Rotili, S. Valente, U. Guerrini, D. Caruso, A. Mai, E. Saez, E. De Fabiani, M. Crestani, *Diabetes* **2013**, *62*, 732.
[21] Z. Gao, J. Yin, J. Zhang, R. E. Ward, R. J. Martin, M. Lefevre, W. T. Cefalu, J. Ye, *Diabetes* **2009**, *58*, 1509.
[22] M. Lundh, T. Galbo, S. S. Poulsen, T. Mandrup-Poulsen, *Diabetes Obes Metab* **2015**, *17*, 703.
[23] V. Kameswaran, M. L. Golson, M. Ramos-Rodríguez, K. Ou, Y. J. Wang, J. Zhang, L. Pasquali, K. H. Kaestner, *Diabetes* **2018**, *67*, 1807.
[24] X. S. Liu, H. Wu, X. Ji, Y. Stelzer, X. Wu, S. Czauderna, J. Shu, D. Dadon, R. A. Young, R. Jaenisch, *Cell* **2016**, *167*, 233.
[25] K. Ou, M. Yu, N. G. Moss, Y. J. Wang, A. W. Wang, S. C. Nguyen, C. Jiang, E. Feleke, V. Kameswaran, E. F. Joyce, A. Naji, B. Glaser, D. Avrahami, K. H. Kaestner, *J. Clin. Invest.* **2019**, *129*, 209.
[26] C. Ling, K. Bacos, T. Rönn, *Nat Rev Endocrinol* **2022**, *18*, 433.
[27] R. L. Jirtle, M. K. Skinner, *Nat. Rev. Genet.* **2007**, *8*, 253.
[28] E. Nilsson, C. Ling, *Clin. Epigenet.* **2017**, *9*, 105.
[29] M. Kato, R. Natarajan, *Nat Rev Nephrol* **2019**, *15*, 327.
[30] R. Natarajan, *Diabetes* **2021**, *70*, 328.
[31] E. E. Nilsson, I. Sadler-Riggleman, M. K. Skinner, *Environ. Epigenet.* **2018**, *4*, 26510870.
[32] M. J. Xavier, S. D. Roman, R. J. Aitken, B. Nixon, *Hum Reprod. Update* **2019**, *25*, 519.
[33] C. Gawad, W. Koh, S. R. Quake, *Nat. Rev. Genet.* **2016**, *17*, 175.
[34] E. Ahlqvist, N. R. van Zuydam, L. C. Groop, M. I. Mccarthy, *Nat. Rev. Nephrol.* **2015**, *11*, 277.
[35] K. M. Sullivan, K. Susztak, *Nat. Rev. Nephrol.* **2020**, *16*, 628.
[36] C. Coco, L. Sgarra, M. A. Potenza, C. Nacci, B. Pasculli, R. Barbano, P. Parrella, M. Montagnani, *Int. J. Mol. Sci.* **2019**, *20*, 2949.
[37] M. A. Reddy, R. Natarajan, *Cardiovasc. Res.* **2011**, *90*, 421.
[38] N. B. Ramakrishna, K. Murison, E. A. Miska, H. G. Leitch, *Sexual Dev.* **2021**, *15*, 411.
[39] M. F. Fraga, E. Ballestar, M. F. Paz, S. Ropero, F. Setien, M. L. Ballestar, D. Heine-Suner, J. C. Cigudosa, M. Urioste, J. Benitez, M. Boix-Chornet, A. Sanchez-Aguilera, C. Ling, E. Carlsson, P. Poulsen, A. Vaag, Z. Stephan, T. D. Spector, Y. Z. Wu, C. Plass, M. Esteller, *Proc Natl Acad Sci USA* **2005**, *102*, 10604.
[40] A. Baccarelli, M. Rienstra, E. J. Benjamin, *Circ. Cardiovasc. Genet.* **2010**, *3*, 567.
[41] A. Portela, M. Esteller, *Nat. Biotechnol.* **2010**, *28*, 1057.
[42] D. E. Handy, R. Castro, J. Loscalzo, *Circulation* **2011**, *123*, 2145.
[43] S. Costantino, S. A. Mohammed, S. Ambrosini, F. Paneni, *Vasc. Biol.* **2020**, *2*, H19.
[44] T. B. Miranda, P. A. Jones, *J. Cell. Physiol.* **2007**, *213*, 384.
[45] M. Loh, L. Zhou, H. K. Ng, J. C. Chambers, *Mol. Metab.* **2019**, *27*, S33.
[46] A. P. Feinberg, R. A. Irizarry, D. Fradin, M. J. Aryee, P. Murakami, T. Aspelund, G. Eiriksdottir, T. B. Harris, L. Launer, V. Gudnason, M. D. Fallin, *Sci. Transl. Med.* **2010**, *2*, 20844285.
[47] J. C. Chambers, M. Loh, B. Lehne, A. Drong, J. Kriebel, V. Motta, S. Wahl, H. R. Elliott, F. Rota, W. R. Scott, W. Zhang, S.-T. Tan, G. Campanella, M. Chadeau-Hyam, L. Yengo, R. C. Richmond, M. Adamowicz-Brice, U. Afzal, K. Bozaoglu, Z. Y. Mok, H. K. Ng, F. Pattou, H. Prokisch, M. A. Rozario, L. Tarantini, J. Abbott, M. Ala-Korpela, B. Albetti, O. Ammerpohl, P. A. Bertazzi, et al., *Lancet Diabetes Endocrinol* **2015**, *3*, 526.
[48] M. Volkmar, S. Dedeurwaerder, D. A. Cunha, M. N. Ndlovu, M. Defrance, R. Deplus, E. Calonne, U. Volkmar, M. Igoillo-Esteve, N. Naamane, S. Del Guerra, M. Masini, M. Bugliani, P. Marchetti, M. Cnop, D. L. Eizirik, F. Fuks, *EMBO J.* **2012**, *31*, 1405.
[49] S. A. Mohammed, S. Ambrosini, T. Lüscher, F. Paneni, S. Costantino, *Front. Cardiovasc. Med.* **2020**, *7*, 28.
[50] S. Costantino, F. Paneni, R. Battista, L. Castello, G. Capretti, S. Chiandotto, L. Tanese, G. Russo, D. Pitocco, G. A. Lanza, M. Volpe, T. F. Lüscher, F. Cosentino, *Diabetes* **2017**, *66*, 2472.
[51] Z. H. Liu, L. L. Chen, X. L. Deng, H. J. Song, Y. F. Liao, T. S. Zeng, J. Zheng, H. Q. Li, *J Endocrinol Invest* **2012**, *35*, 585.
[52] K. Bacos, L. Gillberg, P. Volkov, A. H. Olsson, T. Hansen, O. Pedersen, A. P. Gjesing, H. Eiberg, T. Tuomi, P. Almgren, L. Groop, L. Eliasson, A. Vaag, T. Dayeh, C. Ling, *Nat. Commun.* **2016**, *7*, 11089.
[53] T. Dayeh, T. Tuomi, P. Almgren, A. Perfilyev, P.-A. Jansson, V. D. De Mello, J. Pihlajamäki, A. Vaag, L. Groop, E. Nilsson, C. Ling, *Epigenetics* **2016**, *11*, 482.
[54] A. Cardona, F. R. Day, J. R. B. Perry, M. Loh, A. Y. Chu, B. Lehne, D. S. Paul, L. A. Lotta, I. D. Stewart, N. D. Kerrison, R. A. Scott, K.-T. Khaw, N. G. Forouhi, C. Langenberg, C. Liu, M. M. Mendelson, D. Levy, S. Beck, R. D. Leslie, J. Dupuis, J. B. Meigs, J. S. Kooner, J. Pihlajamäki, A. Vaag, A. Perfilyev, C. Ling, M.-F. Hivert, J. C. Chambers, N. J. Wareham, K. K. Ong, *Diabetes* **2019**, *68*, 2315.
[55] M. Ouni, S. Saussenthaler, F. Eichelmann, M. Jähnert, M. Stadion, C. Wittenbecher, T. Rönn, L. Zellner, P. Gottmann, C. Ling, M. B. Schulze, A. Schürmann, *Diabetes* **2020**, *69*, 2503.
[56] E. Agardh, A. Lundstig, A. Perfilyev, P. Volkov, T. Freiburghaus, E. Lindholm, T. Rönn, C.-D. Agardh, C. Ling, *BMC Med.* **2015**, *13*, 182.
[57] H. Kulkarni, M. Z. Kos, J. Neary, T. D. Dyer, J. W. Kent, H. H. H. Göring, S. A. Cole, A. G. Comuzzie, L. Almasy, M. C. Mahaney, J. E. Curran, J. Blangero, M. A. Carless, *Hum. Mol. Genet.* **2015**, *24*, 5330.
[58] A. Fernández-Sanlés, S. Sayols-Baixeras, I. Subirana, I. R. Degano, R. Elosua, *Atherosclerosis* **2017**, *263*, 325.
[59] S. Zaina, H. Heyn, F. J. Carmona, N. Varol, S. Sayols, E. Condom, J. Ramírez-Ruz, A. Gomez, I. Gonçalves, S. Moran, M. Esteller, *Circ. Cardiovasc. Genet.* **2014**, *7*, 692.
[60] M. E. Pepin, C. Schiano, M. Miceli, G. Benincasa, G. Mansueto, V. Grimaldi, A. Soricelli, A. R. Wende, C. Napoli, *Exp. Cell Res.* 112485, **2021**, *400*.
[61] G. Benincasa, M. Franzese, C. Schiano, R. Marfella, M. Miceli, T. Infante, C. Sardu, M. Zanfardino, O. Affinito, G. Mansueto, L. Sommese, G. F. Nicoletti, M. Salvatore, G. Paolisso, C. Napoli, *Annals Med. Sur.* **2020**, *60*, 218.

[62] A. T. Lu, A. Quach, J. G. Wilson, A. P. Reiner, A. Aviv, K. Raj, L. Hou, A. A. Baccarelli, Y. Li, J. D. Stewart, E. A. Whistel, T. L. Assimes, L. Ferrucci, S. Horvath, *Aging (Albany NY)* **2019**, *11*, 303.
[63] M. E. Levine, A. T. Lu, A. Quach, B. H. Chen, T. L. Assimes, S. Bandinelli, L. Hou, A. A. Baccarelli, J. D. Stewart, Y. Li, E. A. Whitsel, J. G. Wilson, A. P. Reiner, A. Aviv, K. Lohman, Y. Liu, L. Ferrucci, S. Horvath, *AGING* **2018**, *10*, 573.
[64] S. Horvath, K. Raj, *Nat. Rev. Genet.* **2018**, *19*, 371.
[65] K. Kim, B. T. Joyce, Y. Zheng, P. J. Schreiner, D. R. Jacobs, J. M. Catov, J. M. Shikany, M. R. Carnethon, P. Greenland, L. V. van Horn, N. B. Allen, D. M. Lloyd-Jones, E. P. Gunderson, L. Hou, *Diabetes* **2021**, *70*, 1404.
[66] L. Sommese, A. Zullo, F. P. Mancini, R. Fabbricini, A. Soricelli, C. Napoli, *Epigenetics* **2017**, *12*, 401.
[67] A. J. Bannister, T. Kouzarides, *Cell Res.* **2011**, *21*, 381.
[68] T. Kouzarides, *Cell* **2007**, *128*, 693.
[69] G. V. Denis, *Discov Med* **2010**, *10*.
[70] D. E. Sterner, S. L. Berger, *Microbiol. Mol. Biol. Rev.* **2000**, *64*, 435.
[71] R. Margueron, P. Trojer, D. Reinberg, *Curr. Opin. Genet. Dev.* **2005**, *15*, 163.
[72] N. Di Pietrantonio, P. Di Tomo, D. Mandatori, G. Formoso, A. Pandolfi, *Cells* **2023**, *12*, 431.
[73] P. Di Tomo, N. Alessio, S. Falone, L. Pietrangelo, P. Lanuti, V. Cordone, S. J. Santini, N. D. Pietrantonio, M. Marchisio, F. Protasi, N. D. Pietro, G. Formoso, F. Amicarelli, U. Galderisi, A. Pandolfi, *FASEB J.* **2021**, *35*, e21662.
[74] H. Ü. Kaniskan, M. L. Martini, J. Jin, *Chem. Rev.* **2018**, *118*, 989.
[75] E. L. Greer, Y. Shi, *Nat. Rev. Genet.* **2012**, *13*, 343.
[76] K. Hyun, J. Jeon, K. Park, J. Kim, *Exp Mol Med* **2017**, *49*, e324.
[77] A. Berezin, *BBA Clinical* **2016**, *6*, 31.
[78] P. A. Andreeva-Gateva, I. D. Mihaleva, I. I. Dimova, *Postgrad Med* **2020**, *132*, 109.
[79] A. El-Osta, D. Brasacchio, D. Yao, A. Pocai, P. L. Jones, R. G. Roeder, M. E. Cooper, M. Brownlee, *J. Exp. Med.* **2008**, *205*, 2409.
[80] F. Paneni, S. Costantino, R. Battista, L. Castello, G. Capretti, S. Chiandotto, G. Scavone, A. Villano, D. Pitocco, G. Lanza, M. Volpe, T. F. Lüscher, F. Cosentino, *Circ. Cardiovasc. Genet.* **2015**, *8*, 150.
[81] L. M. Villeneuve, M. A. Reddy, L. L. Lanting, M. Wang, L. Meng, R. Natarajan, *Proc Natl Sci USA* **2008**, *105*, 9047.
[82] X.-Y. Yu, Y.-J. Geng, J.-L. Liang, S. Zhang, H.-P. Lei, S.-L. Zhong, Q.-X. Lin, Z.-X. Shan, S.-G. Lin, Y. Li, *Mol. Biol. Rep.* **2012**, *39*, 8891.
[83] F. Paneni, J. A. Beckman, M. A. Creager, F. Cosentino, *Eur. Heart J.* **2013**, *34*, 2436.
[84] Y. Liao, L. Gou, L. Chen, X. Zhong, D. Zhang, H. Zhu, X. Lu, T. Zeng, X. Deng, Y. Li, *Free Radic Biol Med* **2018**, *115*, 383.
[85] I. Floris, B. Descamps, A. Vardeu, T. Mitic, A. M. Posadino, S. Shantikumar, G. Sala-Newby, G. Capobianco, G. Mangialardi, L. Howard, S. Dessole, R. Urrutia, G. Pintus, C. Emanueli, *Arterioscler Thromb Vasc Biol* **2015**, *35*, 664.
[86] P. Han, D. Gao, W. Zhang, S. Liu, S. Yang, X. Li, *Life Sci.* **2015**, *130*, 103.
[87] F. Miao, I. G. Gonzalo, L. Lanting, R. Natarajan, *J. Biol. Chem.* **2004**, *279*, 18091.
[88] Z. Zheng, H. Chen, J. Li, T. Li, B. Zheng, Y. Zheng, H. Jin, Y. He, Q. Gu, X. Xu, *Diabetes* **2012**, *61*, 217.
[89] K. K.-H. Farh, A. Marson, J. Zhu, M. Kleinewietfeld, W. J. Housley, S. Beik, N. Shoresh, H. Whitton, R. J. H. Ryan, A. A. Shishkin, M. Hatan, M. J. Carrasco-Alfonso, D. Mayer, C. J. Luckey, N. A. Patsopoulos, P. L. De Jager, V. K. Kuchroo, C. B. Epstein, M. J. Daly, D. A. Hafler, B. E. Bernstein, *Nature* **2015**, *518*, 337.
[90] C. Buecker, J. Wysocka, *Trends Genet.* **2012**, *28*, 276.
[91] S. H. Park, K. Kang, E. Giannopoulou, Y. Qiao, K. Kang, G. Kim, K.-H. Park-Min, L. B. Ivashkiv, *Nat. Immunol.* **2017**, *18*, 1104.
[92] M. Diedisheim, E. Carcarino, C. Vandiedonck, R. Roussel, J.-F. Gautier, N. Venteclef, *Mol. Metab.* **2020**, *41*, 101041.
[93] S. Saeed, J. Qiuintin, H. H. D. Kerstens, N. A. Rao, A. Aghajanirefah, F. Matarese, S. C. Cheng, J. Ratter, K. Berentsen, M. A. van der Ent, N. Sharifi, E. M. Janssen-Megens, M. T. Huurne, A. Mandoli, T. vanSchaik, A. Ng, F. Burden, K. Downes, M. Frontini, V. Kumar, E. J. Giamarellos-Bourboulis, W. H. Ouwehand, J. W. M. van derMeer, L. A. B. Joosten, C. Wijmenga, J. H. A. Martens, R. J. Xavier, C. Logie, M. G. Netea, H. G. Stunnenberg, *Science* **2014**, *345*.
[94] R. Kamada, W. Yang, Y. Zhang, M. C. Patel, Y. Yang, R. Ouda, A. Dey, Y. Wakabayashi, K. Sakaguchi, T. Fujita, T. Tamura, J. Zhu, K. Ozato, *Proc. Natl. Acad. Sci. U. S. A.* **2018**, *115*, E9162.
[95] S. Naik, S. B. Larsen, N. C. Gomez, K. Alaverdyan, A. Sendoel, S. Yuan, L. Polak, A. Kulukian, S. Chai, E. Fuchs, *Nature* **2017**, *550*, 475.
[96] S. Sun, L. B. Barreiro, *Curr. Opin. Immunol.* **2020**, *65*, 7.
[97] J. Gupta, S. Kumar, J. Li, R. Krishna Murthy Karuturi, K. Tikoo, *Biochimie* **2012**, *94*, 2656.
[98] S. Bekkering, L. C. A. Stiekema, S. Bernelot Moens, S. L. Verweij, B. Novakovic, K. Prange, M. Versloot, J. E. Roeters Van Lennep, H. Stunnenberg, M. De Winther, E. S. G. Stroes, L. A. B. Joosten, M. G. Netea, N. P. Riksen, *Cell Metab.* **2019**, *30*, 31204280.
[99] J. Domínguez-Andrés, S. Fanucchi, L. A. B. Joosten, M. M. Mhlanga, M. G. Netea, *Curr. Opin. Cell Biol.* **2020**, *63*, 68.
[100] K. C. Wang, Y. W. Yang, B. Liu, A. Sanyal, R. Corces-Zimmerman, Y. Chen, B. R. Lajoie, A. Protacio, R. A. Flynn, R. A. Gupta, J. Wysocka, M. Lei, J. Dekker, J. A. Helms, H. Y. Chang, *Nature* **2011**, *472*, 120.
[101] M. S. Klein, J. Shearer, *J. Diabetes Res.* **2016**, *2016*, 26636104.
[102] L. A. Filla, J. L. Edwards, *Mol. BioSyst.* **2016**, *12*, 1090.
[103] A. Gonzalez-Franquesa, A. M. Burkart, E. Isganaitis, M.-E. Patti, *Curr Diab Rep* **2016**, *16*, 74.
[104] M. J. Pena, H. J. Lambers Heerspink, M. E. Hellemons, T. Friedrich, G. Dallmann, M. Lajer, S. J. L. Bakker, R. T. Gansevoort, P. Rossing, D. De Zeeuw, S. S. Roscioni, *Diabet Med* **2014**, *31*, 1138.
[105] L. A. Filla, W. Yuan, E. L. Feldman, S. Li, J. L. Edwards, *J. Proteome Res.* **2014**, *13*, 6121.
[106] W. Yuan, J. Zhang, S. Li, J. L. Edwards, *J. Proteome Res.* **2011**, *10*, 5242.
[107] V. T. Dang, L. H. Zhong, A. Huang, A. Deng, G. H. Werstuck, *Metabolomics* **2018**, *14*, 92.
[108] L. Berkowitz, F. Cabrera-Reyes, C. Salazar, C. D. Ryff, C. Coe, A. Rigotti, *Front Cardiovasc Med* **2022**, *8*, 35097004.
[109] A. Mousa, N. Naderpoor, N. Mellett, K. Wilson, M. Plebanski, P. J. Meikle, B. De Courten, *Biochim. Biophys. Acta Mol. Cell Biol. Lipids* **2019**, *1864*, 335.
[110] M. Fraga-Corral, M. Carpena, P. Garcia-Oliveira, A. G. Pereira, M. A. Prieto, J. Simal-Gandara, *Crit. Rev. Anal. Chem.* **2020**, *7*, 33026841.
[111] L. Qi, Q. Qi, S. Prudente, C. Mendonca, F. Andreozzi, N. Di Pietro, M. Sturma, V. Novelli, G. C. Mannino, G. Formoso, E. V. Gervino, T. H. Hauser, J. D. Muehlschlegel, M. A. Niewczas, A. S. Krolewski, G. Biolo, A. Pandolfi, E. Rimm, G. Sesti, V. Trischitta, F. Hu, A. Doria, *JAMA – J. Am. Med. Assoc.* **2013**, *310*, 821.
[112] C. Pipino, H. Shah, S. Prudente, N. Di Pietro, L. Zeng, K. Park, V. Trischitta, S. Pennathur, A. Pandolfi, A. Doria, *Diabetes* **2020**, *69*, 2206.
[113] M. Z. Huang, X. R. Lu, Y. J. Yang, X. W. Liu, Z. Qin, J. Y. Li, *Int. J. Mol. Sci.* **2019**, *20*, 31267111.
[114] P. Gut, E. Verdin, *Nature* **2013**, *502*, 489.
[115] E. Tzika, T. Dreker, A. Imhof, *Front. Genet.* **2018**, *9*.
[116] S. H. Kwak, K. S. Park, *Exp. Mol. Med.* **2016**, *48*, e220.
[117] P. Schrauwen, M. K. C. Hesselink, *Diabetologia* **2008**, *51*, 1694.
[118] G. D. Lopaschuk, J. R. Ussher, *Circ. Res.* **2016**, *119*, 1173.
[119] M. Holecek, *Int. J. Mol. Sci.* **2023**, *24*, 1724.
[120] S. C. Lu, L. Alvarez, Z. Z Huang, L. Chen, W. An, F. J. Corrales, M. A. Avila, G. Kanel, J. M. Mato, *Proc. Natl Acad Sci USA* **2001**, *98*, 5560.

[121] S. J. Mentch, M. Mehrmohamadi, L. Huang, X. Liu, D. Gupta, D. Mattocks, P. Gómez Padilla, G. Ables, M. M. Bamman, A. E. Thalacker-Mercer, S. N. Nichenametla, J. W. Locasale, *Cell Metab.* **2015**, *22*, 861.
[122] S. M. Kooistra, K. Helin, *Nat. Rev. Mol. Cell Biol.* **2012**, *13*, 297.
[123] G. Benincasa, G. Mansueto, C. Napoli, *J Clin Pathol* **2019**, *72*, 785.
[124] G. Benincasa, P. Candia, D. Costa, M. Faenza, G. Mansueto, G. Ambrosio, C. Napoli, *Lipids* **2021**, *56*, 259.
[125] C. Napoli, G. Benincasa, S. Ellahham, *Curr Diabetes Rev* **2022**, *18*, e221221199301.
[126] A. T. Lu, A. Quach, J. G. Wilson, A. P. Reiner, A. Aviv, K. Raj, L. Hou, A. A. Baccarelli, Y. Li, J. D. Stewart, E. A. Whitsel, T. L. Assimes, L. Ferrucci, S. Horvath, *Aging* **2019**, *11*, 303.



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