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Review

Omics Insights into Epicardial Adipose Tissue: Unravelling Its Molecular Landscape

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Abstract: Epicardial adipose tissue (EAT) is a unique fat depot located around the heart, intimately associated with the myocardium and coronary arteries. The secretion of bioactive molecules and their interaction with neighbouring cardiac tissues makes it an active organ with important implications in cardiovascular health and disease. In recent years, omics technologies have provided valuable insights into the molecular characteristics and functional relevance of EAT in patients with coronary atherosclerosis, myocardial infarction, atrial fibrillation and associated metabolic disorders. This review aims to summarize the current understanding of EAT biology through the lens of genomics, transcriptomics, proteomics and lipidomics approaches. We discuss key findings from omics studies on EAT, including gene expression profiles, metabolic activity, signalling pathways and regulatory network, in order to explore in depth the disease mechanisms, possible therapeutic strategies, and cardiovascular risk assessment. Further advances in this field and integrating data from multiple omics platforms hold promise for unlocking personalized cardiometabolic profiles with EAT as a possible biomarker and therapeutic target in cardiovascular disease.

Keywords: epicardial adipose tissue; omics; EAT genomics; EAT transcriptomics; EAT proteomics; EAT lipidomics; cardiovascular disease

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1. Introduction

Cardiovascular diseases (CVDs) remain a significant global health burden, with obesity, particularly visceral adiposity, contributing independently of other risk factors to CVD development and mortality [1]. Furthermore, significant attention is directed towards epicardial adipose tissue (EAT) as a visceral adipose depot responsible for metabolic changes that are specific to the myocardium [2].

A notable positive correlation exists between EAT and overall body adiposity, with several studies documenting high EAT thickness in obese individuals compared to their non-obese counterparts [3,4]. Interestingly, even though EAT is strongly correlated with poor CVD outcome [2], recent evidence also suggests a potential beneficial role. Obesity could lead to hyperplastic remodelling of EAT as a proposed mechanism of expansion rather than hypertrophy, which is predominant in other adipose depots [3], suggesting a unique feature of this tissue. However, this study has limitations and the proposed mechanism requires further investigation. Another study reported that even if the cellular immune infiltrate in EAT is similar in obese vs. non-obese individuals, obesity significantly modifies the expression of metabolic and inflammatory signalling genes in EAT, suggesting the presence of a proinflammatory state [5]. Moreover, in a comparative study involving rats with post-myocardial infarction, it was observed that the excision of EAT following

the infarction led to enhanced cardiac function [6]. Adipose tissue has always played a critical role in the regulation of different metabolic pathways [7], leading to the recognition of obesity as a "chronic relapsing disease, which in turn acts as a gateway to a range of other non-communicable disease" by the European Commission in 2021 [8]. This new definition as a non-communicable disease (NCD) integrates obesity alongside CVD, cancers, chronic respiratory diseases, and diabetes, as a disease by itself and not just a risk factor. It also grants access to programmes engaged in prevention and treatment of NCD in general, emphasising the importance of research and primary care in this area alone. Since EAT volume can be reduced alongside obesity with diet-based strategies or cardiometabolic drugs [9–11], both therapeutic and preventive interventions are widely embraced in this domain.

EAT represents a factor that is involved in CVD pathogenesis, promoting, for example, atrial structural and electrical remodelling leading to atrial fibrillation [12] or generating high levels of inflammatory mediators in coronary artery disease [13]. Moreover, the obese heart has difficulties in generating sufficient energy for cardiac contraction, describing an altered cardiac metabolism which is a contributing factor to the cause of heart failure and CVD [14].

Therefore, this unique active organ that comes in direct contact with the myocardium is of great importance and all the data gathered until now reveal its potential for becoming a possible biomarker and therapeutic target in CVD. Traditional approaches to understanding and managing these complex diseases generally focus on individual components that provide significant insight on the pathophysiological and biochemical changes, but possibly overlook the intricate interplay of molecular processes that could describe the phenomenon in more detail. In recent years, multiomics approaches have revolutionized our ability to comprehensively characterize the molecular landscape of CVD, paving the way for personalized medicine tailored to individual patient profiles.

The molecular signature associated with cardiovascular health and disease is now more precisely assessed by integrating data from genomics, epigenomics, transcriptomics, proteomics, metabolomics and other omics technologies. This integrative analysis can be performed to describe the transition from a healthy state to a disease state, therefore offering insights into prevention or early diagnosis. Moreover, it can elaborate on the progression of the disease, predict treatment responses and develop targeted interventions tailored to individual patient needs. This fundamental shift from a minimalist approach to a systems biology perspective holds immense promise for unlocking personalized cardiovascular profiles and advancing precision medicine in the field of cardiovascular health.

In this literature review we present recent advancements in the field of EAT biology through the lens of genomics, transcriptomics, proteomics and metabolomics approaches. Additionally, investigating the clinical implications of omics findings related to EAT could enhance risk stratification, accurately identify disease stages, and reveal new therapeutic targets. Through this comprehensive review, we aim to shed light on the transformative potential of omics in elucidating the molecular complexity of EAT, ultimately enhancing cardiovascular health and paving the way towards personalized medicine.

2. Biological and Pathophysiological Relevance of EAT

EAT is located between the myocardium and the visceral epicardium and is different from pericardial adipose tissue, which is located on the external surface of the parietal pericardium [15]. These two types of adipose tissue surrounding the heart should not be confused as they present differences in terms of embryogenic origin, blood supply and metabolic properties [14,16]. Even though both have important roles, EAT has gained more interest over the years since clear evidence has shown its role as an active endocrine organ, serving as a source of several bioactive molecules [17]. Moreover, EAT has a unique characteristic: it is the only visceral fat depot that comes in direct contact with the target organ, with no muscle fascia separating them. This allows crosstalk between EAT and the myocardium, also describing a shared microcirculation [2]. Therefore, the lack of a

barrier reveals interaction mechanisms (paracrine and vasocrine) that exert effects on the myocardium and coronary vasculature by expressing various cytokines [17]. These effects can be protective or harmful and are the results of various molecules with the following properties: proinflammatory/proatherogenic (MCP-1, TNF-α, and interleukines), anti-inflammatory/anti-atherogenic (adiponectin and adrenomedullin), thermogenic (UCP 1), insulin-mimetic (resistin, visfatin and omentin), brown fat differentiation transcription factors (PRDM16 and PGC-1α), vascular remodelling, blood pressure control, and adipogenesis or myocardial hypertrophy factors (angiotensin, angiotensinogen, and leptin) [18]. The hypothesis that EAT may play an active role in heart disease is still under debate, with recent publications reporting multiple correlations between these molecules and heart physiopathology, but they are still not proven to be cause-related. Whether beneficial in lean subjects or detrimental when in excess, EAT presents a high association with CVDs [19,20].

In normal physiological states, EAT constitutes around 20% of the total heart mass. The distribution is different around the heart and, moreover, each regional EAT depot has different effects as a result of its own transcriptome and proteome [21]. EAT serves not only as an energy reservoir, but also as an endocrine organ that plays a crucial role in regulating heart homeostasis. Besides vasocrine and paracrine interaction mechanisms between EAT and the myocardium, extracellular vesicles (EVs) containing microRNAs serve as novel means of communication. EAT-secreted vasoactive products facilitate free fatty acid influx assuring energy to heart cells, while fatty-acid-binding protein-4 (FABP-4), expressed by EAT, may contribute to intracellular free fatty acid transport from EAT to the myocardium [22].

Clinical studies have reported high EAT volume in patients with metabolic syndrome [23], although EAT density might be a better predictor of cardiometabolic risk [24]. Furthermore, EAT volume appears to be an autonomous predictor of diabetes in patients with coronary artery disease (CAD) who are already undergoing treatment for elevated cholesterol values [25]. Thus, while statins have been suggested as potential EAT modulators [26,27], this hypothesis still requires validation. Multiple studies robustly support the role of EAT in CVDs including atherosclerosis, arrhythmias, aortic stenosis, thromboembolism, and heart failure. High EAT thickness correlates with slow coronary flow, serving as a predictive indicator for the presence of subclinical atherosclerosis [28], while also affecting the stability of the plaque in the coronary artery [29] and possibly exerting a systemic influence on the progression of atherosclerosis [30]. A prospective study on 4093 participants followed for approximatively 8 years reported an increase in fatal and non-fatal coronary events, together with EAT thickness, independent of cardiovascular risk factors [31]. All these data support the idea that EAT volume demonstrates its utility in predicting cardiovascular mortality, hospitalization for heart failure, stroke, and myocardial infarction [32], while also supporting a relevant association with the presence of atrial fibrillation [33]. Moreover, its specific anatomical localization may contribute to a more precise diagnosis, as demonstrated in this study where periatrial EAT was found to reliably predict the onset of atrial fibrillation [34]. Given the significant progress in non-invasive imaging techniques for analysing EAT composition, its integration into clinical practice may soon provide documented arguments for precise risk assessment of CVD [22].

3. Genomics and Transcriptomics of EAT

Genomics and transcriptomics are complementary fields that offer comprehensive insights into the genetic makeup and gene expression dynamics of organisms. EAT genomics involves the systematic analysis of all genes within EAT, facilitated by various sequencing technologies such as DNA microarrays or next-generation sequencing (NGS). These techniques enable researchers to investigate gene mutations and identify their associated role with diseases. For instance, in the context of EAT and CVDs, genomics has led to the identification of numerous genes linked to an increased risk of cardiometabolic diseases, enhancing our understanding of its genetic basis. On the other hand, transcriptomics focuses on studying all RNA transcripts and is essential for deciphering the genetic

network involved in diseases due to the variation in gene expression across tissues in general or across developmental stages of tissues in particular. By integrating genomics and transcriptomics, researchers can gain a holistic understanding of genetic variation, gene expression patterns, and their implications for health and disease.

A recent study selected a number of 33 SNPs associated with CAD or atherosclerosis, from GWAS and other candidate-gene association studies, and identified the MTHFR677 polymorphism (rs1801133) as the only significant and independent predictor of a higher volume of EAT, which is known to be associated with various heart conditions. The cohort included 996 healthy subjects and also tested the importance of genetic risk scores based on SNPs of specific biological pathways as a way of predicting heart disease. Interestingly, patients with a high EAT volume presented not only a high global genetic risk score, but also high values for scores including variants associated with inflammation/oxidation and obesity/diabetes pathways, separately [35]. At the same time, another study accounted for the importance of adding an EAT volume parameter to a genetic risk score in order to better predict major adverse cardiovascular events [36].

EAT consists mainly of white adipocytes which present brown fat-like properties that unfortunately decrease with age. For example, miR-1-3p and miR-133a-3p released by EAT and considered potential targets in atrial fibrillation are also specific for brown adipose tissue and not white adipocytes, therefore suggesting the brown fat-like feature [37]. Another example is miR-455-3p expressed by EAT, which induces PPARγ expression, resulting in increased expression of brown adipose tissue-specific genes [38]. miR-455-3p expression is down-regulated in CAD, leading to a reduced anti-inflammatory effect for the cardiovascular system [39]. In time, epicardial adipocytes become increasingly vulnerable to environmental, metabolic and hemodynamic influences, gradually shifting the function of EAT from thermogenesis to energy storage. However, in the case of advanced phases of CAD, we also see a suppression of brown fat-like activity within EAT. Interestingly, this process could be inversed by pharmacological enhancement of gene expression for proteins involved in the browning of adipose tissue. The positive outcome is associated with a reduction in inflammation and left ventricular mass [2]. Uncoupling protein-1 (UCP1), the main marker of brown adipose tissue, is highly expressed in EAT as opposed to other adipose tissues, suggesting a protective role in thermogenesis for the myocardium against hypothermia [14]. The mechanism by which UCP1 is involved in preserving EAT homeostasis is largely unknown, but high UCP-1 expression in EAT was linked to suppression of reactive oxygen species production and immune responses. Interestingly, a bidirectional connection between UCP-1 and adaptive immunity at the extensive transcriptome level is suggested [40]. Moreover, the expression of EAT UCP-1 and two other thermogenic genes, peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1α) and PR-domain-missing 16 (PRDM16), was down-regulated in patients with reduced ejection-fraction heart failure relative to those with preserved ejection fraction [41]. More unique features add to this unique transcriptome of EAT [21], like an increased fatty acid release [42] and metabolism capacity [43] or the systemic effect on lipid metabolism generated by a high UCP-1 mRNA expression in EAT [44].

Regarding the link between EAT and atherosclerosis, a recent study profiled miRNA for atherosclerosis and discovered among the 250 differently expressed miRNA in EAT from CAD patients an up-regulation of miR-200b-3p. This overexpression is related to oxidative stress, which seems to target histone deacetylase 4 (HDAC4) inhibition and promote endothelial cell damage [45]. HDAC4 is an important regulator of gene expression and participates in the apoptosis process of various cells [46]. The same study supports the hypothesis that EAT accelerates the progression of atherosclerosis by reporting the upregulation of several pro-inflammatory miRNAs (e.g., miR155-3p, miR-206, miR-146a-5p) and the downregulation of anti-inflammatory miRNAs (e.g., Let-7i, miR-127-5p) [45]. Iacobellis et al. have shown that mRNA levels and protein expression of protective adiponectin and adrenomedullin are lower in patients with CAD than in control subjects. However, when comparing plasma adrenomedullin in the left coronary artery with levels in the

coronary sinus, the values were not statistically significant, suggesting that EAT may not be responsible for adrenomedullin secretion into the coronary lumen [47]. Omentin-1 is another anti-inflammatory adipokine which is highly expressed in EAT [21,48] and its supplementation has promising results in reducing atherosclerotic plaque [49]. However, even if circulating omentin-1 levels are lower in CAD, a recent study demonstrated similar results for mRNA omentin levels in the EAT of CAD and non-CAD subjects, suggesting no change in gene expression during the progression of the pathology. Moreover, the pro-inflammatory adipokine FABP4, which is also secreted by EAT, presented a down-regulated expression in CAD, but only when obesity was present [50].

EAT is also studied in metabolic diseases, particularly diabetes, a multifaceted condition associated with cardiovascular outcomes. EAT samples among diabetic and non-diabetic subjects showed a pronounced alteration of genes associated with inflammatory response and cytokine activity in diabetic patients: IL-1β, CD274, PDCD1, ITGAX, PRDM1, LAG3, TNFRSF18, CCL20, IL1RN and SPP1 [51]. Considering that EAT is a source of inflammatory mediators and cytokines in patients at high risk of heart disease [13,52], this might be a pathway through which diabetes accelerates CAD development. A possible target for reducing cardiovascular inflammation could be IL-1β, since it was the most significant hub gene in diabetic EAT [51]. Another suggested pathway is related to an overexpressed AGE-RACE (advanced glycation end-products receptor advanced glycation end-products) pathway that generates upregulated transcription factors, like NF-kB and FOSL. The increase in these factors is correlated with a higher diabetic EAT gene expression in the innate immune response when compared to the subcutaneous adipose tissue (SAT) transcriptome. In addition, the SAT gene profile is similar in patients with diabetes and those without, suggesting that EAT changes could indeed be representative of diabetes as an important risk factor for CVD [53]. The expression of EAT key genes linked to diabetes mellitus, as a common associated pathology for CVD, is presented in Table 1.

Table 1. Expression of EAT key genes linked to diabetes mellitus.

Gene/Product Name	mRNA Expression in Diabetic EAT vs. Non-Diabetic EAT	Biological Process	Reference
IL-1b (interleukin-1 beta)	Up-regulated	positive regulation of MAP kinase activity, cytokine activity, positive regulation of canonical NF-kappaB signal transduction	Yang H., et al. [51]
CD274 (programmed cell death 1 ligand 1)	Up-regulated	regulation of activated CD4-positive, alpha-beta T cell apoptotic process, transcription coactivator activity	
PDCD1 (programmed cell death protein 1)	Up-regulated	programmed cell death protein 1	
ITGAX (integrin alpha-X)	Up-regulated	receptor tyrosine kinase binding, integrin binding, cell adhesion	
PRDM1 (PR domain zinc finger protein 1)	Up-regulated	DNA-binding transcription repressor activity, RNA polymerase II-specific	
LAG3 (lymphocyte activating 3)	Up-regulated	adaptive immune response, negative regulation of interleukin-2 production, cell surface receptor signalling pathway	
TNFRSF18 (TNF receptor superfamily member 18)	Up-regulated	tumour necrosis factor-mediated signalling pathway, positive regulation of cell adhesion, negative regulation of apoptotic process	
CCL20 (C-C motif chemokine 20)	Up-regulated	chemotaxis, immune response, positive regulation of T cell migration	
IL1RN (interleukin-1 receptor antagonist protein)	Up-regulated	lipid metabolic process, immune response, cytokine activity	
SPP1 (osteopontin)	Up-regulated	cytokine activity, integrin binding	

Table 1. *Cont.*

Gene/Product Name	mRNA Expression in Diabetic EAT vs. Non-Diabetic EAT	Biological Process	Reference
PTX3 (pentraxin-related protein 3)	Up-regulated in diabetic EAT vs. diabetic SAT	complement component C1q complex binding, beta-D-glucan binding	Camarena V. et al. [53]
LIPG (endothelial lipase G)	Up-regulated in diabetic EAT vs. diabetic SAT	phospholipase and triglyceride lipase activity, heparin binding, lipid metabolic process, response to nutrient	
UCP-1 (mitochondrial brown fat uncoupling protein 1)	Down-regulated in diabetic with CAD EAT vs. non-diabetic with CAD EAT	oxidative phosphorylation uncoupler activity, GTP binding, long-chain fatty-acid binding, cardiolipin binding, diet-induced thermogenesis	Moreno-Santos I. et al. [54]
PGC1α (peroxisome proliferator-activated receptor gamma coactivator 1-alpha)	Down-regulated in diabetic with CAD EAT vs. non-diabetic with CAD EAT	negative regulation of smooth muscle cell proliferation, energy homeostasis, transcription coactivator activity	

A comparison of EAT and visceral adipose tissue depots from the abdomen show a clearly distinct gene expression signature. At a rigorous p value ($<1.1 \times 10^{-6}$) COL4A4 and HBM presented high expression levels in EAT compared to visceral samples [21], emphasizing the importance of pathways like extracellular matrix remodelling, immune signalling, beigening, thrombosis, and coagulation [48]. Moreover, there is evidence that specific transcriptomic signatures of EAT depend on the pericoronary, periatrial, or periventricular anatomical location (Figure 1). Interestingly, periventricular, and not pericoronary EAT, is the most proinflammatory depot at the gene expression level. However, peri-coronary EAT remains more involved in the process of atherosclerosis [21], since it associates with the sphingolipid metabolism pathway and sphingolipids promote the retention of oxidized LDL, favouring the formation of atherosclerotic plaque [55,56]. On the other hand, periatrial EAT is involved in atrial fibrillation with up-regulation of genes encoding pro-arrhythmogenic factors, the extracellular matrix structural constituent conferring tensile strength, and also genes involved in cardiac muscle contractility and actomyosin structure organization.

Considering the limitation of studying EAT only in patients undergoing cardiac surgery, subcutaneous adipose tissue (SAT) was considered a possible second-best option, leading the way to comparison studies between the two tissues. Table 2 documents the expression of key EAT genes involved in CAD, alongside a comparison with their expression level in SAT. In patients undergoing coronary artery bypass grafting surgery, the ADORA1 (adenosine A1 receptor) gene involved in myocardial ischemia and PTGDS (prostaglandin D2 synthase) gene associated with the progression of atherosclerosis have a significantly up-regulated expression in EAT versus SAT [57]. One study identified 14 genes (4 up-regulated, 10 down-regulated), which can discriminate EAT from SAT with 100% accuracy, independently of the patients' disease [39]. The data emphasize in the end the irreplaceable role of EAT, and its special characteristics as a tissue with a more pronounced inflammatory profile than SAT even in the absence of CAD. One study reports that inflammation is the result of differences in gene expression dictated by EAT itself and not by the disease [58]. A comprehensive bioinformatic analysis merged the expression profiles from these three studies [39,57,58] and identified differentially expressed genes between EAT and SAT, with 10 hub genes being involved in CAD development: HOXA5, HOXB5, HOXC6, HOXC8, HOXB7, COL1A1, CCND1, CCL2, HP and TWIST1. The study confirms the upregulation of pro-inflammatory and immunological pathways in the process of CAD, while the intestinal immune system, coagulation cascade, complement function and vascular endothelial growth factor production seem to also have a role in EAT metabolism. To enhance precision, these results were further validated in the same study on samples from eight patients with CAD [59].

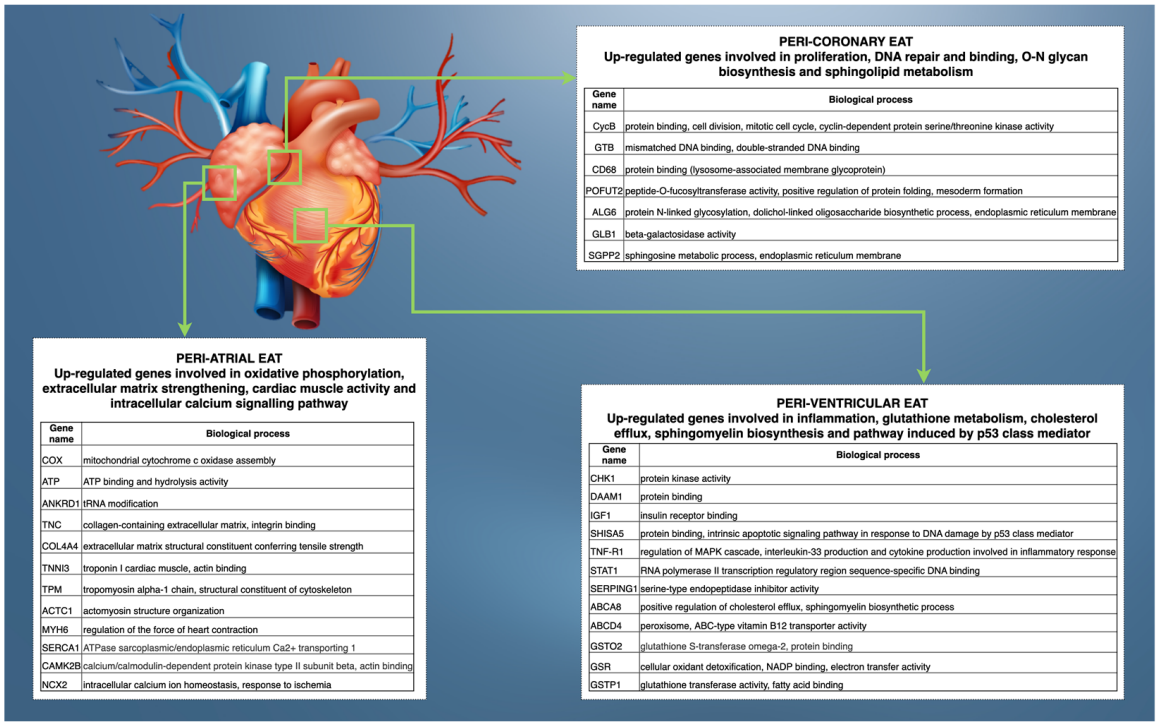


Figure 1. Transcriptomic signature of periatrial, periventricular and pericoronary EAT. [Image designed with Freepik, data adapted from Gaborit B. et al. [21] and analysed with gene ontology].

Table 2. Expression of EAT key genes in coronary artery disease.

Gene/Product Name	mRNA Expression in CAD EAT vs. Control	mRNA Expression in CAD EAT vs. CAD SAT	EAT Anatomical Location	Reference	Conclusion
Chemerin	Up-regulated	Up-regulated	Near the proximal right coronary artery	Gao X. et al. [60]	the severity of CAD is positively associated with the level of chemerin mRNA in EAT and not with its circulating level
Adiponectin	Down-regulated	Down-regulated	Near the left anterior descending artery	Zhou Y. et al. [61]	adiponectin might inhibit atherosclerosis through decreasing TLR4 expression on macrophage/monocytes
			Near the proximal right coronary artery	Gao X. et al. [60]	low adiponectine expression level in EAT suggests a reduced anti-inflammatory protection, while the change is not reflected in circulating levels of CAD patients
			Near the right coronary artery	Du Y. et al. [62]	adiponectin expression level in EAT did not differ between stenotic and non-stenotic segments in CAD
			Near the right coronary artery	Bambace C. et al. [63]	mRNA expression of adiponectin is lower in EAT than SAT in CAD subjects
			Near the right coronary artery	Eiras S. et al. [64]	the extension of CAD is significantly associated with the expression of adiponectin and IL-6 mRNA in EAT
IL-6	Up-regulated	Up-regulated	Near the left anterior descending artery	Zhou Y. et al. [61]	secretion of IL-6 in stimulated monocytes is inhibited by adiponectin
			Near the right coronary artery	Eiras S. et al. [64]	the imbalance between low adiponectin and high IL-6 mRNA levels in EAT may contribute to the progression of CAD

Table 2. *Cont.*

Gene/Product Name	mRNA Expression in CAD EAT vs. Control	mRNA Expression in CAD EAT vs. CAD SAT	EAT Anatomical Location	Reference	Conclusion
TNF-alpha	Up-regulated	Up-regulated	Near the left anterior descending artery	Zhou Y. et al. [61]	secretion of TNF-alpha in stimulated monocytes is inhibited by adiponectin
			Near the proximal right coronary artery	Gao X. et al. [60]	EAT in CAD expresses high pro-inflammatory status
Omentin-1	Down-regulated	Up-regulated	Near the right coronary artery	Du Y. et al. [62]	circulating and EAT-derived omentin-1 levels were reduced in patients with CAD. EAT adjacent to coronary segments exhibiting stenosis presents low omentin-1 expression, in contrast to non-stenotic segments
	Not modified		Near the right coronary artery	Miroshnikova V. et al. [50]	No change in gene expression for omentin during the progression of the pathology
TLR4	Up-regulated	Up-regulated	Near the left anterior descending artery	Zhou Y. et al. [61]	adiponectin might inhibit atherosclerosis through decreasing TLR4 expression on macrophage/monocytes
UCP-1	Up-regulated		Near the right coronary artery	Sacks H. et al. [65]	UCP-1 is notably prevalent in EAT, exhibiting molecular characteristics similar to those observed in beige adipocytes
PRDM16	Up-regulated		Near the right coronary artery	Sacks H. et al. [65]	a unique transcriptome describes high expression levels of genes that induce browning of white adipose tissue and/or help the development of brown adipose tissue
PGC-1α	Up-regulated				
PPARγ	Up-regulated				
CD137 (beige adipocyte-specific marker)	Up-regulated				
HLA-C	Down-regulated		Near the right ventricle	Chechi K. et al. [40]	UCP1 can be targeted to maintain EAT homeostasis to manage CAD
DDX39B	Down-regulated				
HOXs COL1A1 CCND1 TWIST1		Down-regulated		Yang H. et al. [59]	proinflammatory and immunological pathways may serve as pivotal regulators of EAT, contributing to the progression of CAD
CCL2 HP		Up-regulated			
sPLA2-IIA	Up-regulated	Up-regulated		Dutour A. et al. [66]	sPLA2-IIA has a potential role in CAD pathophysiology and is an independent risk factor for CAD

Perivascular EAT overexpresses genes responsible for regulating vascular morphology, angiogenesis, inflammation and haemostasis, emphasizing the role of cross talk between EAT and vessel wall in atherosclerosis [67]. However, transferring this knowledge into clinical practice is hard, since serum inflammatory markers are not specific for a certain local inflammation site [18], making it challenging to find a marker for inflammation that reports changes in EAT metabolism. Moreover, hsCRP, homocysteine, insufficient vitamin D levels and TNF-α have similar circulating levels in patients with CAD versus the control group [68]. One study suggests the possibility of clinically assessing EAT dysfunctionality by measuring circulating CCL13, which is the only chemokine that presents a significant increase both in plasma and in EAT in patients with CAD, presenting a sensitivity of 73% and a specificity of 67% as a biomarker. miR-103-3p has been found to be a modulator of CCL13 in CAD [39]. Other findings emphasize na MCP-1 expression significantly up-regulated in CAD patients after adjusting for cofounders like hypertension, diabetes, dyslipidaemia, age, gender, and BMI, together with the down-regulation of adiponectin as a protective molecule [68]. To further emphasize the inflammatory pathway in CAD, EAT describes an increased expression of $sPLA_2$-IIA (secretory type II phospholipase A_2), which is responsible for catalysing the rate-limiting step in the synthesis of proinflammatory lipid mediators [66].

We should be careful in interpreting these results, since inflammation seems to be associated with a proper adipose tissue function, and therefore the presence of inflammatory infiltrates does not necessarily assess the presence of the disease [69]. Nevertheless, the inflammatory profile of EAT seems to be altered in the presence of obesity or diabetes, rather than in the presence of cardiac disease [5]. At the same time, atherosclerotic plaque develops only in sections of coronary arteries that are surrounded completely by EAT to an extent that the amount of fat correlates with the width and composition of the plaque [70,71]. Therefore, it is still challenging to determine the precise factors that trigger EAT changes and whether they represent a cause or a consequence of diseases.

Considering the proximity of EAT and the myocardium, the exosomal miRNAs secreted by adipose tissue could be taken up by myocytes. Few studies have been performed on the role of EVs in CVD. The first study of this kind addressing the pathogenesis of atrial fibrillation was conducted in 2021 and described a proinflammatory, profibrotic and proarrhythmic profile of EVs from EAT in patients with fibrillation [72]. Ernault C.A. et al. analysed the secretome of EAT and showed that EVs which are more concentrated in the EAT than in the SAT secretome are involved in the physiopathology of atrial fibrillation by shortening the repolarization action's potential duration to 80%. EAT secretome overexpresses miR-1-3p and miR-133a-3p, which down-regulates Kcnj2 gene expression related to cardiac electrophysiology, therefore leading to a reduced arrhythmogenic conduction and suggesting new therapeutic targets for fibrillation [37,73,74]. Moreover, the distinct pre-operatory transcriptome of EAT described a pre-existing inflammatory state in subjects that developed postoperative atrial fibrillation (POAF) [75]. POAF emerges as the predominant complication and a significant predictor of mortality and morbidity in the immediate period following cardiac surgery [76]. A recent study profiled for the first time the expression of lncRNA in EAT of patients with atrial fibrillation. A total of 57 lncRNAs were expressed differentially in AF versus the control group and most of them interacted with genes associated with cardiac remodelling pathogenesis: myofibroblast differentiation, TGF-β1-induced epithelial–mesenchymal transition, NF-κB-mediated inflammatory signalling, and mitochondrial transcription and functionality in endothelial cells linked to a dysfunctional lipid metabolism [77]. The potential interplay between mRNA and lncRNA in myocardial fibrosis or ion channel regulation might be intricately linked to the initiation of POAF [78].

A recent study describes a signature of new small RNA microparticles expressed by EAT in heart failure, called transfer RNAs (tsRNAs), which present different biological activities that produce changes in cellular function [79,80]. Only 24 out of 343 tsRNAs were differentially expressed when comparing controls with patients with heart failure. Two down-regulated tsRNAs (tRF-Tyr-GTA-010 and tRF-Tyr-GTA-011) presented an important interaction of target genes and contributed to calcium ion transport and nitric oxide synthase binding [80]. Another novel category of non-coding RNA, circular RNAs (circRNAs), induce cardiomyocyte hypertrophy, proliferation and cardiac fibrosis [81]. The role of circRNAs in EAT of patients presenting heart failure with preserved ejection fraction (HFpEF) has been recently investigated and the 131 differently expressed circRNAs are associated with the regulation of cellular and metabolic processes. KEGG analysis revealed that the predominant pathways associated with upregulated circRNAs included the thyroid hormone signalling pathway, platinum drug resistance and renal cell carcinoma, while downregulated circRNAs were found to be linked to ubiquitin-mediated proteolysis, nucleotide excision repair, morphine addiction and adherens junction-related pathways. The most significant upregulated circRNA in this study corresponds to HECW2. This gene is responsible for encoding a member of the E3 ubiquitin ligases and performs a crucial function in angiogenesis through the stabilization of endothelial cell-to-cell junctions. It is involved in cardiac hypertrophy, fibrosis, regulation of oxidized-LDL-induced cardiovascular endothelial cell dysfunction and possibly in inflammation, which is a key factor in HFpEF [82].

4. Proteomic Insights of EAT

The proteome governs cellular function and provides valuable insights into disease mechanisms. In contrast to the genome, the proteome provides a more direct connection to the disease phenotype, offering a more precise perspective on disease initialization and progression. There are few proteomic studies performed on EAT and the relationship between EAT proteome and CVD needs further clarification.

Salgado-Somoza et al. compared EAT and SAT proteome of patients undergoing heart surgery and concluded that EAT is associated with myocardial stress, since oxidative stress proteins (catalase, glutathione *S*-transferase P, protein disulfide isomerase, and phosphoglycerate mutase 1) were more expressed in EAT than SAT of patients with CAD [83].

In atrial fibrillation, myeloperoxidase presented the highest protein levels expressed by the EAT secretome as compared to subjects without atrial fibrillation, together with gene-set neutrophil degranulation. These molecules seem to be involved in structural remodelling, since they aggregate into fibrofatty infiltrates within the atrial myocardium. Moreover, EAT myeloperoxidase presented high expression levels in patients that had no atrial fibrillation at baseline but developed it afterwards, even if there were no differences in cardiovascular risk factors initially between the two groups [84]. By secreting the adipofibrokine Activin A, the secretome of EAT facilitates fibrosis of the atrial myocardium [85]. Moreover, proteins responsible for extracellular matrix organization were increased in EAT of ischemic cardiomyopathy patients, suggesting pathologic remodelling [86]. Patients with ischemic cardiomyopathy reveal a distinct EAT proteome from healthy subjects, with a total of 165 proteins significantly changed. These proteins are mainly involved in cytoskeleton organization, cellular metabolism, and immune response [86].

There is also a different EAT proteome in patients who later develop POAF, with low expression levels of a protein associated with maintaining the sinus rhythm, gelsolin. This protein exerts an important role in inflammation and ion channel regulation pathways. At the same time, a favourable effect was expressed by antioxidant enzymes catalase and selenium binding protein-1 (SBP-1), which were up-regulated in the group with POAF [87]. The balance between these proteins and their effect on myocardium processes needs further clarification, since the onset of POAF is linked to an increase in inflammatory and thrombotic proteins in EAT, alongside a decrease in cardioprotective proteins exhibiting anti-inflammatory and anti-lipotoxic properties [88].

Another proteomic study focused on patients with heart failure and demonstrated that serine proteinase inhibitor A3 (Serpina3) was up-regulated in EAT of patients with heart failure vs. the control group (4.63 HF/non-HF ratio). Plasma levels of Serpina3 were elevated in the group with HF compared to the non-HF cohort. Even though this protein exerts an important role in the inflammatory response pathway, there were no plasma changes in immunity markers. However, high levels of Serpina3 were associated with high BNP, ESR and CRP levels [89].

A recent study characterized the cardiac visceral adipose tissue proteome between lean and obese rats. Even though it was not a study that targeted only EAT, but also pericardial and pericoronary adipose tissue, the results highlight an up-regulated expression of UCP-1 protein in lean rats as a marker of brown adipose tissue [90]. However, rodents are not a suitable model for studies on EAT, since persistent disparities exist in the biology of brown fat between mice and humans, and, notably, fat accumulation in rodents frequently occurs outside the pericardium [91]. A proteomic study performed on human EAT does not report differences in UCP-1 expression levels between lean and obese subjects, even if it confirms the fact that EAT is richer in UCP-1 than SAT. However, results underline a higher expression level of another beige fat marker, Slc36a2, in lean subjects compared to levels in overweight subjects. Interestingly, when analysing whether expression levels of all the known beige markers (Tmem26, Slc36a2, Tnfrsf9, Tbx1, P2rx5) clustered with UCP-1 are modified in obesity, no significant difference was observed. However, in the case of CAD, this cluster was down-regulated. The same study reported a positive association of EAT thermogenic markers with plasma HDL-cholesterol and a negative association with

circulating TG, confirming the important role it has in lipid metabolism [92]. However, ABCA1 gene expression in EAT decreases, suggesting an impairment in reverse cholesterol transport process [93].

A systematic review of the literature concerning dysregulated proteins emphasizes the role EAT has in CAD physiopathology. The immune system triggers pathways linked to elevated levels of secreted proteins, whereas pathways associated with the binding and uptake of ligands by scavenger receptors were correlated with low levels of secreted protein. These results support the cardioprotective effects of physiological EAT via the paracrine or vasocrine secretion of anti-inflammatory adipokines. Simultaneously, they highlight the shift in the epicardial fat secretome equilibrium when adipocyte dysfunction occurs, resulting in the release of proinflammatory adipokines from epicardial adipocytes [94,95]. Patients with CAD also present high levels of MMP-9 expression in EAT, suggesting vascular remodelling processes and vascular smooth muscle migration [96]. Meanwhile, clusterin, a molecule recognized for its cardioprotective effects against ischemia and necrosis, demonstrates upregulated EAT expression according to proteomic data, which aligns with increased plasma levels observed in studies [96,97].

The EAT proteome was also studied in patients with HFpEF, identifying 96 proteins (71 upregulated and 25 downregulated) differentially expressed from the group of patients without the pathology. The results suggest that these proteins (such as CD36, POSTN, and TRAP1) play a predominant role in HFpEF, encompassing lipid metabolic disorder, inflammation, and mitochondrial dysfunction [98]. Another study that compared the group with HFpEF with the group with heart failure with reduced ejection fraction (HFrEF) identified TGM2 as a possible new marker for discriminating between the two diseases. There is insufficient evidence to suggest this protein is secreted by EAT and then released into the circulation, but TGM2 is decreased in EAT and also in the plasma of patients with HFrEF, suggesting a poorer prognosis for HFrEF. TGM2 is a calcium-dependent acyltransferase involved in the progression of heart failure with an important role in stiffening the extracellular matrix and contractility of the myocardium [99].

GLO1 emerges as a distinguishing protein for increased EAT thickness, associated with oxidative stress and implicated in heart failure differentiation. Conversely, MMP-2 shows a negative association with EAT thickness, previously linked to myocardial fibrosis in coronary bypass-surgery patients and atrial fibrillation. Additionally, lower levels of vascular endothelial growth factor-D were observed in patients with increased EAT thickness, hinting at endothelial dysfunction as a component in HFpEF disease development [100].

5. Lipidomic Insights of EAT

As a derivative of metabolomics, lipidomics is considered an opportunity to approach EAT phenotypes from a biochemical perspective. More than genes and proteins, metabolites act as direct indicators of the physiological and pathological changes in the biochemical activity of EAT.

An untargeted lipidomic study showed that EAT and SAT have completely different lipidomic profiles. For example, in comparison to SAT, the expression level of phosphatidylethanolamine in EAT was 20 times higher. Moreover, this molecule was the most important in discriminating patients with CAD from patients without. These data reflect a high number of cell membranes and emphasize the small nature of adipocytes in EAT compared to SAT [101]. High levels of phosphatidylethanolamine plasmalogens present in EAT suggest that these molecules could be involved in the regulation of mitochondrial dynamics, and therefore in the brown activation of EAT. Additionally, the lipidomic signature of EAT in CAD compared to non-CAD subjects presented more ceramides, diglycerides, and monoglycerides, and fewer unsaturated TGs [101]. Amongst these molecules, ceramides are of particular interest as they play a pivotal role in numerous inflammatory processes. Not only the total EAT ceramide level in CAD, but also the atherogenic ceramide ratios, report a strong association with the activity of an enzyme that could largely contribute to the EAT volume increase in CAD, lipoprotein lipase (LPL). This enzyme enhances the

influx of free fatty acids from circulating TG-rich lipoproteins into EAT [102]. Ceramides have also been shown to lead to cellular dysfunction and apoptosis, a phenomenon referred to as lipotoxicity [103,104]. Inflammation highlighted by transcriptomics and proteomics is considered a driver of the dyslipidemic phenotype associated with EAT, resulting in increased levels of triglycerides-rich lipoproteins that offer a protection by neutralizing inflammatory triggers [105].

Minor lipids could also have an important role in EAT metabolism. They can be detected by optimizing the preanalytical phase of lipid analysis in adipose tissue and separating triglycerides. This method allowed the identification of 37 lipid molecules that were under the limit of detection before because high molecular-mass molecules suppressed their ionization. EAT and SAT differed mainly in the following lipid classes: sphingomyelins, glycerophosphatidylcholines, glycerophosphatidylinositols, and glycerophosphatidylethanolamine [106]. A more in-depth analysis identified differences in glycerolipids by means of saturation/unsaturation and the number of carbons of fatty acids present in these molecules. CAD was associated with high levels of saturated and monounsaturated fatty acids in TG. Meanwhile, in patients with both diabetes and CAD, these EAT levels were lower, especially for fatty acids with an odd number of carbons [107].

Interestingly, the plasma lipoprotein profile only partially reflects the EAT lipidome; therefore, circulating lipoproteins cannot be considered biomarkers for EAT lipid content [101,107]. A relevant positive correlation was observed between dihydroxycholesterol in EAT and total plasma cholesterol in patients with diabetes and CAD, but not in patients with CAD and without diabetes [107]. Concerning the fact that high levels of oxysterols are associated with CAD, further lipidomic studies that include other molecules from the same class need to be performed on EAT in subjects with CAD to confirm or negate their direct role.

Different diacylglycerols present a significant but weak correlation with total cholesterol and HDL-cholesterol [107]. In patients with CAD, Tomasova et al. attribute an EAT diacylglycerol (18:2/18:2) increase to the presence of type II diabetes [107], while Pezeshkian et al. did not report distinct values in similar conditions [108]. Diacyglycerol acts as a second-messenger signalling lipid that could be involved in mediating insulin resistance [109], while fatty acids 18:2 have a role in reducing LDL values and preserving mitochondrial function by means of cardiolipins, therefore preventing cardiac diseases [110].

Assessing all EAT lipid species and reconciling the data on both beneficial and detrimental effects contributes relevant metabolic information to previous genome-wide association studies, while delving deeper into EAT metabolism. Although integration into clinical practice is difficult, particularly because plasma lipids do not mirror changes in EAT lipidomics and are influenced by dietary factors, a deeper comprehension would be valuable for prevention and the identification of new drug targets.

6. Conclusions

Providing comprehensive definitions of EAT genome, proteome and metabolome in patients with CVDs is of great interest, assuring a gateway to multiomics approaches. Moreover, it can elaborate on the progression of the disease, predict treatment responses and develop targeted interventions. The data already obtained describes new pathways and the molecular interplay at the level of this unique tissue that comes in direct contact with the myocardium. In recent years, multiomics approaches have revolutionized our ability to comprehensively characterize the molecular landscape of diseases, paving the way for personalized medicine tailored to individual patient profiles. To the best of our knowledge, the literature lacks a multiomics analysis that integrates the big data from omics studies concerning EAT and CVD, probably primarily due to specific challenges in obtaining tissue samples, resulting in a relatively limited number of data compared to other tissues. This type of analysis would characterize in even more depth the mechanisms of action of certain molecules secreted by EAT under pathological conditions and would define with more accuracy the phenotypic transformation experienced by EAT when switching

from a healthy to an unhealthy state. However, whether the different functional changes in EAT genome, proteome and metabolome of patients with CVDs represent causal factors or consequences still needs further clarification. Nevertheless, there is a consensus that the inflammatory status of EAT contributes to cardiac dysfunction, as evidenced by its association with heart failure and other CVDs. Despite the variability of circulating EVs in healthy individuals, EAT-derived EVs hold promise as prognostic and diagnostic tools for CVDs, together with EAT volume or density. Additionally, transcriptomic and proteomic analyses have revealed that EAT expresses a unique set of genes and proteins, influencing myocardial function through paracrine signalling and modulation of the immune and endocrine systems. Further studies addressing the regulation of EAT gene expression and post-translational modifications of proteins could provide new insights into its role in health and disease.

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