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Review

Metabolomics in Cardiovascular Diseases

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Abstract: Cardiovascular diseases (CVDs) are the leading cause of death worldwide, and disorders of cardiac energy metabolism are the main contributors to many cardiovascular pathologies. Metabolomics is a science that examines the types and amounts of metabolites and the patterns of change in biological systems after stimulation or perturbation. Metabolites are widely distributed in the body and have universal regulatory effects on a wide range of physiological activities. Metabolism is at the end of the regulation of life activities, so metabolomics is closer to phenotypes than genomics and transcriptom-ics, and can reflect the state of biological systems more accurately. Metabolomics, a cross-cutting dis-cipline emerging in the post-genomics era, has rapidly penetrated into many fields of medicine, im-proves understanding of complex diseases and generates more new discoveries and hypotheses. Therefore, metabolomics helps detect metabolic changes in the course of CVDs, search for biomarkers, and further study the pathogenesis of CVDs. In this review, we intend to comprehensively summarize the principles, classification and applications in CVDs of metabolomics.

Keywords: cardiovascular diseases; metabolomics; principles; classification; applications

1. Introduction

Cardiovascular diseases (CVDs), which include ischemic heart disease, heart failure, peripheral artery disease, and a number of other heart and vascular diseases, are the leading cause of death worldwide and a major cause of reduced quality of life [1]. In 2019, an estimated 18.6 million people worldwide died from CVDs [2]. Some cardiovascular disease can be explained by the cumulative effects of various cardiovascular disease risk factors, including hypertension, lipids, blood sugar, diabetes, smoking, obesity, and sedentary behavior. However, the complexity of the pathological mechanisms of most cardiovascular diseases is still not fully explained and understood [3]. In addition, the early stages of atherosclerosis development are mostly asymptomatic, especially in young people [4]. Therefore, the early diagnosis of cardiovascular events and the selection of appropriate treatment are very necessary.

When using energy, the human heart hydrolyzes 20 times its own mass of ATP, but it only stores enough energy for a few heartbeats, making heart the most metabolically demanding organ in the body. As a result, the heart must constantly adapt to changing nutrient supplies and physiological needs in order to meet constant energy demands. Therefore, it is not surprising that most cardiovascular diseases involve cardiometabolic disorders [5]. In addition, metabolic disorders that occur in diseases such as diabetes directly affect cardiac metabolism. It is also becoming clear that CVDs itself also affects systemic metabolism. For example, heart failure has long been associated with congestion of the splanchnic circulation, leading to intestinal wall edema and impaired intestinal barrier function. This is thought to heighten the overall

inflammatory state via increasing bacterial translocation and bacterial metabolite in the systemic circulation [6]. So systemic and cardiometabolic disorders can start a vicious cycle that causes and perpetuates cardiovascular disease [7–9].

Metabolomics is a burgeoning field that emerged in the late 1990s. It is a scientific discipline that scrutinizes the diverse array of endogenous metabolites along with their unique patterns of alteration in biological systems. These alterations in metabolites manifest in response to perturbations, such as genetic or environmental changes [10,11]. Metabolites are substrates and products of metabolism that drive basic functions of cell such as energy production and storage, signal transduction, and apoptosis. The biochemical effects of metabolites are profound [12,13]. In addition, metabolite-protein interactions can regulate cellular functions by initiating signal cascades, thus demonstrating the role of metabolites in signal transduction [14,15]. Metabolites indirectly affect the environment in which they are produced, such as changing the pH of the environment [16]. Since metabolites have a wide range of functions in organisms, it is necessary to explore the functions of metabolites through various metabolomics methods, and combine these functional studies with mechanism studies [17]. Therefore, the study of the metabolomics could provide important insights into the pathogenesis of CVDs and offer the potential to identify novel biomarkers of CVDs.

In this review, we intend to provide a systemic summary of the principles and classification of metabolomics, and its application in the research of CVDs.

2. Principles of Metabolomics

Living organisms possess a sophisticated, meticulously regulated system that ensures the production and regulation of substances and energy necessary for vital physiological functions. The intricate metabolic network comprises carbohydrates, lipids, and intermediate metabolites that participate in energy, and substance metabolism, along with substances that regulate metabolic activity. These regulatory substances include neurotransmitters, hormones, and intracellular signal transduction molecules. While chemically, they are peptides, amino acids and derivatives, amines, lipids, and metal ions, and so forth. The interconnectivity between these substances shapes the metabolic network of an organism. Owing to their interrelated interplay, diseases, genetic mutations, environmental stimuli, and dietary factors can influence the metabolic pathways in this network, leading to alterations in metabolites. Such changes in metabolites reflect the state of the organism, thereby contributing to the comprehensive understanding of metabolic physiology [18–20].

The metabolome, often described as the downstream product and end product of the genome, encompasses a collection of small molecule compounds, predominantly endogenous small molecules with relative molecular weights below 1000, that contribute to the metabolism of organisms and sustain their typical function and growth patterns. These molecules exhibit widespread distribution throughout the organism and possess ubiquitous regulatory effects on a broad spectrum of physiological activities, even in trace amounts. In contrast to traditional transcriptomic and proteomic studies, which fail to cover these dynamic and crucial biological substances, metabolomics deals with the molecules that are central to the regulation of life activities [21–23]. Therefore, metabolomics is found to be more proximal to the phenotypes than genomics and transcriptomics and can reflect the state of biological systems with greater accuracy.

The fundamental steps involved in metabolomics research encompass sample collection and preparation, metabolomic data acquisition, data pre-processing, multivariate data analysis, marker identification, and pathway analysis [8]. Biological specimens such as urine, blood, tissues, cells, cultures, and others can serve as sources of samples. Upon collection, these specimens undergo inactivation and pre-treatment by biological reactions. The next step involves detection of the types, contents, and states of metabolites through techniques such as nuclear magnetic resonance (NMR) and mass spectrometry (MS), resulting in metabolic profiles or metabolic fingerprints. Multivariate data analysis is the subsequent step that receives the multidimensional complex data generated by the aforementioned techniques, enabling the mining of crucial information and identification of metabolic markers that demonstrate significant changes. This approach is leveraged in studying the metabolic pathways, characterized by alteration patterns, to understand the response mechanisms exhibited by organisms upon exposure to various stimuli. These steps aid typing and biomarker discovery in metabolomics research [24–26].

In general, similar to other omics disciplines, metabolomics is also a discipline that is highly dependent

on technological platforms. Every major improvement in technological methods, especially in the performance of analytical instruments, can revolutionize the development of metabolomics. It is a branch of systems biology based on group metrics analysis, high throughput detection and data processing, information modeling and systems integration.

3. Untargeted and Targeted Metabolomics

According to the different research objectives and objects, metabolomics is divided into untargeted metabolomics and targeted metabolomics. These subfields of metabolomics differ in their approach and application. Untargeted metabolomics aims to quantify the changes in the metabolic profile of biological systems comprehensively. Targeted metabolomics, on the other hand, focuses on the quantitative analysis of specific metabolites of interest within a sample [27].

Untargeted metabolomics is concerned with identifying all the metabolites in vivo post external perturbations and determining the amount and quantitative variations of metabolites. Although measuring all metabolites at once is presently unachievable, as many metabolites as possible in biological samples are measured. The primary objective of untargeted metabolomics is to provide more precise and dependable quantitative indicators for drug development, efficacy screening, disease diagnosis and prevention, and autonomous pharmacological studies [28]. As for study of therapeutic drugs, untargeted metabolomics aims to highlight the practical decision-making value for the advancement of drug candidates in drug discovery/development including potentially identifying and validating novel therapeutic targets, creating alternative screening paradigms, facilitating the selection of specific and translational metabolite biomarkers, identifying metabolite signatures for the drug efficacy mechanism of action, and understanding potential drug-induced toxicity [29].

In untargeted metabolomics, the target is to measure as many metabolites as possible present in the extracted samples. The types of metabolites that are obtained are affected by the choice of extraction methods and analytical approaches. The collected data sets are quite extensive and complex, which necessitates the use of computational tools. These tools help in the identification and correlation of metabolites between samples, as well as the examination of their association with metabolic pathways, which are linked with normal or abnormal phenotypes. Untargeted metabolomics, therefore, involves both experimental and computational methods to measure and interpret the complex data sets generated [30,31].

Targeted metabolomics is mainly relative to untargeted metabolomics, which generally targets a class of metabolites with specific chemical properties or similar physiological functions and selects specific sample pre-processing methods and instrumentation platforms to monitor changes in such metabolites more precisely, such as lipidomics [32]. Targeted metabolomics is often driven by a specific question or hypothesis that inspires the study of a particular pathway. The approach is highly effective in pharmacokinetic studies and in detecting the effects of genetic modifications on specific enzymes. Overall, targeted metabolomics is more sensitive and selective than untargeted metabolomics and is primarily used to analyze specific metabolites or metabolic pathways of interest [33] (Figure 1, Table 1).

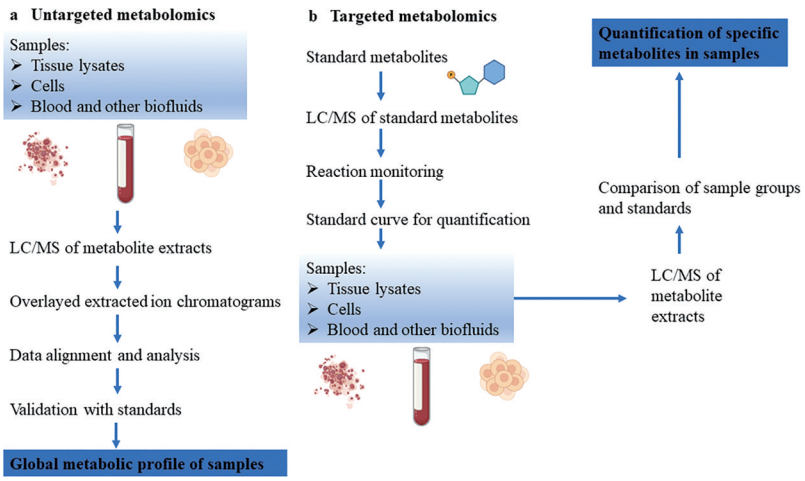

Figure 1. The untargeted (**a**) and targeted (**b**) workflow for LC/MS-based metabolomics.

Table 1. Untargeted vs. Targeted metabolomics.

	Untargeted Metabolomics	Targeted Metabolomics
Description	Systematic and comprehensive analysis of the entire metabolome of a sample; Compare the dynamics of all small molecule metabolites before and after stimulation or perturbation of an organism; Can be combined with bioinformatics analysis to find differential metabolites and perform pathway analysis on differential metabolites; Revealing the correlation between metabolites and pathological changes	For a substance or a class of metabolites, or metabolites of one or more pathways; With standard as reference; Enables quantitative determination of absolute concentrations of target metabolites in biological sample; High specificity, high sensitivity, accurate quantification
Classification	Liquid chromatography coupled with mass spectrometry (LC-MS) untargeted metabolomics, gas chromatography coupled with mass spectrometry (GC-MS) untargeted metabolomics, etc.	Targeted metabolomics for amino acids, short-chain fatty acids, free fatty acids, phytohormones, and other substances
Experimental purpose	Finding differences: finding differential metabolites between different sample groups; relative quantification	Validating differences: specific focus on a particular metabolite or class of metabolites; absolute quantification

Untargeted metabolomics, an intended comprehensive analysis of all the measurable analytes in a sample including chemical unknowns, which is often used for biomarker discovery [28]. There are some limitations of untargeted metabolomics, such as metabolites are complex to extract and isolate; analysis can suffer from signal bias and mass drift resulting from the analysis of complex sample matrices; the data is complex and requires sophisticated statistical and bioinformatics tools for analysis and interpretation [34]. Targeted metabolomics aims to measure defined groups of chemically characterized and biochemically annotated metabolites [33], it has limited coverage of the metabolome, which result in missing information from biologically relevant metabolites that are outside of the predefined subset. In addition, it is difficult to obtain all the required pure chemical standards for the metabolites of interest [35]. Untargeted and targeted metabolomics play different roles in research due to their different characteristics. Cui et al. used untargeted metabolomics to detect the expression of metabolites in the plasma of 20 patients with aortic disease and 20 healthy individuals (discovery cohort), and found that succinate was the most upregulated metabolite; next, a total of 1665 individuals were selected as a validation cohort, succinate was identified as the most upregulated metabolite and its concentration was measured using targeted metabolomics, then its function was further investigated [36].

4. Application of Metabolomics in the Cardiovascular System

According to the World Health Organization (WHO), CVDs, infectious diseases, and cancer remain the top three causes of human mortality. By 2030, the number of deaths attributable to CVDs is estimated to rise to 23.6 million globally. In China, the incidence of CVDs is on the rise, particularly among younger individuals, owing to lifestyle changes and improved living standards. However, the pathological mechanism of CVDs remains elusive, given the complex interplay between genetic and environmental factors. Recent advancements in metabolomics have facilitated a better understanding of the metabolic basis of CVDs. Metabolomics represents a powerful research tool in the cardiovascular field that enables the discovery of novel biomarkers of CVDs. By integrating metabolomics data with stable isotope and metabolic flux approaches, as well as other omics datasets, researchers can elucidate the molecular underpinnings and functional consequences of CVDs-related metabolic disturbances. The timely analysis of changes in endogenous metabolites via metabolomics techniques assumes great significance in the clarification of CVDs pathogenesis, early diagnosis, prevention, and treatment. This review will delve into the application of metabolomics in several common cardiovascular diseases, illuminating the potential for metabolomics to advance our understanding of the etiology of these conditions [8,37].

4.1. Heart Failure

During the process of heart failure, declination of number and function of mitochondrial leads to an

overall decrease in the oxidative metabolism of most fuels and a propagation of energy deficit [38,39]. In 2004, Van Bilsen et al. proposed the concept of metabolic remodeling in failing myocardium, which means that when heart failure occurs, not only the myocardial structure is altered, but also the metabolism of glucose, fatty acids, lactate and other substances in myocardial cells is disturbed and leads to abnormal cardiac function. They point out that cardiac metabolic remodeling may be an important mechanism in the development of chronic heart failure. Disturbances in myocardial metabolism and dysregulation of endogenous metabolites in terms of ratio, concentration and metabolic pathways are reflected in blood, urine and other samples. Therefore, the use of metabolomic approaches to study changes in metabolic profiles over time and to search for biomarkers can help to detect and diagnose heart failure and provide complete information on the overall function during heart failure [40].

In normal conditions, a healthy heart generates its most energy through the mitochondrial oxidation of fatty acids, and the other part was supplied by oxidation of glucose, lactate and ketones. In one study, Kang et al. used ^{1}H-NMR to analyze urine from patients with ischemic heart failure and compared it with the urine metabolic profile of healthy individuals. The results showed that the levels of acetate, acetone, methylmalonic acid, cytosine, and phenaceturic acid were increased in patients with heart failure, while methyl nicotinamide levels were decreased. These differential metabolites suggest disturbances in the Krebs cycle and fatty acid metabolism in heart failure patients [41]. Metabolic profiling of myocardial tissue using an animal model of congestive heart failure revealed elevated levels of glucose, alanine, ADP/ATP, and α-ketoisovaleric acid in metabolite analysis, suggesting alterations in glucose metabolism and α-keto acid metabolism [42]. Fatty acids and glucose are critical substrates for myocardial energy metabolism, with fatty acid oxidation accounting for 60–90% of myocardial energy in normal adult cardiac myocytes, and glucose oxidation providing 10–40% of the myocardial energy. The metabolomic results suggest that in cases of heart failure, the energetic substrate utilization of the myocardium changes to favor glucose oxidation, leading to a shift in the proportion of fatty acid oxidation metabolism. This transformation may be attributed to alterations in the expression levels of enzymes involved in fatty acid oxidation and glucose oxidase lines [39,43].

Through unbiased molecular profiling, there is a specific perspective on changes occur in heart failure, permitting the discovery of previously unappreciated biological pathways that contribute to the pathogenesis. Zheng et al. employed GC-MS and LC-MS to analyze 204 serum metabolites and evaluated their correlation with heart failure. Of these, 16 metabolites were associated with the disease, but only six metabolites were characterized, with four of them involved in amino acid metabolism, and the remaining two were dipeptide compounds and sugar alcohols [44]. Another study utilizing LC-MS to examine plasma metabolic profiles discovered 19 metabolites associated with heart failure, with biological properties including extracellular matrix remodeling, inflammation, insulin resistance, renal dysfunction, and cardioprotection against ischemic injury [45].

Another study compared the metabolic profiles of blood samples from heart failure patients with or without depression and found lower levels of ketone bodies and increased levels of dihydroxy acids in heart failure patients with depression, suggesting reduced levels of fatty acid β-oxidation and increased levels of ω-oxidation in this group of patients. This study provides an objective indicator for the diagnosis of heart failure patients suffering from depression [46].

4.2. Myocardial Ischemia and Infarction

On account of acute myocardial infarction (MI) is associated with alterations in metabolic pathways, metabolomics may provide a way to identify the early stages of ischemia [47]. Hasselbalch et al. investigated the early changes in metabolites of induced ischemia in humans using NMR. The researchers included 34 patients who underwent elective coronary angiography showing normal coronary arteries. The patients were randomly divided into four groups to receive coronary artery occlusion for 0, 30, 60, and 90 s. Blood was collected over the next 3 h and analyzed using NMR, and the results were observed with the most significant changes in lipid metabolism, showing significant differences in 38 out of 112 lipoprotein parameters (34%) between ischemia patients and controls. Total plasma triglycerides decreased within the first hour and subsequently returned to normal [48].

Revascularization has become the standard procedure for treating patients with acute MI and has

significantly improved patient survival over the last century. However, due to ischemia-reperfusion (IR) injury, this revascularization process causes additional cardiomyocyte death and permanent myocardial structural damage, IR injury is a major cause of adverse revascularization after myocardial infarction [49,50]. To identify the fundamental regulators of reperfusion injury, Zhang et al. performed an unbiased metabolomic analysis in individual plasma before and after revascularization, significant accumulation of arachidonate 12-lipoxygenase (ALOX12) -dependent 12-HETE was found after revascularization. Genetic inhibition of Alox12 protects the mouse heart from reperfusion injury and remodeling, while overexpression of Alox12 aggravates myocardial IR injury. In summary, the study suggests that ALOX12 represents a conservative therapeutic target for the treatment of myocardial reperfusion injury [51].

IR injury can cause several types of cardiomyocyte death, including necrosis, apoptosis, autophagy, and ferroptosis. Prevention of cell death is important to protect cardiac function after IR injury. However, the time point of the occurrence of various cell death patterns after cardiomyocyte reperfusion injury and the mechanism of ferroptosis regulation are still unknown [52, 53]. Cai et al. used the left anterior descending coronary artery ligation mouse model to investigate the occurrence time points of various cell death patterns after reperfusion injury. They used ultra-high performance LC-MS based metabolomics to discover the key molecules of cardiomyocyte ferroptosis. Results showed that apoptosis and necrosis occurred in the early stage of IR injury, and ferroptosis was the main cell death during long-term reperfusion. Metabolomic profiling of eicosanoids shows that ALOX15 metabolites accumulate in cardiomyocytes, and was specifically increased in the injured area of the left ventricle below the suture and co-localized with cardiomyocytes. ML351, a specific inhibitor of Alox15, could inhibit cardiomyocyte apoptosis, protect damaged myocardium, and promote the recovery of cardiac function. Taken together, their findings suggest that ALox15-mediated cardiomyocyte ferroptosis plays an important role in prolongation of IR damage [54].

4.3. Atherosclerosis (AS)

AS is an atherosclerotic disease characterized by thickening, hardening and loss of elasticity of the arterial wall due to the formation of intimal atheromatous plaques by lipid deposits in the arterial vessels. Patients with AS are often accompanied by abnormalities in lipid metabolism and glucose metabolism, and metabolic disorders can further promote the progression of atherosclerosis. Therefore, the prevention and treatment strategies of AS urgently needs to be complemented by new technologies to detect the metabolite levels of the disease [55,56].

Vellejo et al. used GC-MS to detect plasma metabolic profiles in 10 healthy individuals, 9 patients with non-ST-segment elevation acute coronary syndrome (NSTE-ACS), and 10 patients with stable atherosclerosis. Plasma levels of citric acid, 4-hydroxyproline, aspartic acid and fructose were significantly lower in patients with NSTE-ACS, while levels of lactate, urea, glucose and valine were significantly higher, which provided the necessary metabolic markers for early diagnosis of AS and helped prevent further disease progression [57]. Another example is the metabolite trimethylamine oxide (TMAO). A clinical study found that food-derived phosphatidylcholine such as choline, TMAO, and betaine are risk factors for CVDs, and that elevated levels of these substances, especially TMAO, are correlated with CVDs occurrence and adverse cardiovascular events such as myocardial infarction, stroke, and death, and can independently predict CVDs risk. Subsequently, researchers found a decreased alanine/pyruvate ratio in an apolipoprotein E (APOE) knockout mouse model, while TMAO in bile salt metabolism differed between male and female individuals. Supplementation of choline, TMAO, or betaine in the diet caused elevated levels of scavenger receptors in macrophage associated with AS and promoted the development of AS. Plasma TMAO levels are associated with dietary choline intake, the activity of intestinal flora and flavin monooxygenase activity. Imbalance of intestinal flora can promote atherogenesis by promoting cholesterol accumulation, oxidative stress, and release of pro-inflammatory cytokines, but probiotics in the gut can lower plasma cholesterol levels, inhibit the expression of pro-inflammatory cytokines, and have a cardiovascular protective effect. Studies of intestinal flora and gene expression have revealed a relationship between the development of CVDs and food-derived phosphatidylcholine, which is dependent on the metabolism of intestinal flora [58]. Another pre-clinical study using a compound that inhibits trimethylamine production in the gut reduced circulating TMAO levels in atherosclerosis-prone mice fed a high-choline diet while inhibiting atherosclerotic lesion

development, suggesting potential therapeutic options for humans in the future [59]. The above studies have demonstrated that metabolomics techniques can effectively unravel alterations in plasma metabolites associated with AS and its progression. These differential metabolites hold potential as valuable biomarkers for studying the underlying coronary artery-related disease processes [8,60].

In addition to its important role in biomarker discovery and disease diagnosis, metabolomics also plays an important role in the study of disease pathogenesis. Previous studies have shown that a genome-wide methylation status is abnormal in patients with AS and that imbalance of arachidonic acid metabolism in the vasculature may affect the regulation of vascular homeostasis [61]. Bao et al. used a metabolomics approach and found that treatment with the DNA methyltransferase inhibitor 5-aza-2′-deoxycytidine (5-AZA) increase the levels of cyclooxygenase (COX) pathway metabolites in endothelial cells, especially prostaglandin D_2 (PGD_2) and thromboxane B_2 (TXB_2); DNA methylation of prostaglandin D_2 synthase (PTGDS) and TBX-AS1 was regulated by 5-AZA, which led to elevated expression. On the other hand, COX inhibitors blocked 5-AZA-induced elevated levels of PGD_2 and TXB_2, which inhibited endothelial cell activation and monocyte adhesion on endothelial cells. This study used metabolomics to elucidate the role of DNA demethylation in the regulation of eicosanoid metabolism and further screened the major metabolites and their upstream pathways during hypomethylation-induced endothelial cell activation. The study also suggests that aberrant DNA methylation status may be involved in atherogenesis by regulating eicosanoid metabolism [62].

4.4. Other Cardiovascular Diseases

Aortic aneurysm and dissection (AAD) are high-risk cardiovascular disease associated with high mortality from acute aortic complications for which there is currently no effective treatment [63,64]. Cui et al. applied untargeted metabolomics and MS to determine plasma succinate concentrations in 40 and 1665 individuals of discovery and validation cohort, respectively, and used mouse AAD models to determine the role of succinate in the development of AAD. Succinate was the most upregulated metabolite in the cohort. Plasma succinate concentrations were higher in patients with AAD than in healthy controls, patients with acute myocardial infarction (AMI), and patients with pulmonary embolism (PE). In addition, succinate increased angiotensin II-induced AAD and vascular inflammation in mice. The study found that plasma succinate concentrations can be used to distinguish patients with AAD from healthy controls and patients with AMI or PE as a biomarker for AAD [36].

Complex diseases, such as coronary artery disease (CAD), are often caused by multiple underlying pathological mechanisms [65]. Barkan et al. reveals personalized risk factors for CAD through metabolomic and microbiome profiling. The researchers conducted a comprehensive clinical and multi-omics analysis of 199 patients with ACS, serum metabolomics and gut microbiome data were included. Compared to the control group, ACS patients had distinct serum metabolome and gut microbiome signatures and were depleted in previously unknown bacterial species of the Clostridiaceae family. This bacterial species was associated with levels of multiple circulating metabolites, some of which have previously been linked to an increased risk of coronary heart disease. The study found that metabolic biases in patients with ACS were correlated with clinical parameters and cardiovascular outcomes. The results highlight the utility of the serum metabolome in understanding the heterogeneity of risk factors for coronary heart disease [66].

Psoriasis is an autoimmune inflammatory disease, of which the most common coexisting condition is psoriatic arthritis. Psoriasis is more than just a local skin or joint disease, it is associated with CVDs, which may increase cardiovascular events and mortality [67–69].Colaco et al. used NMR metabolomics to search for serum metabolites associated with cardiovascular events in psoriatic disease (PsD) patients, and investigate whether they can improve cardiovascular risk prediction beyond traditional risk factors. The results showed that 70 of the 977 patients with PsD had cardiovascular events. Alanine, tyrosine, fatty acid unsaturated degree, and high-density lipoprotein particles were associated with reduced cardiovascular risk. Glycoprotein acetyl, apolipoprotein B, and cholesterol residues are associated with increased cardiovascular risk. Together, the researchers identified novel metabolites associated with the development of cardiovascular events in patients with PsD, and further study of its potential causal role may shed light on important pathways that contribute to cardiovascular events in this population [70].

5. Summary and Future Directions

Metabolomics is an interdisciplinary field that has rapidly gained momentum in diverse medical domains, including disease diagnosis, pharmaceutical development, nutritional food science, and toxicology, since its origin in the post-genomic era. In contrast to genomics, transcriptomics, and proteomics, metabolomics offers unique features. First, small changes in gene and protein expression are amplified in metabolites, facilitating detection. Second, the technology of metabolomics requires a relatively complete database of metabolite information, which is, however, far less complex than whole-genome sequencing and a large database of expressed sequence tags. Third, the number of metabolite species is much smaller than the number of genes and proteins, and their molecular structure is much simpler. Metabolomics focuses on the study of changes in metabolites produced by an organism (cell, tissue or organism) under different conditions. It extends and complements genomics, transcriptomics, and proteomics by reflecting the pathophysiological state of an organism more accurately and directly. As Billy David remarked, "While genomics and proteomics tell you what is likely to happen, metabolomics tells you what has happened".

Initially, the main application of metabolomics was to identify metabolites and metabolic pathways associated with specific phenotypes, thus playing a crucial role in biomarker discovery. However, as the field of metabolomics has advanced, its use has expanded to include identifying metabolites that may alter the phenotype of an organism or cell. Furthermore, researchers are now seeking to extend beyond merely identifying metabolites as biomarkers and are beginning to explore their direct physiological role and the function they play in the larger metabolic networks, as well as to establish the relationship between changes in their levels and different phenotypes. Such advancements in metabolomics have opened up new avenues for understanding metabolic regulation and ultimately improving human health.

Looking back, it is noteworthy that traditional metabolite analysis is almost a century old, but the concept of metabolomics has only emerged in the past two decades. The rapid pace of development and broad application prospects are highly encouraging. The successful cases in biomarker discovery and the study of mechanisms behind phenotypes aptly illustrate the burgeoning power of metabolomics. In biomedicine, the advancement of medical metabolomics has been proceeding in tandem with the development of medicine in recent years, from systemic biomedicine to translational medicine to the emerging field of "precision medicine". Correspondingly, various companies and institutions have emerged to offer metabolomics analysis services to meet the burgeoning demand. However, despite these promising developments, the full integration of metabolomics into clinical medicine, achieving accurate disease classification and diagnosis, as well as the development of personalized disease prevention and treatment plans, still remains a significant challenge. There is still a long way to go before the potential of metabolomics is fully realized for improving healthcare outcomes.

First of all, it is essential to recognize that metabolomics is ultimately a metabolic analysis, and despite the technological advancements, the accuracy and reproducibility of the method remain the key factors governing its clinical utility. To achieve high standards of excellence, it is vital to cultivate close cooperation among all the relevant staff members, including those responsible for the collection of samples, subsequent data processing, and result reporting. By operating through a unified, standard protocol for processing and analyzing samples and data, one can establish quality control guidelines that ensure traceability of sample origins, standardized output data, and reproducible research results. Such practices will enable metabolic analysis technology to play a significant role in realizing the vision of precision medicine.

Secondly, the collection of information and the establishment of a vast database are also critical for the success of precision medicine. Assembling large numbers of volunteers, collecting their personal data from multiple sources, and constructing a huge database of health information is the key to the success of precision medicine. The establishment of such databases at all levels forms the data foundation for metabolomics and other precision medicine research applications. The construction of databases is not merely a matter of collecting data, but it also requires scientific screening, as well as effective integration and analysis of vast amounts of data. This is the daunting challenge facing major omics and precision medicine programs. Also, the integration and analysis of multi-omics data remains a challenging endeavor. The high cost of data collection is one of the primary challenges, with access to high-throughput MS for proteomics and metabolomics primarily restricted to large hospitals, research institutions, and professional companies. Furthermore, the availability of professional instruments and equipment is not widespread, thereby making it

costly for individuals to procure detailed omics information. Similarly, collecting ample omics information from the community to build a database could also prove to be prohibitively expensive. In addition to these challenges, integrating multi-omics data also requires the resolution of several technical difficulties. These include accounting for sample differences resulting from various factors, establishing a unified informational platform to display diverse multi-omics data formats, correlating multi-omics data, analyzing differences, managing diverse analysis results obtained from various analysis methods, among several others. Despite these challenges, we also hope that by integrating metabolomics with other omics and establishing a good database, in the near future, by integrating and inputting individual health data into this huge database, individual specificity can be accurately analyzed through bioinformatics methods, so that accurate disease classification and diagnosis can be achieved, and personalized disease prevention and treatment plans can be formulated, including accurate prediction of risk, accurate diagnosis and classification of precise diagnosis and classification of diseases, precise application of drugs, precise assessment of therapeutic efficacy, and precise prediction of prognosis, etc.

Lastly, I concur that integrated analysis of multi-omics data markedly enhances our understanding of complex diseases and directs the generation of new discoveries and hypotheses. However, this only serves as the first step of scientific research. Subsequently, researchers need to validate these hypotheses and unveil a complete mechanism. Furthermore, they also need to employ these findings to construct new potential therapeutic interventions. Achieving this transformation from analytical data to practical applications necessitates researchers to conduct extensive molecular biology studies.

In essence, carrying out integrated multi-omics research provides a plausible starting point for scientific inquiry, but understanding how the various molecular pathways interact often necessitates further investigations. Follow-up research involving molecular biology or targeted experiments validates findings and leads to the identification of potential therapeutic targets that pave the way for the development of new disease prevention and treatment strategies. In conclusion, researchers need to delve beyond mere multi-omics data analysis, employing diverse approaches to gain useful insights into complex diseases, and ultimately develop effective therapies.

Given the complexity of CVDs, the utilization of genomics and proteomics technologies to screen for variant genes and expressed proteins associated with the disease can provide valuable insight into the underlying mechanistic pathways. CVDs results in physiological changes in the body that ultimately correspond to alterations in its metabolite profile. Metabolomics offers a means to detect and quantitatively analyze such changes, as well as identify regulatory mechanisms and key control points of metabolic pathways, thus enabling a comprehensive understanding of disease mechanisms. Moreover, combining this analysis with traditional risk factors evaluation can significantly improve the accuracy of CVDs prediction and treatment strategies. These advances not only provide new insight into CVDs pathogenesis but have important implications for patient care and early intervention.

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References

1. Mensah, G. A.; Roth, G. A.; Fuster, V. The Global Burden of Cardiovascular Diseases and Risk Factors: 2020 and Beyond. *J. Am. Coll. Cardiol.* **2019**, *74*, 2529–2532.
2. Roth, G.A.; Mensah, G.A.; Johnson, C.O.; et al. Global Burden of Cardiovascular Diseases and Risk Factors, 1990-2019: Update From the GBD 2019 Study. *J. Am. Coll. Cardiol.* **2020**, *76*, 2982–3021.
3. Ventura, H.O.; Elagizi, A.; Lavie, C.J. Optimal Prevention of Cardiovascular Diseases: The Earlier the Better. *J. Am. Coll. Cardiol.* **2023**, *81*, 1162–1164.

4. Rafieian-Kopaei, M.; Setorki, M.; Doudi, M.; et al. Atherosclerosis: Process, indicators, risk factors and new hopes. *Int. J. Prev. Med.* **2014**, *5*, 927–946.
5. Doenst, T.; Nguyen, T.D.; Abel, E.D. Cardiac metabolism in heart failure: Implications beyond ATP production. *Circ. Res.* **2013**, *113*, 709–724.
6. Tang, W.H.W.; Li, D.Y.; Hazen, S.L. Dietary metabolism, the gut microbiome, and heart failure. *Nat. Rev. Cardiol.* **2019**, *16*, 137–154.
7. Riehle, C.; Abel, E.D. Insulin Signaling and Heart Failure. *Circ Res* **2016**, *118*, 1151–1169.
8. McGarrah, R.W.; Crown, S.B.; Zhang, G.F.; et al. Cardiovascular Metabolomics. *Circ. Res.* **2018**, *122*, 1238–1258.
9. Ussher, J.R.; Elmariah, S.; Gerszten, R.E.; et al. The Emerging Role of Metabolomics in the Diagnosis and Prognosis of Cardiovascular Disease. *J. Am. Coll. Cardiol.* **2016**, *68*, 2850–2870.
10. Nicholson, J.K.; Connelly, J.; Lindon, J.C.; et al. Metabonomics: A platform for studying drug toxicity and gene function. *Nat. Rev. Drug Discov.* **2002**, *1*, 153–161.
11. Jang, C.; Chen, L.; Rabinowitz, J.D. Metabolomics and Isotope Tracing. *Cell* **2018**, *173*, 822–837.
12. Sperber, H.; Mathieu, J.; Wang, Y.; et al. The metabolome regulates the epigenetic landscape during naive-to-primed human embryonic stem cell transition. *Nat. Cell Biol.* **2015**, *17*, 1523–1535.
13. Yanes, O.; Clark, J.; Wong, D.M.; et al. Metabolic oxidation regulates embryonic stem cell differentiation. *Nat. Chem. Biol.* **2010**, *6*, 411–417.
14. Li, X.; Gianoulis, T.A.; Yip, K.Y.; et al. Extensive in vivo metabolite-protein interactions revealed by large-scale systematic analyses. *Cell* **2010**, *143*, 639–650.
15. Hubbard, T.D.; Murray, I.A.; Bisson, W.H.; et al. Adaptation of the human aryl hydrocarbon receptor to sense microbiota-derived indoles. *Sci. Rep.* **2015**, *5*, 12689.
16. Sharma, M.; Astekar, M.; Soi, S.; et al. pH Gradient Reversal: An Emerging Hallmark of Cancers. *Recent Pat. Anti-Cancer Drug Discov.* **2015**, *10*, 244–258.
17. Johnson, C.H.; Ivanisevic, J.; Siuzdak, G. Metabolomics: Beyond biomarkers and towards mechanisms. *Nat. Rev. Mol. Cell Biol.* **2016**, *17*, 451–459.
18. Wang, J.; Wang, C.; Liu, H.; et al. Metabolomics assisted metabolic network modeling and network wide analysis of metabolites in microbiology. *Crit. Rev. Biotechnol.* **2018**, *38*, 1106–1120.
19. Ye, C.; Wei, X.; Shi, T.; et al. Genome-scale metabolic network models: From first-generation to next-generation. *Appl. Microbiol. Biotechnol.* **2022**, *106*, 4907–4920.
20. Mi, K.; Jiang, Y.; Chen, J.; et al. Construction and Analysis of Human Diseases and Metabolites Network. *Front. Bioeng. Biotechnol.* **2020**, *8*, 398.
21. Rinschen, M.M.; Ivanisevic, J.; Giera, M.; et al. Identification of bioactive metabolites using activity metabolomics. *Nat. Rev. Mol. Cell Biol.* **2019**, *20*, 353–367.
22. Bauermeister, A.; Mannochio-Russo, H.; Costa-Lotufo, L.V.; et al. Mass spectrometry-based metabolomics in microbiome investigations. *Nat. Rev. Microbiol.* **2022**, *20*, 143–160.
23. Mandal, R.; Chamot, D.; Wishart, D.S. The role of the Human Metabolome Database in inborn errors of metabolism. *J. Inherit. Metab. Dis.* **2018**, *41*, 329–336.
24. Muthubharathi, B.C.; Gowripriya, T.; Balamurugan, K. Metabolomics: Small molecules that matter more. *Mol. Omics* **2021**, *17*, 210–229.
25. Bujak, R.; Struck-Lewicka, W.; Markuszewski, M.J.; et al. Metabolomics for laboratory diagnostics. *J. Pharm. Biomed. Anal.* **2015**, *113*, 108–120.
26. Guijas, C.; Montenegro-Burke, J.R.; Warth, B.; et al. Metabolomics activity screening for identifying metabolites that modulate phenotype. *Nat. Biotechnol.* **2018**, *36*, 316–320.
27. Patti, G.J.; Yanes, O.; Siuzdak, G. Innovation: Metabolomics: The apogee of the omics trilogy. *Nat. Rev. Mol. Cell Biol.* **2012**, *13*, 263–269.
28. Schrimpe-Rutledge, A.C.; Codreanu, S.G.; Sherrod, S.D.; et al. Untargeted Metabolomics Strategies-Challenges and Emerging Directions. *J. Am. Soc. Mass Spectrom.* **2016**, *27*, 1897–1905.
29. Caldwell, G.W.; Leo, G.C. Can Untargeted Metabolomics Be Utilized in Drug Discovery/Development? *Curr. Top. Med. Chem.* **2017**, *17*, 2716–2739.
30. Crook, A.A.; Powers, R. Quantitative NMR-Based Biomedical Metabolomics: Current Status and Applications. *Molecules* **2020**, *25*, 5128.
31. Cui, L.; Lu, H.; Lee, Y.H. Challenges and emergent solutions for LC-MS/MS based untargeted metabolomics in diseases. *Mass Spectrom. Rev.* **2018**, *37*, 772–792.
32. Griffiths, W.J.; Koal, T.; Wang, Y.; et al. Targeted metabolomics for biomarker discovery. *Angew. Chem.* **2010**, *49*, 5426–5445.
33. Roberts, L.D.; Souza, A.L.; Gerszten, R.E.; et al. Targeted metabolomics. *Curr. Protoc. Mol. Biol.* **2012**, *98*, 30.2.1–30.2.24.
34. Amer, B.; Baidoo, E.E.K. Omics-Driven Biotechnology for Industrial Applications. *Front. Bioeng. Biotechnol.* **2021**, *9*, 613307.
35. Chen, L.; Zhong, F.; Zhu, J. Bridging Targeted and Untargeted Mass Spectrometry-Based Metabolomics via Hybrid Approaches. *Metabolites* **2020**, *10*, 348.
36. Cui, H.; Chen, Y.; Li, K.; et al. Untargeted metabolomics identifies succinate as a biomarker and therapeutic target in aortic aneurysm and dissection. *Eur. Heart J.* **2021**, *42*, 4373–4385.
37. Kordalewska, M.; Markuszewski, M.J. Metabolomics in cardiovascular diseases. *J. Pharm. Biomed. Anal.* **2015**, *113*, 121–136.
38. Zhou, B.; Tian, R. Mitochondrial dysfunction in pathophysiology of heart failure. *J. Clin. Investig.* **2018**, *128*, 3716–3726.

39. McMurray, J.J.; Pfeffer, M.A. Heart failure. *Lancet* **2005**, *365*, 1877–1889.
40. van Bilsen, M.; Smeets, P.J.; Gilde, A.J.; et al. Metabolic remodelling of the failing heart: The cardiac burn-out syndrome? *Cardiovasc. Res*. **2004**, *61*, 218–226.
41. Kang, S.M.; Park, J.C.; Shin, M.J.; et al. ^{1}H nuclear magnetic resonance based metabolic urinary profiling of patients with ischemic heart failure. *Clin. Biochem.* **2011**, *44*, 293–299.
42. De Souza, A.I.; Cardin, S.; Wait, R.; et al. Proteomic and metabolomic analysis of atrial profibrillatory remodelling in congestive heart failure. *J. Mol. Cell Cardiol.* **2010**, *49*, 851–863.
43. Baman, J.R.; Ahmad, F.S. Heart Failure. *Jama* **2020**, *324*, 1015.
44. Zheng, Y.; Yu, B.; Alexander, D.; et al. Associations between metabolomic compounds and incident heart failure among African Americans: The ARIC Study. *Am. J. Epidemiol.* **2013**, *178*, 534–542.
45. Chan, C.X.; Khan, A.A.; Choi, J.H.; et al. Technology platform development for targeted plasma metabolites in human heart failure. *Clin. Proteom.* **2013**, *10*, 7.
46. Steffens, D.C.; Wei, J.; Krishnan, K.R.; et al. Metabolomic differences in heart failure patients with and without major depression. *J. Geriatr. Psychiatry Neurol.* **2010**, *23*, 138–146.
47. Bodi, V.; Marrachelli, V.G.; Husser, O.; et al. Metabolomics in the diagnosis of acute myocardial ischemia. *J. Cardiovasc. Transl. Res.* **2013**, *6*, 808–815.
48. Hasselbalch, R.B.; Kristensen, J.H.; Strandkjær, N.; et al. Metabolomics of early myocardial ischemia. *Metabolomics Off. J. Metabolomic Soc.* **2023**, *19*, 33.
49. Bax, J.J.; Di Carli, M.; Narula, J.; et al. Multimodality imaging in ischaemic heart failure. *Lancet* **2019**, *393*, 1056–1070.
50. Reed, G.W.; Rossi, J.E.; Cannon, C.P. Acute myocardial infarction. *Lancet* **2017**, *389*, 197–210.
51. Zhang, X.J.; Liu, X.; Hu, M.; et al. Pharmacological inhibition of arachidonate 12-lipoxygenase ameliorates myocardial ischemia-reperfusion injury in multiple species. *Cell Metab.* **2021**, *33*, 2059–2075.e2010.
52. Del Re, D.P.; Amgalan, D.; Linkermann, A.; et al. Fundamental Mechanisms of Regulated Cell Death and Implications for Heart Disease. *Physiol Rev* **2019**, *99*, 1765–1817.
53. Angeli, J.P.F.; Shah, R.; Pratt, D.A.; et al. Ferroptosis Inhibition: Mechanisms and Opportunities. *Trends Pharmacol. Sci.* **2017**, *38*, 489–498.
54. Cai, W.; Liu, L.; Shi, X.; et al. Alox15/15-HpETE Aggravates Myocardial Ischemia-Reperfusion Injury by Promoting Cardiomyocyte Ferroptosis. *Circulation* **2023**, *147*, 1444–1460.
55. Kobiyama, K.; Ley, K. Atherosclerosis. *Circ. Res*. **2018**, *123*, 1118–1120.
56. Libby, P. The changing landscape of atherosclerosis. *Nature* **2021**, *592*, 524–533.
57. Vallejo, M.; García, A.; Tuñón, J.; et al. Plasma fingerprinting with GC-MS in acute coronary syndrome. *Anal. Bioanal. Chem.* **2009**, *394*, 1517–1524.
58. Wang, Z.; Klipfell, E.; Bennett, B.J.; et al. Gut flora metabolism of phosphatidylcholine promotes cardiovascular disease. *Nature* **2011**, *472*, 57–63.
59. Wang, Z.; Roberts, A.B.; Buffa, J.A.; et al. Non-lethal Inhibition of Gut Microbial Trimethylamine Production for the Treatment of Atherosclerosis. *Cell* **2015**, *163*, 1585–1595.
60. Cheng, K.K.; Benson, G.M.; Grimsditch, D.C.; et al. Metabolomic study of the LDL receptor null mouse fed a high-fat diet reveals profound perturbations in choline metabolism that are shared with ApoE null mice. *Physiol. Genom.* **2010**, *41*, 224–231.
61. Xue, S.S.; He, J.L.; Zhang, X.; et al. Metabolomic analysis revealed the role of DNA methylation in the balance of arachidonic acid metabolism and endothelial activation. *Biochim. et Biophys. Acta* **2015**, *1851*, 1317–1326.
62. Bao, Q.K.; Zhang, X.; Zhu, Y. [Research progress of eicosanoid metabolomics in cardiovascular diseases]. *Sheng Li Xue Bao Acta Physiol. Sin.* **2021**, *73*, 606–616.
63. Wang, S.W.; Huang, Y.B.; Huang, J.W.; et al. Epidemiology, Clinical Features, and Prescribing Patterns of Aortic Aneurysm in Asian Population from 2005 to 2011. *Medicine* **2015**, *94*, e1716.
64. Erbel, R.; Aboyans, V.; Boileau, C.; et al. 2014 ESC Guidelines on the diagnosis and treatment of aortic diseases: Document covering acute and chronic aortic diseases of the thoracic and abdominal aorta of the adult. The Task Force for the Diagnosis and Treatment of Aortic Diseases of the European Society of Cardiology (ESC). *Eur. Heart J.* **2014**, *35*, 2873–2926.
65. Poulter, N. Coronary heart disease is a multifactorial disease. *Am. J. Hypertens.* **1999**, *12*, 92s–95s.
66. Talmor-Barkan, Y.; Bar, N.; Shaul, A.A.; et al. Metabolomic and microbiome profiling reveals personalized risk factors for coronary artery disease. *Nat. Med.* **2022**, *28*, 295–302.
67. Gelfand, J.M.; Neimann, A.L.; Shin, D.B.; et al. Risk of myocardial infarction in patients with psoriasis. *JAMA* **2006**, *296*, 1735–1741.
68. Armstrong, E.J.; Harskamp, C.T.; Armstrong, A.W. Psoriasis and major adverse cardiovascular events: A systematic review and meta-analysis of observational studies. *J. Am. Heart Assoc.* **2013**, *2*, e000062.
69. Manolis, A.A.; Manolis, T.A.; Melita, H.; et al. Psoriasis and cardiovascular disease: The elusive link. *Int. Rev. Immunol.* **2019**, *38*, 33–54.
70. Colaco, K.; Lee, K.A.; Akhtari, S.; et al. Targeted metabolomic profiling and prediction of cardiovascular events: A prospective study of patients with psoriatic arthritis and psoriasis. *Ann. Rheum. Dis.* **2021**, *80*, 1429–1435.