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Lipidomic insight into cardiovascular diseases

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ABSTRACT

Cardiovascular disease is a primary cause of mortality worldwide. Therefore, it is of major interest to identify sensitive molecular markers that predict cardiovascular events and point to therapeutic strategies that will increase lifespans. Dysregulated lipid metabolism is recognized as an established risk factor in cardiovascular diseases. However, it is still largely unknown which specific lipid molecular species reflect cardiovascular risk. In addition, understanding the whole lipidome signature in vascular pathophysiology is challenging. Recent advancements of mass-spectrometry allow researchers to detect each individual lipid species from unbiased small samples. In this review, we update the current research on lipidomic approaches in cardiovascular diseases.

1. Introduction

Cardiovascular diseases (CVD) account for approximately 30% of all deaths in the world [1]. Establishing an effective biomarker of CVD is essential to CVD therapy and effective screening for potential risk of CVD. The study of lipid and cardiometabolic diseases began in the 1950s with the classic diet-heart hypothesis based on ecological studies linking saturated fat and cardiovascular disease (CVD) mortality [2]. In addition to saturated fat, higher levels of total cholesterol and low-density lipoprotein cholesterol (LDL-C) have been established as risk factors for atherosclerotic pathology. However, a number of coronary artery disease (CAD) or acute myocardial infarction patients have LDL-C levels within the recommended range [3]. Our laboratory determined that fully saturated phosphatidic acids (PAs) such as 1,2-distearoyl-PA (18:0/18:0-PA) and deoxycholic acid mediate vascular calcification in mouse models and patients with chronic kidney disease [4,5]. These studies are examples of how a specific lipid molecular species can explain individual pathophysiological metabolic pathways in CVD. Therefore, exploring correlations between novel unique lipid species and disease signatures is an attractive strategy. However, profiling the many structurally similar yet biologically distinct lipid species is challenging. Because of the technical difficulty, effects of lipids in the progression of CVD were investigated in large lipid classes such as triglycerides (TGs), free fatty acids (FFAs) and cholesterol, rather than individual lipid species.

Following whole genome sequencing, omics research such as transcriptomic, proteomics and metabolomics, was performed. Metabolomics are closest to phenotyping because metabolites are the end products of omics (transcriptomicsproteomics). Therefore, it is a promising strategy to identify and characterize unique metabolites in diseases. Lipidomics, closely linked to metabolomics, uses mass spectrometry-based profiling to evaluate the comprehensive lipid profile in a sample [6,7]. The term lipidomics was added to PubMed in 2003 [8], and lipidomic research has rapidly grown over the last decade (Fig. 1) [9]. Because dysregulation of lipid metabolism is commonly observed in CVD and is one of the fundamental mechanisms that cause development of these diseases, lipidomic profiling is a powerful tool to explore novel biomarkers and mechanisms in cardiovascular diseases. Lipidomics approaches are rapidly growing in CVD research as well as research of other metabolic diseases (Fig. 1). In this review, we summarize the current updates on lipidomic research in cardiovascular diseases and related areas.

2. Cardiovascular event: mortality

Cardiovascular events such as myocardial infarction directly result in death. Thus, lipidomic technologies were primarily

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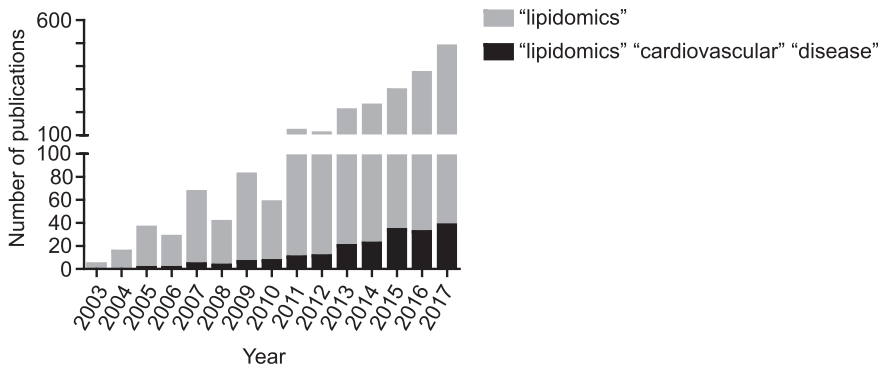

Fig. 1. Rapid expansion of lipidomics in CVD research. The histogram represents the number of publications using lipidomics. The numbers were obtained by using "lipidomics" or "lipidomics cardiovascular disease" as a search term in PubMed.

utilized to identify unique lipid species that potentially predict cardiovascular events. In 2011, Meikle reported differences in the plasma lipidome between unstable and stable CAD, and between stable CAD and healthy control individuals using high-performance liquid chromatography–mass spectrometry analysis (HPLC-MS) with multiple reaction monitoring (MRM) [10]. In this study, plasma lipid profiles containing 305 lipids were measured. One of the most prominent differences in the plasma lipid profiles between unstable and stable CAD was lower levels of 10 species of alkylphosphatidylethanolamines (PE(O)) in unstable CAD compared with stable CAD. A similar relationship was observed with the phosphatidylethanolamine plasmalogen (PE(P)) species. Importantly, there is no difference of PE(O) and PE(P) between stable CAD and the healthy control, indicating that these lipid species might be related to plaque stability. These findings identify the potential use of plasma lipid profiling in diagnostics and prognostics to identify individuals at risk for unstable CAD. Stegemann and colleagues reported on individual and combined lipid species in incident CVD [11]. They performed shotgun lipidomics, which is a direct lipid extraction analysis using electrospray ionization tandem mass spectrometry (ESI-MS/MS) without chromatographic separation. The prospective Bruneck study includes incident CVD end-point measures in 685 individuals [12]. The resultant lipidomic analyses detected 135 distinct lipids within the following lipid types and phospholipid (PL) classes: cholesterol ester (CE), triacylglycerol (TG), phosphatidylcholine (PC), lysophosphatidylcholine (LPC), phosphatidylethanolamine (PE), lysophosphatidylethanolamine (LPE), phosphatidylserine (PS), and sphingomyelin (SM). 50 plasma lipid species were significantly associated with CVD risk, and 28 of those associations maintained significance when controlling for multiple comparisons. Interestingly, the majority of the neutral lipid species linked to CVD risk contained primarily saturated fatty acyl and monounsaturated fatty acyl chains. Collectively, 3 key lipids (TG-54:2, CE-16:1, and PC-36:5) were identified as most consistently linked to incident CVD. These results, along with results from Meikle and Stegemann, identify pro-inflammatory and oxidative pathways as being associated with incident CVD. Other investigations also identified oxidized cholesterol and PLs in circulation and plaques [13–16]. Sigruener et al. performed lipidomics with plasma samples using ESI-MS/MS [17]. Highly polyunsaturated PC species together with LPC species and long chain saturated sphingomyelin and ceramide species were associated with having a protective effect. The predominantly circulating PC-based ether species, PE-based ether species and PE species were positively associated with total and cardiovascular mortality. Saturated and monounsaturated PC species, especially PC-32:0 (most probably dipalmitoyl-PC), palmitate containing SM, and ceramide (CM) species together with 24:1 containing SM and CM species showed the strongest positive association with mortality. A quotient of the sums of the six most protective species and the six species with the strongest positive mortality association indicated an almost 3-fold increased risk of mortality. This provides evidence that plasma lipid species levels and ratios of certain species may be valuable prognostic markers for cardiovascular and total mortality.

Ganna et al. also identified that PLs in blood are correlated with incident CVD using UPLC-TOF-MS [18]. Incident CVD cases were defined as hospitalization or death with a primary diagnosis for acute myocardial infarction or unstable angina. Their results indicated that four metabolites were associated with incident CVD: LPC-18:1, LPC-18:2, and SM-28:1. Wurtz et al. utilized nuclear magnetic resonance (NMR)-based high-throughput metabolomics with 3 population-based cohorts to screen for metabolites correlated with CVD events [19]. They analyzed 68 metabolites from a total of 13441 subjects and identified 4 metabolites that were associated with incident CVD: higher phenylalanine, higher monounsaturated fatty acids, lower omega-6 fatty acids and lower docosahexaenoic acids. In addition to shotgun lipidomics, Havulinna and colleagues performed targeted lipidomics to analyze serum ceramides using UHPLC followed by MS [20]. Four circulating CMs (CM-d18:1/16:0, CM-d18:1/18:0, CM-d18:1/24:0, and CM-d18:1/24:1) were quantified in 8101 serum samples. CM-d18:1/18:0 had the strongest association with incident CVD. In addition to total incident CVD, authors identified CM-d18:1/18:0 as the strongest biomarker for cardiovascular mortality from serum ceramides.

Recently, Sun et al. compared 19 plasma-free fatty acids using targeted GC-MS/MS [21]. Circulating long-chain n-3 fatty acids and stearic acid were associated with a lower myocardial infarction risk, and arachidonic acid was associated with a higher risk in this Chinese population.

Low high-density lipoprotein cholesterol (HDL-C) and loss of atheroprotective functions of HDL are associated with coronary artery disease (CAD). To investigate the associations of HDL PLs with acute and stable CAD, Sutter and colleagues performed LC-MS/MS analysis of HDL-associated PLs [22]. HDL samples were isolated from patients with stable CAD or acute CAD and healthy patients. They detected 29 PC species, 4 LPC species and 16 SM species, and identified a negative association of three PCs (PC-33:3, PC34:2 and PC-35:2) with CAD. These PCs were positively associated with anti-apoptotic activity of HDL. Reconstituted-HDL (rHDL) containing apoA-I, PC-34:1 and PC-35:2 inhibited apoptosis of endothelial cells (EC) more effectively than rHDL containing only apoA-I and PC34:1. The inverse association of HDL-plasmalogen levels with both stable

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