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Review

Metabolomics in cardiovascular diseases

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ABSTRACT

Cardiovascular diseases (CVDs) are the main cause of death globally. There is a need for the development of specific diagnostic methods, more effective therapeutic procedures as well as drugs, which can decrease the risk of deaths in the course of CVDs. For this reason, better understanding and explanation of molecular pathomechanisms of CVDs are essential. Metabolomics is focused on analysis of metabolites, small molecules which reflect the state of an organism in a certain point of time. Application of metabolomics approach in the investigation of molecular processes responsible for CVDs development may provide valuable information. In this article we overviewed recent reports employing application of untargeted and targeted metabolomic analyses in particular CVDs. Moreover, we focused on applications of various analytical platforms and metabolomics approaches which may contribute to the explanation of the pathomechanisms of different cardiovascular diseases.

Contents

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1. Introduction

1.1. Cardiovascular diseases

According to WHO reports, cardiovascular diseases (CVDs) are the main cause of death worldwide. In 2008, it was estimated that 17.3 million people died of CVDs which refers to 30% of all deaths globally [1]. In addition to future predictions, in 2030 the number of CVDs deaths might reach 23.3 million [2]. It has been estimated that the cost of all CVDs for European Union reaches 196 billion euro per year. From this quote, 54% is spent on direct health care. Productivity loss and informal care of CVD patients cover 24% and 22% of those expenses, respectively [3]. CVDs are disorders of heart and blood vessels, caused by atherosclerosis, most commonly diagnosed in elderly patients (both men and women). This group of diseases includes: coronary heart disease, hypertension, stroke, hypercholesterolemia, diabetes, chronic kidney disease, peripheral arterial disease and vascular dementia. Despite different symptoms of each disorder, the association between them relates to risk factors (such as: smoking, unhealthy diet, lack of physical activity leading to obesity, elevated blood pressure and high levels of blood glucose). In addition to the common risk factors for CVDs, probability for a patient diagnosed of one CVD to develop another one, is very high [4,5]. Complexity of pathomechanisms of most CVDs is still not fully explained and/or understood. Furthermore, early stages of atherosclerosis development are mostly asymptomatic, especially in young age. For better prevention, risk stratification for cardiovascular events, earlier diagnosis, selection of suitable treatment and new drugs development have contributed a lot to the explanation of molecular processes responsible for atherosclerosis development [6]. The growing number of articles reporting application of metabolomics approaches in the investigation of cardiovascular diseases is presented in Fig. 1.

1.2. Metabolomics

Systems biology employs holistic approaches which aim at controlling and explaining the biological complexity. This discipline includes so-called *omics* sciences: genomics, transcriptomics, proteomics and metabolomics. Systems biology provides an insight into molecular processes in a single cell, tissue, organ and whole organism as well. Metabolomics is focused on metabolites which are the final representations of organisms' phenotype. These

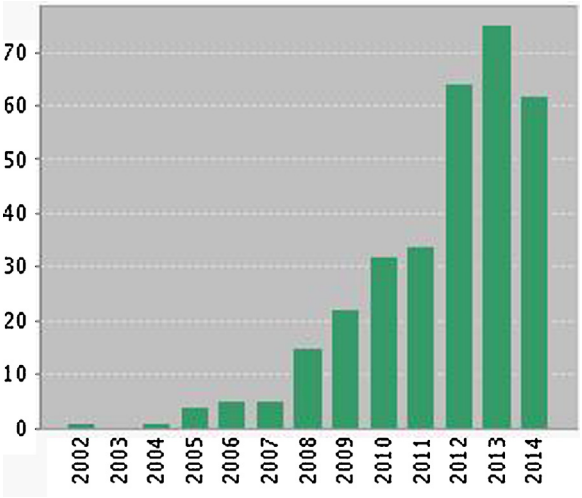

Fig. 1. Diagram presenting the quantity of research papers describing the application of metabolomics approach in the investigation of cardiovascular diseases published each year in XXIst century. Report accessible in the Web of Science.

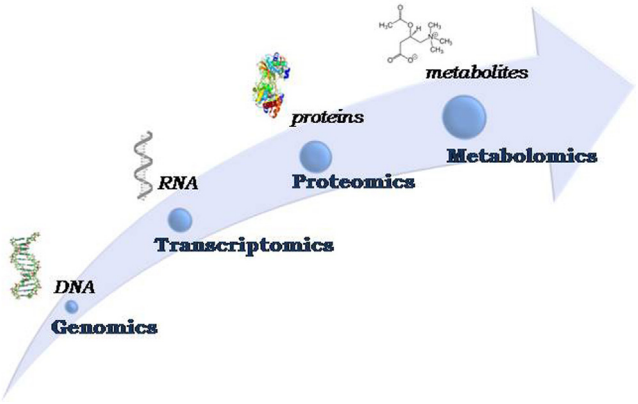

Fig. 2. The scheme of the information flow in the systems biology field.

are low-molecular-weight molecules (molecular mass <1500 Da) which levels reflect changes in the genome, transcriptome and proteome. While genome, transcriptome and proteome provide the prediction of what might had happened or may happen, metabolome offers the most "up-to-date" insight into the state of system. Nowadays, according to its great potential for biomarkers evaluation, metabolomics is one of the most frequently applied approaches in the field of systems biology [7,8] (Fig. 2).

The word *metabolism* originates from Greek language and denotes "change". Ancient cultures used urine color, taste and smell for diabetes diagnosis, as their change are related to different metabolites' levels [9]. In 1970s, the primary attention focused on the determination of only one metabolite was replaced by an approach aimed at determining the total profile of metabolites which proved to be specific for a certain state of an organism. This concept was first proposed by Horning et al. and by Robinson and Pauling [10]. During the development of analytical techniques, the possibilities of measuring metabolome and the interest in metabolomics analyses were given more and more attention. According to Fiehn, metabolomics is a comprehensive and quantitative analysis of all metabolites in a system [11]. Additionally, Nicholson described another term, known as *metabonomics*, as the profiling of whole metabolites' composition in a living system with simultaneous determination of their changes resulting from multiple environmental conditions and genetic background as well [12]. These two definitions may be used interchangeably. Metabolomics may also be a useful tool for biomarkers discovery. Biomarker is defined as a particular value or parameter that correlates with a pathological state and can be used as an early clinical diagnostic test. Determination of metabolites' changes may offer selection of plausible biomarkers [13].

The determination of metabolites in biological materials is defined as metabolic phenotyping (metabotyping) as metabolites are representation of organism's phenotype (or metabotype). The main purpose is to define the relationship between changes in metabolic phenotype and certain biochemical state of the organism [14,15]. In the field of metabolomics, several different research strategies may be applied, e.g. metabolic profiling, metabolic fingerprinting and metabolic footprinting. The metabolic profiling is an example of targeted approach. The aim of this strategy is to determine metabolites of the same physicochemical properties (i.e. amino acids, carbohydrates) or classified to a certain biological pathway (i.e. glycolysis, purine metabolism). Data obtained with this strategy provide qualitative and quantitative information about certain section of metabolome composition. The metabolic fingerprinting approach is an example of untargeted analysis and is applied without previous knowledge which metabolites should be investigated. Thus, the whole metabolome might be determined.