Journal of Neuroimmunology 279 (2015) 25–32

Contents lists available at ScienceDirect

Journal of Neuroimmunology

journal homepage: www.elsevier.com/locate/jneuroim

Review article

Application of metabolomics in autoimmune diseases: Insight into biomarkers and pathology

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ARTICLE INFO

Article history:
Received 5 August 2014
Received in revised form 9 October 2014
Accepted 5 January 2015

Keywords:
Autoimmune diseases
Metabolomics
Biomarkers
Mass spectrometry
Nuclear magnetic resonance

ABSTRACT

Metabolomics has recently become a new technology using mass spectrometry (MS) and high-resolution proton nuclear magnetic resonance (NMR) to access metabolite profiles in biofluids or tissue extracts for the detection of biomarker molecules and biochemical effects induced by a disease or its therapeutic intervention. This review outlines recent advances in the use of metabolomic techniques to study autoimmune diseases (ADs), including multiple sclerosis (MS), rheumatoid arthritis (RA), inflammatory bowel diseases (IBD), autoimmune diabetes et al. Many studies have demonstrated that AD patients including subtypes of some diseases, and healthy individuals can be distinguished using metabolic profiling accompanied with well-established data analysis tools including principal component analysis (PCA) and partial least squares (PLS). These metabolites not only affect glucose, amino acid and lipid metabolism, but also involve alteration of neurotransmitters, nucleotides, immune responses and anti-inflammatory responses. Knowledge of unique metabolomic fingerprint in ADs could be useful for diagnosis, treatment, and detection mechanisms of diseases.

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1. Introduction

There are more than 80 types of autoimmune diseases (ADs), many of them such as type 1 diabetes, multiple sclerosis, rheumatoid arthritis are common (Schmidt, 2011). ADs are a kind of diseases that are poorly diagnosed for its obscure symptoms, or similar symptoms with other diseases. ADs are also a sort of chronic diseases, thus successful treatment is challenging. Many studies have confirmed that genes, epigenetic

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http://dx.doi.org/10.1016/j.jneuroim.2015.01.001
0165-5728/

regulation and environmental factors are relevant in development ADs. For example, the gene codes for an enzyme called sialic acid acetylesterase (SIAE) that regulates the immune system's B cells, which are responsible for producing antibodies against foreign invaders (Pillai, 2013). In 24 of 923 people with conditions such as Crohn's disease, type 1 diabetes, rheumatoid arthritis, systemic lupus erythematosus and multiple sclerosis, the gene was present in a variant form (Surolia et al., 2010). Although many such variants have been identified, they explain little in terms of disease susceptibility. In order to gain more comprehensive understanding on AD biology in terms of disease mechanisms and treatment strategies, there is a growing need for new approaches to improve disease study and drug development related to these disorders. To reach this purpose, the approach must be reliable and validated. Metabolite profiling will be a new perspective for us to understand diseases.

2. Overview of metabolomics

Metabolomics aims at measuring endogenous small molecules or metabolites produced by an organism in biochemical processes, which provide much information on the status caused by changes in gene expression and diseases, also by differences in lifestyle and diet in humans. Thus, metabolomics is used widely to diagnose diseases by newly-discovered biomarkers, elucidate novel pathways of diseases, identify markers of efficacy in preclinical pharmaceutical discovery, and apply in pharmaceutical R&D, as well as uncover mechanisms of Chinese Traditional Medicine. Fig. 1 shows the steps in a typical metabolomics. In this process, the last step that is the biomarkers' verification should be also included in metabolomics study. Because to qualify for a biomarker identified by the metabolomics method, a biomarker must be not only measured by a reliable and sensitive method, but verified by more stringent and wider methods.

The most biological specimens employed in metabolomics are serum/plasma (Kim et al., 2013), urine (Dieme et al., 2014), saliva (Santone et al., 2014), cerebrospinal fluid (Lista et al., 2014), bile (Nagana Gowda et al., 2009), seminal fluid (Kumar et al., 2014), amniotic fluid (Menon et al., 2014), synovial fluid (Giera et al., 2012), exhaled breath condensate (Leung et al., 2013), tissue extract (Wu et al., 2008), blister and cyst fluids (Hosch et al., 2008), fecal extracts (Walker et al., 2014), dialysis fluids (Qi et al., 2011), as well as tissue biopsy samples and their lipid and aqueous extract, such as from vascular tissue in studies of atherosclerosis (Martinez-Pinna et al., 2010). In the fields of autoimmune diseases, the common specimens are serum/plasma, urines, fecal extracts, and different tissue extracts or biological fluids according to different autoimmune diseases affecting different organ systems. For example, cerebrospinal fluid is often used for metabolomic analysis of multiple sclerosis; synovial fluid is used for rheumatoid arthritis. However, serum/plasma, urine, and fecal extracts are the most commonly used specimens because of their low invasiveness and thousands of metabolites being contained.

The main analytical techniques in metabolomics are nuclear magnetic resonance (NMR) spectroscopy and mass spectrometry (MS) (Naz et al., 2014). NMR spectroscopy is a non-destructive technique, widely used in chemistry, that provides detailed information on molecular structure, both for pure compounds and in complex mixture as well as information on absolute or relative concentrations. The NMR spectroscopic methods can also be used to probe metabolite molecular dynamics and mobility. MS requires combining with different separation techniques such as liquid chromatography (LC), gas chromatography (GC), capillary electrophoresis (CE), ultra-high-pressure LC (UPLC) for a pre-separation (Zhang et al., 2012). MS has also been widely used in metabolic fingerprinting and metabolite identification and quantitation of drug metabolites. The differences between MS and NMR methods involve three aspects. Firstly, the MS method is more sensitive, it is thousands of times higher than NMR-based methods. NMR methods can only detect abundant metabolites. Secondly, preparation of biofluid samples for NMR studies typically only requires dilution of the sample with simple buffers. The predominant problem needed to be concerned on NMR-based sample preparation is pH, especially when sample is urine (Rist et al., 2013). Thirdly, the required sample amount in NMR is typically about 300 μl, while MS-based analysis is only 10–30 μl.

3. Application of metabolomics in ADs

3.1. Application of metabolomics in multiple sclerosis

Multiple sclerosis is a chronic immune-mediated demyelinating disorder of the CNS around the axons of the brain and spinal cord, which is one of the most frequent causes of disability in young adults (Wallin et al., 2000; Bradford et al., 2014). MS is difficult to diagnose because symptoms of multiple sclerosis may mimic those of many other nervous system problems and the long-term outcome of multiple sclerosis is difficult to predict. MS diagnosis is performed by clinical evaluation, abnormalities revealed by magnetic resonance imaging (MRI), and analysis of CSF chemistry. Conventional MRI is used to identify demyelinating inflammatory plaques within the white matter with a fairly noninvasive way. However, T2 lesions also occur in other neurological disorders and have been documented in asymptomatic aging brains (Bakshi et al., 2008), and some patients with clinically definite MS display no MRI abnormalities. Therefore, the early and accurate diagnosis of the disease, monitoring of progression, and gauging of therapeutic intervention are important for patients. Moreover, a deeper understanding of the disease pathology is needed, including discovery of accurate biomarkers for multiple sclerosis.

The animal study of multiple sclerosis metabolomics was conducted in experimental autoimmune encephalomyelitis (EAE) that is the most commonly used animal model for multiple sclerosis. CSF samples were collected during the progression of the disease including the onset and peak of the disease and measured using the targeted LC–MS and GC–

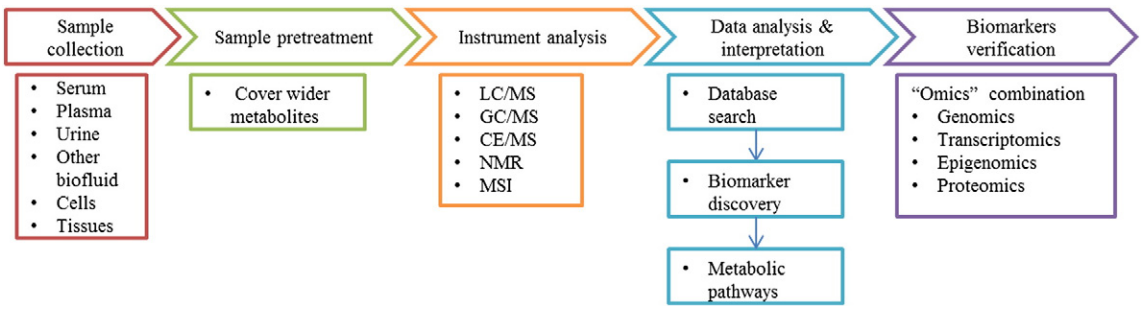

Fig. 1. A typical metabolomics study in autoimmune diseases. MS, mass spectrometry; NMR, nuclear magnetic resonance spectroscopy; IMS, imaging mass spectrometry; LC, liquid chromatography; GC, gas chromatography; CE, capillary electrophoresis.