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Clinical Application of Metabolomics in Pancreatic Diseases: A Mini-Review

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Abstract

Metabolomics is an important part of system biology and an emerging discipline developed after genomics and proteomics. Metabolomics is a powerful new analytical method to describe the metabolomics of cells, tissue or biological body fluids. Metabolomics can provide the detailed information of the organism metabolic changes of these metabolites form represents the metabolic process occurs in the cell, such as anabolic catabolism metabolic distributed and heterogeneous natural absorption metabolism detoxification metabolism of biomass energy utilization metabolism, so some disease specificity of change can be found through metabonomics test, for the early identification of disease and the difference between benign and malignant state provide a new source of biomarkers. Metabolomics has a wide application potential in pancreatic diseases, including early detection, diagnosis and identification of pancreatic diseases, as well as prediction of drug effects and pharmacodynamics markers, but there are few studies on metabolomics in pancreatic diseases. This article reviews the application of metabolomics in the diagnosis, prognosis, treatment and evaluation of pancreatic diseases.

Keywords: Metabolomics; Pancreatic Cancer (PC); Acute Pancreatitis (AP); Chronic Pancreatitis (CP)

Introduction

Metabolomics is the comprehensive quantitative evaluation of endogenous metabolites in biological systems. Metabolomics is the detection and analysis of cell tissues or biological fluids by nuclear magnetic resonance spectroscopy or mass spectrometry, and the tracking of their changes in biological fluids or tissues [1]. The final product of the cell regulatory process is metabolites, and its level can be regarded as the final response of the biological system to genetic or environmental changes, which is the same as the transcriptome and proteome. A series of metabolites synthesized by the biological system constitute its metabolome [2]. Metabolomics is a collection of downstream products such as gene transcription translation and post-translational protein modification. Therefore, metabolomics can be recognized as a more accurate method to express the true cell phenotype. Metabolomics represents a powerful analytical tool for identifying cell differences between discrete populations [3]. By identifying as many metabolites as possible from the samples and analysing the metabolic state under different physical conditions [4,5], The state of biological systems can be distinguished by the identification of metabolites with corresponding specificity and sensitivity [6]. Mass Spectrometry (MS) combined with Liquid Chromatography (LC), namely the LC-MS, metabonomics is emerging proteomics technology and quantitative data, it provides the basis of the structure and can be used in the form of global or target, can be in parts per billion level detection of bioactive metabolites can be expected, as the data handler continues to increase, the development of LC-MS will soon achieve results, to seek a deeper understanding of human disease, resulting in a new method for the diagnosis and treatment [7]. Metabonomics is the use of Nuclear Magnetic Resonance (NMR), Mass Spectrometry (MS), Chromatography (HPLC, GC) and chromatography mass spectrometry technology to detect a series of NMR spectra of samples, and then using the method of pattern recognition, judgment was born object pathological physiology, therefore could find out the related biomarkers (biomarker), thereby to provide a platform to predict related early warning signal. This difference can often be used to distinguish the early diagnosis of related diseases and the distinction between benign and malignant.

Pancreatic diseases include Pancreatic Cancer (PC), Acute Pancreatitis (AP), Chronic Pancreatitis (CP), etc., but the diagnosis and treatment of pancreatic diseases lack specific diagnostic methods and treatment methods. Acute Pancreatitis (AP) is a common acute abdominal disease with an increasing incidence in recent years, about 80% of MAP patients show self-restraint, and 20% of patients show more dangerous clinical course with a total mortality rate of about 5%~10 [8]. Acute pancreatitis often begins quickly and is critical [9], current diagnosis of AP is usually based on clinical examination, patient history, and serum amylase assays. However, this lacks specificity and sensitivity, and the diagnostic threshold changes over time after the initial pancreatic injury [10]. Imaging modality such as USS and CT can also be used to determine the diagnosis of AP [11], however, Ultrasound (USS) is the nonspecific, Computed Tomography (CT) is only used to evaluate the severity of the 72 h or exclude other diagnosis due to organ failure and cell necrosis, clinical phenotype is very complex, these pathological damage will affect the metabolism of patients, which may lead to a difficult early diagnosis and treatment [12,13]. Acute pancreatitis is a very common acute abdominal disease, but the conventional therapeutic method for acute pancreatitis include supportive medical treatments, such as fluids and nutritional supplements, and pancreatic protease inhibitors [14], Therefore, it is

necessary to find more sensitive methods for the diagnosis of pancreatitis and new drugs for the treatment of pancreatitis.

Persistent inflammation of the pancreas is a characteristic of chronic pancreatitis, resulting in progressive loss of endocrine and exocrine function due to atrophy and fibrous tissue replacement, including recurrent or persistent abdominal pain, diabetes, and dyspepsia [15]. Although many risk factors have been studied, such as the use of alcohol and tobacco for gallstones, the exact cause of CP is still unknown to a large extent [16], but it is clear that chronic pancreatitis is caused by many factors. The current diagnosis of chronic pancreatitis depends on clinical symptoms of pancreatic exocrine function testing and imaging techniques [17], however, most imaging methods, such as Endoscopic Retroperitoneal Cholangiopancreatography (ERCP) and Magnetic Retroperitoneal Cholangiopancreatography (MRCP), can only partially reflect the changes in the ductal structure of chronic pancreatitis, and most of them are late changes. Pancreatic function tests also found similar limitations in the insensitivity of early detection of chronic pancreatitis [18]. Therefore, we need to realize the early diagnosis of chronic pancreatitis, so as to prevent the disease damage of the glands, which requires us to develop new diagnostic methods, especially the early diagnosis of chronic pancreatitis.

Pancreatic Cancer (PC) is a highly malignant tumour. Due to the lack of effective early diagnosis, the prognosis of pancreatic cancer patients is poor and the mortality rate is particularly high [19]. Pancreatic cancer patients generally do not have obvious clinical symptoms in the early stage, and the late stage symptoms are usually non-specific and diverse. Once diagnosed, most patients are found to be in advanced metastasis, which brings great difficulty to the early treatment of pancreatic cancer [20]. However, the current imaging examination lacks sensitivity in the early diagnosis of pancreatic cancer. In addition, although the sensitivity of the traditional tumour marker CA 19-9 to PC can reach 80%, the specificity of CA 19-9 is greatly reduced due to the similar increase in the sensitivity to numerous non-neoplastic diseases such as acute and Chronic Pancreatitis (CP) hepatitis and biliary tract obstruction [21]. In addition, chronic pancreatitis is an important factor leading to pancreatic cancer [22], so it is also important to distinguish chronic pancreatitis from early pancreatic cancer.

Currently, the existing diagnostic and therapeutic methods for pancreatic diseases are quite limited, and we need to constantly explore new and more efficient and sensitive diagnostic methods. Metabolomics may be a breakthrough in shadow storage, but relevant experiments and researches are already underway.

Review

To date, only a few metabolomics studies have reported involvement with pancreatitis and related diseases. A high-resolution proton magic angle spinning NMR spectroscopy is used to analyze the metabolites of acute necrotizing pancreatitis and chronic pancreatitis in Wistar rats [23]. In this experiment, it was found that inflammation of the pancreas can lead to changes in the corresponding metabolites (Leucine-Isoleucine-Valine lipids and Taurine), and it suggested that examining the level of metabolites before pancreatic tissue damage would contribute to a better understanding of the pathological and physiological conditions, thus contributing to the early diagnosis of pancreatitis. Gas Chromatography-Mass Spectrometry (GC-MS) is used to analysis patients with AP metabolite changes applied multivariate pattern recognition technology to establish the classification of the AP Patients (APP) and Healthy Participants (HP) model to select 3-hydroxy butyric acid, Glycerol phosphate, Citric acid, D-galactose, D-mannose, D-glucose, Palmitic acid, Serotonin and other important metabolites as AP potential biomarkers for clinical diagnosis, and the analysis of severe and mild symptoms in APP metabolite changes. Their results suggest that GC-MS-based serum metabolomics can be used for clinical diagnosis of AP by analyzing potential biomarkers [24]. Also has a research on Ultra High Performance Liquid Chromatography (HPLC)-High Resolution Mass Spectrometry (UPLC-HRMS) as the analysis platform, using metabonomics method Mild Acute Pancreatitis (MAP) Cholelith Disease (CHO) patients and healthy volunteers serum metabolic profile purpose is closely associated with pancreatitis identification of metabolites and potential biomarkers for the diagnosis of acute pancreatitis treatment course provides the basis for monitoring and prognosis judgement [25]. This study found that with the progress of treatment, four metabolites, i.e. Sphengani, L-thyroxine, acetylcholic acid and 2-tetradecanone, showed a gradual downward trend and gradually approached the normal level. Therefore, they can be used as metabolic biomarkers for AP clinical process detection.

Tang et al. used chemical derivatization and Gas Chromatography/Mass Spectrometry (GC/MS) to detect serum metabolites, and used orthogonal projection latent structure discriminant analysis (opls-da) for gas chromatography/mass spectrometry data. GC/MS data showed that there were differences between healthy mice and HLP mice. Therefore, they have reason to believe that this technique is a new and effective tool to study the pathogenesis of HLP [26]. Villasenor et al. investigated urinary and plasma metabolic phenotypes in patients with acute pancreatitis using ^{1}H NMR spectroscopy and multivariate modeling. According to this study, cholelithiasis and colitis in the non-pancreatitis group can also be distinguished by relevant metabolic phenotypes, and these combined biomarkers play an important role in the diagnosis and prognosis of pancreatitis [27]. Sun et al. using a swine CP model with partial ligation of the Main Pancreatic Duct (MPD), they investigated the potential of metabolic markers obtained from pancreatic tissue samples with HRMAS ^{1}H MRS for CP diagnosed at different stages. Through their analysis, the potential of ^{1}H HRMAS MRS in diagnosis of CP can be clearly seen. The results of this study demonstrate the great potential of metabolic characteristics in differentiating normal pancreatic tissue from different stages of chronic pancreatitis, which may help in the early diagnosis of chronic pancreatitis and thus guide clinicians to timely intervene and prevent irreversible pancreatic injury [18]. There is research shows that metabonomics technology can separate from pancreatitis patients urine samples and urine samples from healthy control group which is a new non-invasive technology, can have a thorough understanding of patients with chronic and acute pancreatitis metabolic state [28], although they are not sure these metabolites are biomarkers of acute pancreatitis, but the methods described here, presents a certain strategy, on the basis of further analysis can test more queue. In addition, a study using GC/MS-based metabolomics led to the discovery of candidate therapeutic agents for pancreatitis [29]. These studies provide new ideas for the diagnosis and treatment of pancreatitis, and further prove the feasibility of metabolomics in the diagnosis of pancreatitis.

There are also studies on metabonomics of pancreatic cancer. Nuclear magnetic resonance spectrum for non-invasive and repeatability of metabolic signal recognition provides a useful tool. Smith used bile samples of ^{1}H NMR spectra of d-Portugal, the content

of Hyaluronic Acid (GlcUA) found that pancreatic cancer patients with bile samples d-Portuguese hyaluronic acid content is higher, and the control group and patients with chronic pancreatitis d-Portuguese hyaluronic acid content in bile or less can be ignored [30]. Although the collection of bile specimens is an invasive method, which brings a lot of inconvenience to diagnosis, this method also provides a new idea and method. There some studies have used ^{1}H NMR spectroscopy combined with multivariate statistical analysis to study the metabolic changes induced by PC [31]. The results showed that some metabolites could be used in the early diagnosis and differential diagnosis of pancreatic cancer. However, further confirmatory studies are needed to confirm these findings before going from the laboratory to the clinic. Kobayashi et al developed a serum metabolomics based diagnostic model for pancreatic cancer using multiple logistic regression analysis [32]. Although no single biomarker can characterize PC, the specific metabolite combination obtained in the experiment can be used as a marker for the diagnosis of pancreatic cancer. Their model is more accurate than traditional tumour markers, especially in the detection of resected patients. This novel diagnostic method is expected to improve the prognosis of pancreatic cancer patients by detecting early cancer when it is still in an early curable state.

Conclusion

The emergence of metabolomics is the necessity of life science research. Metabonomics, developed in the mid-1990s, is a new discipline for qualitative and quantitative analysis of metabolites of small molecules whose relative molecular weight is less than 1,000 in a certain organism or cell. Metabonomics, as an important part of systems biology, has a wide application prospect in clinical medicine. Metabonomics is the metabolome at some point the set of all metabolites in the cell of a discipline of gene and protein expression is closely linked, and metabolites is more reflected the cell's environment, which in turn and cell nutrition state, drugs and the role of environmental pollutants, and other closely related to the impact of external factors so you can think, genomics and proteomics tell you what will happen, and metabonomics, tell you what really happened.

Researchers through the in-depth study of the body's metabolic product, it can be judged whether the body is in normal state, and the study of genes and proteins are unable to come to the conclusion that, in fact, metabonomics studies can already diagnosed with some metabolic diseases, such as diabetes, obesity, metabolic syndrome and related diseases in pancreas also has studied, based on the related research results we can think the metabonomics method to explore new prevention pancreas related diseases differential treatment has broad prospects but before its really applied to clinical, need more to explore and experiment validation.

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