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Innovative Functions of Metabolomics in Individualized Health Care: A Review Study in the Field of Metabolomics VitminD Treatment Change MTH1 and MYH Genes Expression in HUVEK Cell

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Abstract:

Variability in medication reactions and illness susceptibility among individuals is often seen in clinical settings. Personalized medicine is now highly esteemed for its focus on prescribing the appropriate medication to each patient. *Metabolomics* is a developing field that thoroughly assesses all metabolite and low-molecular-weight compounds in a biological sample. Metabolic profiling offers a quick overview of a cell›s physiology, making the technique a direct indicator of an organism›s physiological condition. Quantifiable correlations exist between the metabolome and other cellular components such as the genome, transcriptome, proteome, and lipidome. These correlations can be utilized to forecast metabolite levels in biological samples based on mRNA levels. One of the key problems in systems biology is to incorporate metabolomics with other -omics data to enhance comprehension of cellular biology. Metabolomics is used to assess the effectiveness of clinical substances by analyzing the metabolic characteristics of patients before treatment to predict their responses (pharmacometabolomic) and to identify individuals at risk of developing diseases (patient stratification). The rapid progress in metabolomics technique highlights its significant potential for use in customized treatment. We reviewed the unique benefits of metabolomics, including instances in assessing medication treatment and individual stratification, and emphasized metabolomics› promise in personalized medicine.

INTRODUCTION

Interindividual differences in treatment success or illness susceptibility are often seen in clinical settings due to the complex interplay between hereditary and environmental variables (1). The notion of customized medicine, also known as precision medicine, is now of tremendous interest due to revolutionary advancements in biomedical research and high-throughput analytical technologies (2). Personalized medicine aims to optimize treatment by tailoring medication to individual patients for optimal effectiveness and the fewest side effects or to forecast disease vulnerability in groups (3).

Efforts have been made to link medication reactions with host genetic variations, known as pharmacogenomics (4). Despite notable advancements in pharmacogenomics over the past decades, it does not account for the influence of environmental factors and the co-metabolism of host and intestinal microbiota, which are crucial in drug metabolism and disease development (5).

Metabolomics/metabonomics emerged at the end

of the 20th century to study changes in endogenous metabolites due to biological system modifications like cells, tissues, and body fluids, following genomics, transcriptomics, and proteomics (6). Metabolomics combines genetic and environmental influences to analyze biomarkers and investigate illness mechanisms, medication effects, toxicity, and metabolism (5, 6).

Furthermore, pharmacometabonomics, also known as pharmaco-metabolomics, is described as predicting the effects of a medicine or foreign substance on a person using a mathematical model of their metabolite patterns before the intervention (7). Pharmacometabonomics is used to discover metabolic biomarkers that may predict various reactions to medicinal medications by detecting distinct metabolites at the start and linking their changes to treatment results (8). Metabolomics has been used to assess individual vulnerability to illnesses in communities by combining baseline metabotypes with the likelihood of disease incidence, leading to patient stratification (9).

The following mini-review provides a concise overview of commonly used analytical equipment in metabolomics, including nuclear magnetic resonance (NMR), gas chromatography-mass spectrometry (GC-MS), and liquid chromatography-mass spectrometry (LC-MS). We mainly discussed the unique uses of metabolomics in predicting medication responses and patient classification, highlighting the potential of metabolomics in personalized healthcare soon.

METABOLOMICS TECHNOLOGIES

Metabolomics is a newer field than more established disciplines like genomes, transcriptomics, and proteomics. The rapid progress of metabolomics is attributed to significant advancements in analytical instruments and associated data mining methods during the last decade (10). Three primary metabolomic systems are NMR, GC-MS, and LC-MS. Due to their varied analytical capabilities, these three platforms have been utilized in targeted/untargeted metabolomic research either alone or in conjunction to identify metabolites such as amino acids, organic compounds, lipids, and sugars (11). It is well acknowledged that every technology has strengths and weaknesses in metabolomic research. NMR is often more effective for identifying and quantifying metabolites and for automation, but it has poorer sensitivity and more significant initial costs when compared with MS-based metabolomic methods. GC-MS is a sturdy analytical technique with high sensitivity and allows for easy identification of metabolites utilizing commercial databases and software. However, sample preparation may be time-consuming, and identifying new compounds can be challenging. LC-MS offers greater sensitivity, a broader metabolite detection range, and varied methods, but NMR or GC-MS is more robust and more challenging for chemical identification. Some evaluations have thoroughly compared the merits and downsides of different platforms (10, 11).

Metabolomics for Drug Sensitivity Prediction

A)Simvastatin

These medications are traditional antagonists of HMG-CoA reductase frequently employed to lower LDL-cholesterol levels in the blood and decrease the likelihood of cardiovascular disease (12). Additional biological functions of statins have been documented, including anti-inflammatory actions and immune system regulation. These activities may result in therapeutic advantages or adverse consequences involving type 2 diabetes mellitus and myopathy. Furthermore, individuals clearly differ in how effective simvastatin is as a therapy (13).

Researchers analyzed the lipid profiles before and after treatment using focused on the lipidomics method in favorable and poor participants (24 subjects in each group) based on the percentage alteration in LDL-c decrease or secondary result of C-reactive protein (CRP) in the Cholesterol and Pharmacogenetics (CAP) research (14). Approximately 40 metabolites exhibited substantial changes in excellent participants but not poor rescuers. In excellent responders, 13 saturated or monounsaturated fatty acids were up, while those of 15 polyunsaturated fatty acids (PUFAs) went down. Upon further examination, it was shown that the initial levels of n-6 and n-3 were favorably associated with the decrease in LDL-c, although CE and DG SFA showed a negative correlation. The variables DG-n6 and FA-n3 showed a favorable correlation with the treatment result. Baseline concentrations of PE plasmalogens showed a positive correlation, whereas PC plasmalogens showed a negative correlation with CRP changes post-therapy. The findings suggest that the initial lipid profiles are biomarkers for predicting various responses to simvastatin therapy (15).

They found lower starting point plasma concentrations of both primary and secondary bile acids were closely linked to decreased LDL-c during simvastatin treatment in randomly chosen subjects. This included greater initial LCA, TLCA, GLCA, and coprostanol (COPR) in individuals who responded well to the treatment. The study suggests that the gut microbiota influences the effectiveness of simvastatin via the production of secondary bile acids. Recent research found that the effectiveness of simvastatin as a treatment was reduced by altering the gut microbiota using antibiotics, which suppressed the production of bile acids from cholesterol (15, 16).

B)Aspirin

Aspirin is a commonly used medicine for its strong pain-relieving, fever-reducing, anti-inflammatory, and

blood-thinning properties (17). Approximately 25% of high-risk individuals exhibit resistance to aspirin to platelet activation and atherothrombotic incidents (18). Researchers studied the metabolic processes related to aspirin resistance by analyzing the metabolic patterns before taking aspirin and comparing them to individual responses after aspirin treatment in the Heredity and Phenotype Intervention (HAPI) heart investigation. Seventy-six healthy adults were chosen for their response to collagen-induced ex vivo platelet aggregation. They were divided into 40 good responders and 36 poor responders (19). All participants completed a two-week aspirin therapy. GC/MS-based untargeted metabolomics was used to analyze blood samples taken before and after the dosage. Initially, 18 distinct metabolites were detected in post-dose specimens from all 76 participants, and it was shown that the purine metabolic pathway was notably influenced by aspirin. A comparison was made between excellent and poor responders' purine metabolism pathway metabolites before and after taking an aspirin dosage. Aspirin increased inosine levels in both good- and poor-responders, with more significant levels seen in poor-responders after taking the medication. Subsequently, the medication response-related metabolites were confirmed in a separate cohort of participants (19 good responders and 18 poor responders) within the same research (15, 19).

After conducting a metabolomic study, the authors investigated the genetic connection of purine metabolism-related genes using a "pharmacometabolomics-informed pharmacogenomics" technique. Association studies were conducted between single-nucleotide polymorphisms (SNPs) in nine purine metabolism-related genes and ex vivo platelet aggregation. Researchers identified 51 single nucleotide polymorphisms (SNPs) in the adenosine kinase (ADK) gene related to purine metabolism, significantly correlated with platelet aggregation alterations after aspirin use. The most influential SNP was the intronic variation rs16931294. The G allele was linked to increased platelet aggregation following aspirin exposure compared to the more prevalent A allele. The G allele of rs16931294 was substantially linked to elevated levels of AMP, xanthine, and hypoxanthine before taking aspirin, as well as inosine and guanosine after aspirin treatment, compared to the A allele (19). It was determined that changes in metabolites within the purine metabolism pathway contribute to differences in aspirin effectiveness among individuals. Combining pharmacometabolomics with pharmacogenomics can enhance comprehension of how genetic and metabolic factors influence variations in drug responses.

C)Acamprosate

Acamprosate is an amino acid derivative authorized for treating Alcohol Use Disorders (AUDs). Only a subset of people with Alcohol Use Disorders are responsive to acamprosate treatment. Therefore, it is crucial to identify biomarkers that might forecast the treatment results of acamprosate in individuals with alcohol use disorders in clinical settings (20).

Researchers examined the initial and post-treatment metabolic profiles in a cohort of 120 individuals with alcohol dependence. The sample consisted of 71 individuals who responded well to therapy and 49 who did not react throughout 12 weeks of acamprosate treatment using a pharmacometabolomic method. The scientists first analyzed 36 metabolites in blood samples before and after acamprosate therapy in an identified cohort (51 responses and 39 non-responders) utilizing UPLC-MS/MS. Fourteen different metabolites were found between the starting point and post-treatment of acamprosate. Of the 14 divergent metabolites in the replication cohort, 4 exhibited comparable changes to those in the discovery cohort, with glutamate showing significant alterations. Responders had greater baseline levels of glutamate compared to non-responders. Glutamate concentrations decreased significantly in responders but not in non-responders after acamprosate administration. The baseline ammonia concentrations were more significant in those who responded to acamprosate therapy and decreased following the treatment (15,21).

Furthermore, multivariable logistic regression showed that elevated baseline glutamate or ammonia levels were strong indicators of positive responses to acamprosate therapy. The authors of the animal research found that acamprosate increased glutamine production from glutamate and ammonia via activating glutamine synthetase, leading to a decrease in glutamate levels after acamprosate therapy. Thus, the initial levels of glutamate may serve as a possible indicator for forecasting the treatment results of acamprosate in a clinical setting (21).

Metabolomics in the Identification of Disease Susceptibility Biomarkers

Individuals with the same ailment may respond differently to similar medication treatment due to varied genetic or metabolic backgrounds, leading to significant differences in disease susceptibility across populations. Identifying biomarkers that predict illness risk among individuals is crucial for personalized medicine (22).

Variability in branched-chain amino acids determine the risk of diabetes.

Metabolic illnesses result from the disruption of energy balance control, with obesity being the primary risk factor. Metabolic changes often occur years before metabolic illness develops, and susceptibility

Table1. Details of drugs using for genotyping SIRT1 and SOD1 polymorphisms.

Drugs	Metabolomics	Key Metabolite	Drug Efficacy
Simvastatin	GC/MS-based untargeted metabolomics	LCA, TLCA, GLCA, COPR	reducing plasma LDL-cholesterol
	GC/TOFMS-based untargeted metabolomics	fructose	
Acamprosate	UPLC-MS/MS-based untargeted metabolomics	glutamate	treating Alcohol Use Disorders (AUDs)
Aspirin	GC-MS-based untargeted metabolomics	inosine	antiplatelet aggregation
	MS-based targeted metabolomics	serotonin	

to the condition varies significantly, even among fat individuals. Approximately one-third of obese individuals do not have any metabolic abnormalities, as shown by a recent meta-analysis (23). Discovering metabolic biomarkers that can categorize individuals into distinct risk groups for disease progression is crucial (24, 25). Researchers conducted a nested case-control metabolomic research in the Framingham Offspring Project (26). They assessed the baseline metabolic profiles of 189 individuals who developed diabetes over a 12-year follow-up period and compared them to matched controls. Through paired analysis, researchers found five metabolites at the beginning of the study that showed significant differences between the two groups: three branch-chained amino acids (leucine, isoleucine, and valine) and two aromatic amino acids (phenylalanine and tyrosine). Additional examination revealed that individuals in the highest quartile of plasma amino acids had a minimum of double the risk of developing diabetes over the next 12 years, contrasting those with the lowest concentrations of plasma amino acids. This association was significantly stronger when only three specific branch-chained amino acids were considered. The predictive ability of the discovered amino acids for the development of diabetes was validated in separate replication samples and a random subset of the Framingham Offspring cohort. This work emphasized the significance of amino acids in the development of diabetes and indicated the possibility of identifying metabolic biomarkers for metabolic illnesses by metabolomic analysis (26, 27).

CONCLUSION

Metabolomics is a recent method in comparison to other “omics” disciplines. Metabolomics has been widely tested in clinical and experimental investigations due to the fast advancement of analytical technologies and growing interest in precision medicine. An individual’s metabotype at the beginning of therapy may help predict responses to medication treatment and susceptibility to illnesses throughout the follow-up period. The contrasting metabolic profiles before and after therapy might uncover new pharmacological mechanisms by linking the changed metabolites with related metabolic pathways. To understand how genetic and metabolic factors affect treatment results, it is essential to integrate metabolomics and genomics to uncover the processes behind various medication reactions, as the suggested GWAS-metabolomics approach [39]. Pharmacometabolomics remains in its early stages since most research primarily aims to identify the relationship between initial metabotypes and how individuals respond to drugs or are susceptible to diseases. Baseline metabotypes are often affected by diet, age, medication usage, and gut flora. These factors must be considered when planning pharmacometabolomic research to reduce metabolic biases. Furthermore, the interaction between gut microbiota variations and host metabotype might impact host metabolism and responses to pharmacological treatment, making the combination of metabolomic and gut microbiome studies crucial for a comprehensive knowledge of the functions of gut microbiota. There is limited knowledge about how these “biomarkers” influence drug reactions or disease susceptibility. However, it is crucial to explore the new functions of individual metabolites or their combination in specific conditions through interdisciplinary methods. Although there are large hurdles, confirming the predictive capacity of possible “biomarkers” and defining their functions will be gratifying to hasten the reality of personalized

treatment in clinics. We anticipate that metabolomics and pharmacometabolomics will see growing use and advancement in the future due to technology innovation and their integration with other omics methodologies, driven by a strong interest in customized medicine.

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Conflicts of Interest

The authors declare no conflict of interest.

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