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Metabolomics in the Research of Viral Infectious Disease Mechanisms

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Abstract: *Viral invasion of the body causes metabolic changes involving pathways such as gluconeogenesis, amino acid metabolism, lipid metabolism, the TCA cycle, and energy metabolism and affects vital bodily processes such as nucleic acid, protein, and lipid synthesis. During antiviral therapy, the immune response is closely related to the metabolic balance, and numerous metabolites, including glycolytic metabolites, amino acids, and nucleotides, can influence the immune response. Monitoring metabolites by metabolomics technology can aid in continuously optimizing the efficacy of medications used to treat viral infectious diseases. It also provides diagnostic and prognostic value in the clinic, making it a valuable technological platform. This review concentrates on applying metabolomics technologies to study viral infectious disease pathogenesis and treatment.*

Keywords: *Metabolomics; Viral Infectious Diseases; Hand-foot-mouth disease (HFMD); Influenza; Coronavirus disease 2019 (COVID-19)*

1. Introduction

As your paper will be an important component in the journal, we highly recommend that all the When viruses invade the body, they induce infectious diseases as pathogenic microorganisms. Viral infectious diseases are unquestionably a significant public health concern, and metabolomics is frequently used in conjunction with other histological techniques to investigate the pathogenesis of viral infectious diseases, where metabolite changes often precede clinical manifestations and changes in their levels are more accessible to monitor than changes in gene expression [1,2]. Metabolomics eliminates the need to construct genome-wide sequencing databases and extensive tagging databases, which are required for gene, protein, and transcriptomics [3]. In light of this, metabolomics has been extensively applied to the discovery of biomarkers, the diagnosis, treatment, and prognosis of diseases such as brain tumors, prostate, breast, and ovarian cancers. Viruses are specialized intracellular parasitic microorganisms that induce the reprogramming of host cell metabolism to support their own replication. This includes increased glycolysis, elevated pentose phosphate activity to support nucleotide production, amino acid production, and lipid synthesis [4]. In 2006, Munger et al. [5] discovered that human cytomegalovirus is not only extremely dependent on extracellular carbon sources but also induces substantial changes in host cell metabolism that are necessary for normal virus replication. This paper reviews the literature on the application of metabolomics techniques in the pathogenesis and treatment of viral infectious diseases with the goal of informing future approaches to optimize drug efficacy.

2. Metabolomics

Metabolomics is the study of an organism's metabolic network by analyzing changes in the structure of its metabolite profile in response to a stimulus or perturbation (such as a gene mutation, drug action, or the onset of a disease). Modern analytical techniques are used to detect and analyze multi-parameter

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changes in the metabolites of a particular tissue, blood, urine, saliva, etc. Typically, the objects of investigation are small molecules or metabolites (termed metabolomes) with relative molecular masses of less than 1000. Common analytical techniques in metabolomics include liquid chromatography-mass spectrometry (LC-MS), gas chromatography-mass spectrometry (GC-MS), and metabolomics. The techniques comprise liquid chromatography-mass spectrometry (LC-MS), gas chromatography-mass spectrometry (GC-MS), and nuclear magnetic resonance (NMR) spectroscopy. Depending on the requirements of the research, metabolomics is divided into targeted metabolomics and untargeted metabolomics. Targeted metabolomics is the detection and quantification of a small number of specific metabolites or metabolomics on a large scale in a disease state or in response to physiological stimuli; non-targeted metabolomics is the detection of a broad range of metabolites and contributes to the discovery of new biomarkers [6]. Due to the large number of analytes to be measured in non-targeted metabolomics, the dearth of standard substances and analytical standards, and the absence of guidelines or protocols for non-targeted metabolomics, it is difficult to conduct non-targeted metabolomics experiments [7]. Due to the large number of analytes required for non-targeted metabolomics, the absence of standards and analytical criteria, and the lack of guidelines or protocols for non-targeted metabolomics, there is no way to validate them fully; thus, quality control samples must be included in the sample batch sequence [8]. In addition, the choice of the column is determined by the polarity of the target metabolite, with reversed-phase columns used for the analysis of low and medium-polarity metabolites and hydrophilic interaction separation used for highly polar compounds. In conclusion, the choice of method is determined by the sample matrix, the number of samples, their concentration, and the nature of the metabolites, with different methods having varying sensitivities and stabilities [9].

3. Applications of Metabolomics to Viral Infectious Diseases

As viruses rely on host cells for the macromolecules they require for normal replication, they have evolved a variety of strategies to influence the cellular metabolism and biosynthetic machinery of their hosts to meet their specific requirements. Most viruses enhance particular anabolic pathways and are highly dependent on these alterations, typically the upregulation of the uptake of extracellular carbon sources (e.g. glucose or glutamine) and the redirection of these carbon supplies to metabolic pathways essential for viral replication, including lipogenesis, nucleotide metabolism, and the TCA cycle. Viruses also induce a reorganization of cellular membranes and biosynthetic machinery, which is commonly accompanied by changes in lipid metabolism [10]. Numerous infected cells and patients have exhibited these alterations, which affect vital biological processes like cellular energy metabolism, nucleic acid, and protein synthesis. For instance, a rise in phosphatidylethanolamine (PE) has been observed in Zika virus-infected patients [11]. Levels of glucose or mannose are decreased, and significant alterations have been made to the metabolic pathway associated with Nicotinamide adenine dinucleotide (NAD+) [12,13]. The metabolic pathway associated with Nicotinamide adenine dinucleotide (NAD+) is significantly altered. Respiratory syncytial virus (RSV) infection of mice caused a decrease in plasma triacylglycerols and free fatty acids (FA) and an increase in large amounts of PE and acetal phosphatidylcholine [14]. Several metabolites were downregulated in the nicotinic acid and nicotinamide metabolic pathways [15]. L-lactate, phosphatidylcholine, and phosphatidylcholine (PC) levels are significantly higher in children with recurrent wheezing after RSV infection compared to children without wheezing. Pyrimidine metabolism, glycerophospholipid metabolism, and arginine biosynthesis were identified as the most significant pathways of change between the two groups [16]. The analysis of urinary metabolites revealed a substantial negative correlation between citrate/isocitrate and the severity of RSV [15]. In fatal cases of Ebola virus disease, plasma phosphatidylserine, PE, diglycerides, and ceramides decreased, while mono-sialylated hexose gangliosides increased [17]. Oxyproline concentrations were higher in patients with hepatitis C virus (HCV) liver fibrosis, choline and histidine were elevated in serum filtrates from patients with severe fibrosis/cirrhosis relative to patients with early fibrosis HCV, and serum cysteine concentrations were also higher in patients with HCV liver fibrosis relative to non-HCV controls [18]. In HCV progression to hepatocellular carcinoma, N-fructose tyrosine, and hydroxy indole acetic acid was elevated, whereas L-aspartate-L-phenylalanine and thyroxine were decreased [19]. The findings of numerous researchers employing metabolomics to study recent epidemic viral infections, such as influenza, Hand-foot-mouth disease (HFMD), and novel coronavirus disease 2019 (COVID-19), are described in detail below.

3.1. Implementation of Metabolomics Methods in Influenza

Influenza has caused numerous global outbreaks over the years, with seasonal epidemics occurring

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annually in countries around the world; it is a significant global public health concern. Each year, approximately 1 billion individuals are infected with the influenza virus, with between 0.3% and 0.5% becoming seriously ill. Influenza viruses are members of the family Orthomyxoviridae, which consists of single-stranded, negative-stranded, segmented RNA viruses classified into four types: A, B, C, and D. Influenza A viruses are the H1N1 and H3N2 subtypes and the Victoria and Yamagata strains of influenza B viruses that infect humans [20]. Influenza A viruses are the H1N1 and H3N2 subtypes and the Victoria and Yamagata strains of influenza B viruses that infect humans. A549 cells infected with the influenza A virus exhibited alterations in purine metabolism, lipid metabolism, and glutathione metabolism [21]. Similarly, many distinct metabolites in hormone biosynthesis, amino sugar and nucleotide metabolism, vitamin B6 metabolism, cysteine, and methionine metabolism, vitamin uptake, arginine, and proline metabolism, amino acid biosynthesis, and folic acid biosynthesis, and metabolic pathways were observed in canine kidney cells infected with the influenza A H3N2 virus [22]. Ten metabolites are altered in severe pneumonia caused by H7N9 virus infection compared to normal controls, including palmitic acid, erucic acid, tetramethylhexadecenal and palmitamide, with changes in palmitic acid levels, indicating disease recovery and a significant decrease in erucic acid and tetramethylhexadecenal during rapid H7N9 virus replication [23].

3.2. Implementation of Metabolomics Strategies in HFMD

HFMD is a childhood infectious disease caused by enterovirus infection; cases are primarily in children five years old and can be transmitted through contact, respiratory and digestive tracts; the epidemic of HFMD occurs in all continents of the world but is highly prevalent in China, since 2010, HFMD has been at the top of the incidence of statutory infectious diseases in China, due to its complex transmission route, strong infectiousness and the number of cases, making the etiology of the disease public health This public health issue poses a grave threat to the health of neonates and children[24]. From 2008 to 2018, the United States reported a total of 20,537,199 cases of HFMD, with an average annual rate of severe illness of 1.05/100,000 and a severe morbidity and mortality rate of 2.34%, resulting in a significant disease burden [25].

Using targeted metabolomics analysis, Shi et al. [26] discovered increased glucose uptake and glycolytic metabolites after EV71 infection, with four glycolytic metabolites elevated in EV71-infected cells compared to controls: phosphoenolpyruvate, 2,3-diphosphoglycerate, fructose 6-phosphate, glucose 6-phosphate, and -pyridyl diphosphate nucleotide (NAD). Moreover, WU et al. [27] A metabolomics study using NMR technology revealed that children with HFMD had significantly higher concentrations of metabolites such as lipoproteins, leucine, valine, -hydroxybutyric acid, acetone, glucose, glycoproteins, glycerol, glycine, choline, trimethylamine oxide, and lactate and significantly lower concentrations of metabolites such as acetic acid and creatine compared to the healthy population. In contrast to the normal type, the concentrations of lipoproteins and trimethylamine oxide decreased. In contrast, another study, also based on MRI, found elevated levels of a total of 10 metabolites (inositol, valine, leucine, lysine, isoleucine, and 3-hydroxybutyric acid) as potential biomarkers in patients with HFMD but no differences were found between the severe and typical forms. In addition to metabolic differences, the study revealed that inflammation-impaired intestinal absorption and immune response have a major impact on seven metabolic pathways associated with HFMD (valine, leucine, and isoleucine catabolism, gluconeogenesis, alanine, aspartate, and glutamate metabolism, glutamate and glutamine metabolism, ketone body synthesis and catabolism, lipid digestion and absorption, and lysine catabolism) [28]. Lu et al.[29] demonstrated that lipid metabolism is altered in patients with HFMD, with lower levels of diglycerides (DAG) and phosphatidylethanolamine (PE) and higher levels of choline, uronic acid (UCA), and prostaglandin E2 (PGE2) compared to healthy controls.Zou et al.[30] utilized a targeted metabolomics approach to examine the metabolic changes in EV71 infection-induced pluripotent stem cell (iPSC)-derived neural progenitor cells (NPCs), and targeted quantification of polar metabolites identified 14 altered expression profiles. Following the EV71 infection, pathway analysis revealed that the glucose metabolic pathway was severely perturbed. As an antiviral strategy, the manipulation of EV71-induced metabolic reprogramming of the host has been shown to be feasible.

3.3. Metabolomics Techniques in COVID-19

Coronavirus disease 2019 (COVID-19) is an acute respiratory infection induced by SARS-coronavirus 2 (SARS-CoV-2). Research into the pathogenesis of COVID-19 could contribute to the development of antiviral medications and vaccines, despite the fact that the epidemic has become "sporadic". DNA and RNA viruses modify host cell metabolism by altering central carbon metabolic

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pathways, including glycolysis, gluconeogenesis, the pentose phosphate pathway (PPP), amino acid metabolism, lipid metabolism, and the TCA cycle. The virus that causes COVID-19, SARS-CoV-2, is not an exception. Patients with COVID-19 typically exhibit disturbances in energy metabolism, such as abnormal ATP production and mitochondrial dysfunction. Patients with COVID-19 exhibit abnormalities in the metabolism of NAD+ and its endogenous precursors, and patients frequently exhibit accumulation of tricarboxylic acid cycle metabolites and carnitine esters, markers of rapid metabolic deterioration, mitochondrial function, and bioenergetic crises that are observed long before death [31]. Since the onset of the COVID-19 epidemic, numerous researchers have monitored metabolite alterations in COVID-19 patients; we have compiled their critical findings in Table 1. Notably, the body's metabolic activity is regulated by metabolic enzymes and hormones in an ordered and coordinated manner, and we have categorized the results to make them more understandable.

Table 1: Metabolomics Strategies for Treating COVID-19.

Serial number	Type of sample	Metabolomics techniques	Combining other histological techniques	Key findings	Whether to build a predictive model	References
1	Serum	UPLC-MS/MS Non-targeted metabolomics	Proteomics	Molecular changes involving macrophage dysregulation, platelet degranulation, complement system pathways, and massive inhibition of amino acid metabolism were identified in the sera of COVID-19 patients compared to other groups.	Yes	[32]
2	Plasma	UPLC-MS/MS Non-targeted metabolomics	Proteomics	Plasma glucose, mannose pyruvate, and lactate levels were elevated in COVID-19 patients compared to healthy controls. In vitro, infection models found that most proteins of carbohydrate metabolism and PPP were upregulated in infected cells. In contrast, most proteins of the TCA cycle, oxidative phosphorylation, and FA metabolism were downregulated. Reduced plasma IL-12 levels in critically ill patients.	No	[33]
3	Serum	UHPLC-MS/MS Targeted and untargeted metabolomics	/	Uncovering the potential regulatory roles of arginine metabolism, tryptophan metabolism, and purine metabolism in the pro-inflammatory response.	No	[34]
4	Plasma	LC/Q-TOF/MS Targeted Metabolomics	/	Glycine accumulates in recovering COVID-19 patients with rapidly fading antibodies, down-regulates SARS-CoV-2 receptor binding threshold antibody levels, and suppresses immune responses; DPP4 inhibitors counteract the inhibitory effect of glycine on SARS-CoV-2 vaccination.	Yes	[35]
5	Plasma	LC/Q-TOF/MS Non-targeted metabolomics	/	Longitudinal metabolic profiling reveals that metabolites change early in the disease and eventually return to control levels upon recovery.	Yes	[36]
6	Plasma	UPLC-MS/MS Non-targeted lipidomics	/	Discovery of a lipidomic profile of PLA2 hydrolysis and mitochondrial dysfunction corresponding to COVID-19 severity.	Yes	[37]
7	Plasma	MS Non-targeted lipidomics	/	Decreases in lysophosphatidylcholine, cholesterol, and unsaturated fatty acids, as well as increases in triacylglycerols, diacylglycerols, and purines, are the primary metabolites that distinguish SARS-CoV-2 infected from non-infected individuals.	Yes	[38]
8	Serum	LC-MS/MS	Genomics	Significantly lower serum levels of TCA metabolites such as citric acid, malic acid, and cis-aconitate in the hACE2/SARS-CoV-2 group.	No	[39]
9	Serum	LC/Q-TOF/MS Non-targeted metabolomics	/	Patients showed significant differences in purine, glutamine, leukotriene D4 (LTD4), and glutathione metabolism compared to healthy controls.	No	[40]
10	Plasma	LC-ESI-MS/MS Targeted metabolomics/lipidomics	/	Differential metabolites were enriched in 12 metabolic pathways in all three symptom groups, with the three most critical metabolic pathways being pyrimidine metabolism, fructose, and mannose metabolism, and carbon metabolism; dyslipidemia was also observed in COVID-19 patients.	Yes	[41]
11	Plasma	DI-LC-MS/MS and1 H NMR	/	Identification of positive patients by arginine/kynurenine ratio; prediction of related deaths by creatinine or creatinine/arginine ratio.	Yes	[42]

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3.4. Altered Glucose and Amino Acid Metabolism

The concentration and metabolism of carbohydrates and amino acids, such as glucose, mannose, glutamine, and glutamate, play an essential role in cellular metabolic homeostasis and influence viral replication. SARS-CoV-2 infection modifies central carbon metabolism pathways governed by AKT/mTOR/HIF-1 signaling [43]. These pathways modulate Glucose transporter (GLUTs) across the cell membrane to regulate glycolysis. In addition to increased glucose uptake, GLUT1 upregulation increases PPP intermediates, thereby increasing the pool of nucleotides required for viral replication [10]. Monomeric mannose is essential to protein N-linked glycosylation, and plasma mannose levels indicate glycogenolysis and glucose tolerance [33]. Suggested that plasma mannose could be a significant biomarker of COVID-19 severity. Under physiological conditions, the hormone or bilirubin binds to gluconic acid, a glucose derivative, for hepatic detoxification, Shen et al. [32] discovered that elevated glucose, glucuronide, bilirubin degradation products, and four bile acid derivatives in critically ill patients indicated a decrease in hepatic detoxification. Whereas amino acid metabolism is highly dependent on the deamidation of transaminases, which are most abundant in the liver and myocardium, the reduced detoxification capacity of the liver has a significant impact on amino acid metabolism, as evidenced by decreased concentrations of 10 metabolites involved in arginine metabolisms, such as glutamate, arginine, citrulline, ornithine, and glutamine. Additionally, Xiao et al. [34] observed a down-regulation of glutamine and citrulline and an up-regulation of glutamate and aspartate as disease severity increased. Krishnan et al. [33] also proposed the down-regulation of amino acids such as glycine, proline, tryptophan, glutamine, arginine, alanine, and histidine and the up-regulation of aspartate and phenylalanine in COVID-19 patients. Zhu et al. [35] discovered that glycine accumulates in recovering COVID-19 patients with swiftly fading antibodies, down-regulates SARS-CoV-2 receptor binding threshold antibody levels, and suppresses the immune system.

3.4.1. Altered Lipid Metabolism

Shen et al. [32] reported that 100 lipids are downregulated in critically ill patients, including sphingolipids and glycerophospholipids, which are essential biological membrane components that mediate signal transduction and immune activation, and sphingolipids, which regulate cell migration, adhesion, apoptosis, senescence, and inflammation. Phospholipases degrade glycerophospholipids, and Justin et al. [37] demonstrated in their study that patients with severe or fatal COVID-19 had higher levels of circulating, enzymatically active secretory phospholipase A2-IIA than uninfected or mildly ill patients, indicating a high hydrolytic activity of PLA2, which explains the downregulation of glycerophospholipids in COVID-19 patients. In addition, the high hydrolytic activity of PLA2 allowed the concentration of lysophosphatidylcholine (Lyso-PC) to remain stable since Lyso-PC is formed by the hydrolysis of PC by PLA2. Jeany et al. [38] proposed a downregulation of Lyso-PC, and Sindelar et al. [36] collected samples from patients at six-time intervals for longitudinal metabolic profiling and discovered a downregulation of Lyso-PC. In addition to the reductions in cholesterol, cholesteryl esters, PC, unsaturated fatty acids, diacylglycerols, triglycerides, and purines, they also observed a reduction in cholesterol and cholesteryl esters in COVID-19-positive patients, as well as bis(monoacylglycerol) phosphate, a lipid phosphate. Song et al. [44] found a correlation between the abundance of cholesteryl ester and bis(monoacylglycerol) phosphate.

3.4.2. Modifications to the Energy Metabolism and TCA Cycle

Li et al. [39] constructed a mouse model of SARS-CoV-2 infection with multi-organ damage (hACE2/SARS-CoV-2 group) by expressing human angiotensin-converting enzyme 2 (hACE2) and performed a multi-omics analysis, in which metabolomics studies demonstrated that hACE2/ SARS-CoV-2 group patients had significantly lower serum levels of metabolites of the TCA cycle, such as citric acid, malic acid, and cis-aconitate, suggesting that inhibition of the TCA cycle and oxidative phosphorylation may exist in COVID-19 patients with multiple organ dysfunction. In addition, Xiao et al. [34] discovered decreased levels of isocitrate and oxalosuccinate in COVID-19 patients, indicating diminished energy production following SARS-CoV-2 infection. Zhu et al. [35] found elevated levels of adenosine monophosphate in both the general antibody-recovered and rapidly fading antibody-recovered groups, suggesting increased energy demand in recovered patients and, correspondingly, a decrease in isocitrate and succinate intermediates of the TCA cycle in both groups and the decrease in acylcarnitine plasma levels observed in both recovery groups is consistent with this trend. These data suggest that in order to meet this increased energy demand, recuperating patients may upregulate the FA -oxidation pathway, an alternative energy supply pathway.

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3.4.3. Altered Nucleotide Metabolism-Related Markers

Guanosine monophosphate (GMP) is mediated by CD39 and CD73 in addition to GMP synthase. Wu et al. [41] discovered significant differences in GMP levels between healthy individuals and COVID-19 patients, as well as between mild and fatal cases. In addition, Doan et al. [40] discovered significant differences in purine metabolism between patients and healthy groups, and it is believed that the upregulation of hypoxanthine and inosine is associated with increased ATP catabolism under hypoxic conditions in COVID-19 patients and that purinergic signaling has a regulatory role in COVID-19 against inflammatory and hypoxic conditions. Inhibition of adenosine deaminase and purine nucleoside phosphorylase reduces the severity of COVID-19 disease by inhibiting the conversion of adenosine and inosine to hypoxanthine.

4. Overview and Prognosis

The technologies of metabolomics provide new perspectives for fundamental biological and disease research. Changes in metabolite levels can objectively reflect the intricate pathophysiological mechanisms of disease, and metabolomics' diagnostic and prognostic potential merits further investigation. Due to the high protection requirements of COVID-19, however, the majority of studies have small sample sizes to permit large-scale replication, can only be conclusively validated by large cohorts, and are frequently cross-sectional studies with limited longitudinal dynamic monitoring. In addition, all non-targeted metabolomics cannot precisely quantify metabolite concentrations, necessitating additional quantification by targeted metabolomics in the absence of standardized techniques and conditions of use to facilitate data sharing, reproducibility, and comparability. The practical application of metabolomic methods requires consideration of the following: (1) sample comparability; (2) differences between SARS-CoV-2 variants; (3) longitudinal dynamic monitoring of disease; (4) identification and application of new biomarkers taking into account the cost of diagnosis and the influence of factors such as age and underlying disease; and (5) comprehensive evaluation of metabolomics in combination with proteomics and genomics. Establishing a standardized multi-omics testing procedure, rigorously limiting the screening criteria for multi-omics indicators, and conducting large-scale clinical trials to verify their applicability and usefulness can help us diagnose and classify diseases more precisely. Numerous advancements based on multi-omics techniques could aid in the comprehension of the complexity and heterogeneity of viral infectious diseases, as well as in the development of viable diagnostic indicators and novel therapeutic agents. Metabolomics technologies are a valuable resource for surveillance, diagnosis, treatment, and clinical decision-making in the context of viral infectious diseases.

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