

The role of multi-omics in the diagnosis of COVID-19 and the prediction of new therapeutic targets

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ABSTRACT

The global pandemic of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus causing COVID-19, has led to more than 170 million confirmed cases in 223 countries and regions, claiming 3,872,457 lives. Some patients with COVID-19 have mild clinical symptoms despite severe respiratory failure, which greatly increases the difficulty of diagnosis and treatment. It is therefore necessary to identify biological characteristics of SARS-CoV-2, screen novel diagnostic and prognostic biomarkers, as well as to explore potential therapeutic targets for COVID-19. In this comprehensive review, we discuss the current published literature on COVID-19. We find that the comprehensive application of genomics, transcriptomics, proteomics and metabolomics is becoming increasingly important in the treatment of COVID-19. Multi-omics analysis platforms are expected to revolutionize the diagnosis and classification of COVID-19. This review aims to provide a reference for diagnosis, surveillance and clinical decision making related to COVID-19.

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Introduction

Coronavirus disease 2019 (COVID-19) is a global pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. As of 22 June 2021, COVID-19 has caused more than 170 million confirmed cases in 223 countries and regions, claiming 3,872,457 lives [2]. It is obvious that COVID-19 has become a life-threatening emergency to human health and public safety. According to phylogeny and taxonomy, SARS-CoV-2 belongs to the Betacoronavirus genus. The main structure of SARS-CoV-2 contains four structural proteins, including the spike (S), nucleocapsid (N), membrane (M) and envelope (E) proteins [3]. The spike protein of SARS-CoV-2 binds to angiotensin-converting enzyme 2 (ACE2) and then enters hosts cells through endocytosis, dysregulating the angiotensin system and inducing subsequent cytokine storms. During this process, the transmembrane serine protease TMPRSS2 plays an important role in activating S-protein [4]. Regrettably, the specific pathogenesis of COVID-19 and the definite mechanisms of SARS-CoV-2 variants have not yet been clarified, leading to difficulty in eradicating rampant SARS-CoV-2 infection. Current

evidence suggests that COVID-19 possesses high heterogeneity, with diverse clinical manifestations varying among different individuals, ranging from asymptomatic, mild to severe, and even fatal [5]. When the disease progresses to a severe state, the survival rate drops dramatically. Notably, some patients with COVID-19 have mild clinical symptoms despite severe respiratory failure. This puzzling phenomenon, known as “happy hypoxaemia,” greatly increases the difficulty of diagnosis and treatment [6]. Taken together, it is necessary to identify biological characteristics of SARS-CoV-2, screen novel diagnostic and prognostic biomarkers, as well as to explore potential therapeutic targets for COVID-19.

In recent years, omics technologies such as next-generation-sequencing (NGS) and mass spectrometry have undergone significant development. Omics research has been accelerated towards quantitative and high-throughput modalities. Multi-omics, which integrates genomics, proteomics, metabolomics and transcriptomics from a comprehensive perspective, plays an important role in revealing specific characteristics, assisting efficient diagnosis, and informing patient-tailored management of

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diseases [7]. The integration and analysis of multi-omics data has revolutionized biology and revealed complex interaction networks between different molecular levels [8], providing a new horizon for basic biology and disease research. Great efforts have been devoted to elucidating the correlation between multi-omics data and COVID-19 disease outcomes. A series of breakthroughs based on multi-omics approaches have helped us comprehend the complexity and heterogeneity of COVID-19, aiding the development of feasible diagnostic indicators and innovative therapeutics. We focus on the progress of multi-omics analysis of COVID-19, encompassing genomics, transcriptomics, proteomics and metabolomics, in order to provide reference for the diagnosis, surveillance and clinical decision-making related to COVID-19.

Multi-Omics in the diagnosis and classification of COVID-19

Given the urgency of the COVID-19 pandemic, it is crucial to discover a precise, high-efficiency and inexpensive diagnostic approach that can be used on a large scale to successfully limit the risk of contagion and reduce associated mortality. At present, rapid serological tests, molecular tests based on reverse transcription quantitative PCR (RT-qPCR) and computed tomography (CT) scans have been approved for the diagnosis of COVID-19 [9]. Unfortunately, each method has its limitations. Although RT-PCR has high sensitivity in the detection of viral RNA, it is time-consuming and RNA extraction is no longer needed for current PCR assays of SARS-CoV-2 [10,11]. Serological tests can reflect the duration and intensity of acquired immunity to a certain extent, but their results are easily affected by sampling time and preservation conditions, limiting their sensitivity and specificity. The delay between initial infection and the production of antibodies exerts momentous influence on antibody tests [12]. CT imaging is of great value in disease classification and selection of targeted treatments, but it lacks specificity [13]. Furthermore, there is a need to accurately discern infected persons who are likely to progress to severe disease or even to multiple organ failure and those who will remain stable, so that personalized treatments and optimized allocation of medical resources can be implemented. Thus, cutting-edge multi-omics analysis platforms are expected to revolutionize the diagnosis and classification of COVID-19.

Genomics

Genomics, the quantitative analysis and representation of an organism's genome by sequencing technology,

mainly includes structural genomics, functional genomics, epigenomics and metagenomics [14,15]. Genomics is a fundamental tool for understanding the molecular mechanisms of infectious diseases, tracing the source of infection, decoding transmission routes and detecting host susceptibility during the epidemic process. There is mounting evidence of the importance of genomics in COVID-19. Metagenome sequencing, which extracts genetic information directly from environmental samples, is a high-throughput method for the sequencing of the total microbiota. With wide coverage, unbiased metagenomics has unparalleled advantages for rapid identification of emerging pathogens, as well as providing a basis for accurate diagnosis of other pathogens and mixed infections [16]. At the same time, metagenomics provided guidance for the early detection and rapid identification of the newly emerging pathogen SARS-CoV-2, along with the diagnosis and treatment of COVID-19. Using shotgun metagenomics approaches, researchers identified 96% genome-wide similarity between the novel coronavirus (2019-nCoV) and bat coronaviruses in the early stage of the pandemic [17]. Lu et al [18]. revealed the origin and evolution of SARS-CoV-2 by high-throughput metagenomic sequencing of bronchoalveolar lavage fluid and culture isolates from 9 hospitalized COVID-19 patients through NGS and nanopore sequencing. Under selection pressure, SARS-CoV-2 is rapidly mutating and developing different epidemiological characteristics [19]. Shotgun metagenomics, which does not rely on either culture methods or any prior knowledge of the genome sequence, is the first choice for monitoring newly emerging mutant strains in an epidemic, but the high viral load and high sequencing depth requirements limit its application [18]. Lin et al [17]. sequenced 310 clinical samples from 248 COVID-19 patients using untargeted metagenomics and multiplex PCR approaches followed by nanopore sequencing. Thirty-five mutant strains were detected, 20% of which had a deletion spanning the coding region of the same non-structural protein 1 (NSP1, Δ 500–532). They also demonstrated that this mutation inhibited downstream type I interferon (IFN-I) signalling by reducing the activity of the IFNB1 promoter. This suggests that genomic markers can illustrate the genetic diversity and molecular epidemiology of SARS-CoV-2. It is worth noting that metagenomics technology is still not mature, and an automated, cost-effective, and accessible workflow should be established in the future.

Amplicon sequencing can capture the targeted region for NGS analysis of specific genomic features. In contrast to whole-genome sequencing, it can be used to characterize uncultivable organisms. Moreover, it

takes less time and is more sensitive, allowing the analysis of clinical specimens with low viral load, so it is of great value in the aetiological detection of SARS-CoV-2 [20,21]. High-density amplicon sequencing of symptomatic cases can demonstrate the epidemiological characteristics and evolutionary variation of SARS-CoV-2 [22]. Marotz et al [23]. detected SARS-CoV-2 virus by RT-qPCR, and identified the epidemic characteristics of viral RNA in host and hospital environments by sequence analysis of amplicons corresponding to the 16S rRNA gene. They found that amplicon sequence variation in the genus *Rothia* strongly predicted the presence of SARS-CoV-2 in different sample types. This facilitates early detection of potential infection risk and early diagnosis. RT-PCR for the detection of viral nucleic acids is a special type of amplification sequencing that has been promoted in clinical practice and is regarded as the gold standard for identifying COVID-19 [24]. In the future, the design and optimization of SARS-CoV-2 nucleic acid detection targets, improving the efficiency of gene library construction, and minimizing variation during primer annealing will be important research areas for improved diagnosis.

Hybrid capture-enrichment sequencing captures the targeted genome region onto a specific hybridization probe and enriches the target gene fragment, enabling NGS with high throughput and low cost [25]. Furthermore, it allows the identification of mixed infection. For example, Kim et al [26]. conducted pan-viral hybridization-capture and sequencing using hybrid-capture and a Twist Respiratory Virus Panel on nasopharyngeal swabs of 92 SARS-CoV-2 positive cases, and demonstrated its application value in diagnosing SARS-CoV-2 combined with other pathogens, emphasizing the importance of recognizing co-infections which may occur at rate of approximately 8%. Controversially, some studies have shown that hybridized-capture technology has a good detection rate for samples with low viral load [27], while others argued that its sensitivity is inferior to amplicon sequencing [20]. Therefore, further studies are needed to resolve the dispute.

In addition, genomics is helpful for determining the severity and prognosis of COVID-19. It has been proved that SARS-CoV-2 affects adaptive immunity and the structure of immune cells [28]. Schulthei et al [29]. detected more than 14 million T cell and B cell receptor (BCR) sequences of COVID-19 patients through NGS, and found that severe patients requiring mechanical ventilation and extracorporeal membrane oxygenation carried more somatic mutations of BCR. Somatic hypermutation is a mechanism through which the immune system adapts to an antigen it has never

encountered before, mainly by diversifying immune cell receptors. Somatic hypermutation of BCR causes a decrease in the percentage of naive B cells, and the degree of mutation is related to the severity of the disease.

Nowadays, genomics has become a practical method for the diagnosis and stratification of COVID-19. A joint effort is expected to enable the detection of low viral loads without cross-reaction with other virus strains. At the same time, genomics is also hoped to provide reference for disease classification through in-depth studies of the host immune response. However, in the application of genomics based on sequencing methods, strict data quality control and the establishment of a thoroughly curated virus information database are still necessary. It is crucial to establish a standardized sequencing platform to ensure the repeatability of results by optimizing sampling and preservation methods. Moreover, it should be noted that the construction of gene libraries often causes gene rearrangement or single nucleotide polymorphisms (SNP), which can obscure underlying genetic information.

Transcriptomics

Transcriptomics relies on next- and third-generation sequencing technology to analyse the genomic transcripts and regulation rules of microbiota in a specific period and environment, with temporal and spatial resolution [30]. To date, several transcriptomic techniques have shown outstanding advantages in obtaining SARS-CoV-2 gene expression information, elucidating virus-host interactions, guiding treatment decisions, and assessing the prognosis.

Kim et al [31]. used direct RNA sequencing which can read the full length sequence of a single high quality RNA molecule from 5-terminal to 3-terminal poly A tail to determine the transcriptome and epigenetic modification of SARS-CoV-2. The analysis of viral transcripts revealed that there might be at least 41 sites of RNA 5-methyl-cytosine (5mC) modification, which may be related to the stability of viral RNAs and immune escape. Transcriptomics has unique advantages in revealing the immune characteristics of different stages of COVID-19, and multi-omics analysis can shed light on the pathogenesis of COVID-19.

Through integrated “big data” analysis of single-cell transcriptomes from COVID-19 patients, Ren et al [32]. found that ANXA1, S100A8 and S100A9 were upregulated in SARS-CoV-2-positive squamous epithelial cells. ANXA1, S100A8 and S100A9 interact with FPR1 and TLR4, which are highly expressed on

neutrophils and macrophages, to trigger the body's innate immunity and cause a cytokine storm. The expression of ANXA1 and S100A8/9 in peripheral blood immune cells of severe patients was generally upregulated, and the ratio of plasma cells to T cells in the proliferating state was greatly increased, while the overall T cell level was significantly lower than that of mild cases and patients in the recovery phase or healthy controls. These findings suggest that single-cell transcriptomics has broad application prospects in elucidating the immune characteristics and classifying the severity of COVID-19 patients.

Tang et al [33]. found that miR-146a-5p, miR-21-5p, miR-142-3p and miR-15b-5p were related to the severity of COVID-19 by sequencing non-coding RNAs and mRNAs in the peripheral blood of patients with moderate and severe COVID-19. These RNAs are expected to be promising biomarkers and therapeutic targets for severe COVID-19. Transcriptional profiling suggests immune overactivation, T cell depletion and dysregulation in severe patients. These findings suggest that single-cell transcriptomics has broad application prospects in elucidating the heterogeneity and immune characteristics of COVID-19 and classifying its severity.

In view of the dynamic nature of transcriptome sequencing, Suet al [34] found an important immunological shift between mild and moderate COVID-19 infection through a comprehensive analysis of multi-omics datasets, with new proliferative depletion of CD8 + T cell subsets increasing with disease severity in moderate cases. A dysfunctional S100^{high}HLA-DR^{low} monocyte subpopulation uncovered via plasma multi-omics was also found to be related to COVID-19 severity. Transcriptomics-based immune signatures provide a feasible approach for early identification and differentiation between levels of severity, which is conducive to accurate diagnosis and timely intervention in COVID-19.

Proteomics

Proteins are the main molecules of all living cells. Proteolytic processing and post-translational modifications can further diversify the structures and physiological roles of proteins. Proteomics based on mass spectrometry is mainly used to study the composition, localization, change and interaction of proteins in cells, tissues or organisms, enabling researchers to integrate and analyse the spatiotemporal interaction network of proteins, so as to reveal the detailed mechanisms underlying pathogenesis and physiological changes related to disease states [35]. Nie et al [36]. analysed the multi-organ proteomic profile of COVID-19

autopsies and found that 5336 protein molecules were altered after SARS-CoV-2 infection, with significant upregulated of cathepsin L1 in the lungs. The infected patients exhibited dysregulation of key factors related to hypoxia, angiogenesis, coagulation and fibrosis in multiple organs. These differentially expressed proteins are candidate biomarkers for diagnosis and prognosis of severe COVID-19 cases.

Shu et al [37]. performed a quantitative proteomic analysis of plasma samples from COVID-19 patient cohorts and developed a model based on machine learning called Prioritization of Optimal biomarker Combinations for COVID-19 (POC-19) to identify 11 biomarkers and a series of biomarker combination that can accurately distinguish patients with different prognosis. This study showed that the differentially expressed proteins of patients with different symptoms and progression of COVID-19 are mainly involved in platelet degranulation, complement coagulation cascade reactions, immune response and metabolism. POC-19 identified a combination of four protein biomarkers, including orosomucoid-1/alpha-1-acid glycoprotein-1 (ORM1/AGP1), ORM2, fetuin-B (FETUB), and cholesteryl ester transfer protein (CETP), which could be used to classify COVID-19 patients. In addition, the clinical outcomes of patients from mild to severe COVID-19 were successfully determined based on zinc- α -glycoprotein 1 (AZGP1), ORM2, and complement factor I (CFI) alone or in combination. The combination of serine proteinase inhibitor A3/a1-antichymotrypsin (SERPINA3/ACT), lymphocyte cytosolic protein 1/L-plastin (LCP1/LPL), and peptidase inhibitor 16 (PI16) showed prominent advantages in predicting convalescence. The application value of the abovementioned indicators needs to be further investigated in larger cohorts, preferably with multi-centre verification, while analysing the influence of different therapeutic strategies on the proteomic analysis results.

A study combining time-resolved proteomics with clinical features to portray the specificity and dynamics of COVID-19 trajectories provides the possibility of phenotypic identification, diagnosis, and prognosis [38]. In this study, flow chromatography and tandem mass spectrometry were combined to analyse the plasma proteomes of 139 hospitalized COVID-19 patients, and data were processed using flow chromatography, SWATH-MS quantitative and deep-neural network methods. The results showed that 113 proteins and 55 clinical parameters were associated with the WHO grade of COVID-19. The dynamic changes of these markers reflect the progression of disease, including the immuno-inflammatory mediators CD44 and B2 M, complement cascade components CFD and

CFHRs, coagulation components HRG and PLG, apolipoprotein APOA2, APOC3 and angiotensin (AGT), as well as the organ dysfunction indicators NT-proBNP and troponin. Eleven proteins and nine clinical parameters were finally included in the prediction model of disease progression, and oxygen therapy intervention should be applied as early as possible for high-risk groups. This finding is expected to identify early infected individuals and allow direct risk stratification of COVID-19, but translation from *in silico* analysis to clinical needs will require further clinical trials.

Messner et al [39]. designed an ultra-high-throughput proteomic assay using short-gradient high-flow liquid chromatography (LC), which overcomes the batch effect of longitudinal sequencing to improve the accuracy and robustness. This platform was used to record the serum and plasma proteomic signature of COVID-19 patients and identify 27 proteins that are closely associated with IL-6-mediated pro-inflammatory signalling as valuable biomarkers of disease severity.

Metabolomics

Metabolic disorder plays an important role in the occurrence and development of diseases. Metabolite changes are sometimes evident prior to clinical manifestations, and metabolite levels are easier to detect than gene expression changes [40]. These traits provide a solid cornerstone for the application of metabolomics in diagnostic and prognostic stratification of COVID-19. As a pivotal part of systems biology, Metabolomics mainly studies small molecules with a relative molecular weight of less than 1000 [41]. Through quantitative analysis of metabolites, their mechanistic relationship with physiological and pathological changes can be explored.

Using ultra performance liquid chromatography/tandem mass spectrometry (UPLC-MS/MS), Wu et al [42]. conducted targeted metabolomics and lipidomics analysis of plasma samples from COVID-19 patients, and found that the differential metabolites in mild, severe and fatal cohorts were mainly concentrated in pyrimidine metabolism, glucose/mannose metabolism and carbon metabolism. The rapid decrease of plasma metabolites such as malic acid, aspartic acid and guanosine monophosphate (GMP) was found to accelerate the progression of disease. Mechanistically, malic acid in the tricarboxylic acid cycle (TCA) cycle and carboxyl phosphate in the urea cycle might cause energy metabolism disorder and liver damage, while guanosine monophosphate affects metabolic responses mediated by GMP synthase and immunoregulatory enzyme CD39/CD37. Moreover, dyslipidemia was associated

with disease severity. Accordingly, a useful diagnostic panel that included five plasma metabolites was established to distinguish mild, severe and fatal cases. These results illustrate the unique advantages of metabolomics in diagnosing and discerning the risk of COVID-19.

Song et al [43]. constructed a diagnostic panel composed of 10 plasma metabolites that could effectively distinguish COVID-19 patients from the healthy control group through lipidomics and metabolomics (AUC = 0.975). Monosialodihexosyl ganglioside (GM3)-enriched exosomes were significantly more abundant in severe patients. RNA viruses hijack exosomal pathways that mediate endogenous cell-to-cell communication to promote viral assembly and release, and inhibit immune activation [44]. Sialylation mediates the binding and transmission of the virus to host cells and acts as a protective umbrella in immune escape [45]. This study found that GM3 was the only plasma lipid inversely associated with CD4+ T cell count in COVID-19 patients. Therefore, it was speculated that GM3-rich exosomes may be involved in the pathogenesis of COVID-19 by affecting microenvironmental homeostasis. This study showed an association between GM3-enriched exosomes and COVID-19 severity, and it is expected that quantitative detection of subtle changes in GM3 could be used to diagnose and classify COVID-19. Moreover, the changes of GM3 in lower respiratory tract specimens with higher viral load can potentially be analysed by lipidomics to further reveal the significance of GM3 in the COVID-19 immune microenvironment.

Severe extrapulmonary involvement is known to be an adverse prognostic factor for increased morbidity and mortality in COVID-19 [46]. Li et al [47]. constructed a mouse model of SARS-CoV-2 infection with multi-organ injury by expressing human ACE2 and carried out multi-omics analysis. Metabolomic research showed that the serum levels of metabolites of the TCA cycle, such as citric acid, malic acid and cis-aconitic acid, were significantly decreased in the hACE2/SARS-CoV-2 group, suggesting that there may be inhibition of TCA cycle and oxidative phosphorylation in COVID-19 patients with multi-organ dysfunction, which could also affect the β -oxidation of fatty acids and lead to abnormal lipid homeostasis. These results indicate that the replication of SARS-CoV-2 is supported by metabolic reprogramming. Overmyer et al [48]. also confirmed that reduced peripheral blood citric acid levels in COVID-19 patients are associated with a dismal prognosis.

In conclusion, changes of metabolite content can objectively reflect intricate pathophysiological

mechanisms of diseases, and the potential value of metabolomics in diagnosis and prognosis merits further exploration. Multi-omics approaches enable accurate diagnosis and prognostic stratification of COVID-19, whereby deeper exploration should be concentrate on the following aspects: (1) Fully consider the differences among SARS-CoV-2 variants, the heterogeneity of COVID-19 pathogenesis and the spatiotemporal dynamic of biomarkers. Comprehensive assessment of the specific implications of genomic changes, protein expression differences and variations in metabolite levels is needed. (2) The actual predictive value of biomarkers should consider clinical issues such as age, underlying diseases and care conditions. (3) Overcoming technical bottlenecks, establishing a standardized multi-omics detection process, strictly restricting the screening criteria of multi-omics indicators, and conducting large-scale clinical trials to validate the availability and practicability.

Multi-Omics in the treatment of COVID-19

Currently, there is no international standard treatment for COVID-19. Repurposed drugs chloroquine and hydroxychloroquine, antiretrovirals such as lopinavir and ritonavir showed a certain efficacy. Remdesivir and favipiravir, which are in clinical trials, have yet to be proven [49]. Hence, the research and development of antiviral agents is still a long way from a cure. The development of multi-omics approaches has enriched the understanding of the aetiology and infectious mechanism of SARS-CoV-2, providing a theoretical basis for the novel application of older drugs in clinical treatment. More importantly, it provided valuable information to promote the exploration of specific therapeutic targets for the development of new drugs and vaccines. By detecting and validating the rich information of a given biological sample, multi-omics technology plays a considerable role in screening targets for the treatment of COVID-19, thus guiding the development of candidate drugs and accelerating the prevention of SARS-CoV-2 as well as other coronaviruses [50]. The application of NGS and reverse genetics has accelerated the development of vaccines. Reverse genetics refers to the construction of modified genomes containing essential components of the organism through site-directed mutation of the target gene, insertion, deletion and other necessary modifications according to the genetic sequence information of the organism. It is a powerful tool for studying the function of viral proteins and developing new vaccines [51]. Compared with traditional vaccine development strategies, reverse genetics has the advantages of clear dosage,

high efficiency and low toxicity [52]. Gordon et al [53]. identified 332 highly reliable virus-human protein interactions using affinity purification mass spectrometry, which was further used as a basis to identify 66 human proteins and 69 protein-targeting compounds as potential targets. Finally, two groups of drugs with antiviral activity were screened: inhibitors to mRNA translation and predicted modulators of two cell receptor proteins Sigma1/Sigma2. Reports on the repurposing of existing drugs for the treatment of the novel coronavirus can be divided into two categories. The first strategy relies on preventing the virus from binding to the host cell, targeting human receptor ACE2 enzyme, S-protein, or TMPRSS2. The second strategy aims to prevent the production of new viruses in the host cells, mostly by targeting RNA polymerase (RNA polymerase, RdRp), 3C-like protease (3-chymotrypsin-like protease, 3CLpro), or papain-like protease (papain like protease, PLpro) [54]. The following sections briefly describe these potential molecular targets and corresponding drugs.

Human angiotensin-converting enzyme 2 (ACE-2)

ACE2 is the major viral receptor of SARS-CoV-2. Sequence alignment, protein modelling and single-cell RNA sequencing showed that the helical protein binding domain of SARS-CoV-2 was different from that of its homologous SARS-CoV in several key amino acid residues. As a result, SARS-CoV-2 has a stronger affinity for human ACE2 receptor, which may explain its stronger pathogenicity. The combination ACE2 and SARS-CoV-2 activates the renin-angiotensin system (RAS) Hypothesis: angiotensin-converting enzyme inhibitors and angiotensin axis, which may damage of the heart, lungs, kidneys and other organs [4]. ACE2 inhibitors are the most commonly used medication for hypertension, but their use in the treatment of COVID-19 patients with hypertension is controversial, since ACEI or ARB may increase (or decrease) mortality in these patients [55]. Studies have shown that ACE2 inhibitors may potentially aggravate tumour progression during the treatment of COVID-19, as ACE2 is a protective factor that can promote tumour immunotherapy responses [56].

S-Protein (Spike)

Spike is the most important surface membrane protein of SARS-CoV-2, which uses it to enter human cells. Accordingly, the S protein is an important target of neutralizing antibodies and a key target for

vaccine design. Studies have shown that the extramembrane domain of the SARS-CoV-2 virus S protein has a stronger affinity for ACE2 and a 10- to 20-fold higher binding capacity than that of the first SARS virus. It was speculated that this high affinity may be why the SARS-CoV-2 virus more easily spreads from human to human, but this speculation requires more research to verify the possibility [57]. Sotrovimab is a dual SARS-CoV-2 neutralizing antibody binding to a highly conserved epitope on the S-protein's receptor binding domain (RBD), not only neutralizing SARS-CoV-1 activity but also exhibiting the ability to neutralizing the novel coronavirus and many other related viruses. The results of a Phase III COMET-ICE trial confirmed that early use of sotrovimab significantly reduced the risk of hospitalization and death in COVID-19 outpatients, and was stopped early due to the significant clinical efficacy demonstrated in the trial. The results of mid-term studies showed that patients receiving sotrovimab had an 85% reduction in death compared to placebo ($p = 0.002$), the primary end point of the trial. In the trial, the most common adverse events observed in the sotrovimab treatment group were skin rash (2%) and diarrhoea (1%), both grade 1 (mild) or grade 2 (moderate). The sotrovimab did not exhibit a higher incidence of other therapeutic adverse events than the placebo group, and sotrovimab has been authorized by the FDA (EUA) [58]. It was also shown that the SARS-CoV-2 variant carrying the D614G mutation has become the most prevalent form in the global pandemic. However, most therapeutic antibodies target the receptor-binding domain of the spike protein to measure the antibody titres. Although this structural change is not conservative, there remains a question whether it will affect the effectiveness of the therapeutic antibodies currently under development [19].

Tmprss2

Transmembrane serine protease (TMPRSS2) is a cell-surface protein that activates the coronavirus for binding to ACE2 on the host cell [59]. Camostat mesylate is a TMPRSS2 inhibitor that has been approved by the FDA for the treatment of chronic pancreatitis. Since camostat mesylate showed an inhibitory effect in cell experiments with SARS-CoV-2 infection and is expected to become a potential small molecule drug, a clinical trial of camostat mesylate for novel coronavirus infection is ongoing, but it is not clear what its eventual outcome will be [60].

RNA-Dependent RNA polymerase (RdRp)

RNA viruses rely on RNA polymerase (RdRp, also known as Nsp12) for genome replication. Its replication is mediated by the multi-subunit replication/transcription complex of the viral nonstructured protein (Nsp), whose core component is the catalytic subunit (Nsp12) of the RNA-dependent RNA polymerase (RdRp). The Nsp12 protein itself has little activity and its function requires cofactors, including Nsp7 and Nsp8, that can increase the template binding and continuous synthesis capabilities of RdRp [61]. Several clinical trials of remdesivir are ongoing, since it showed the potential to inhibit RdRp activity. Analysis of efficacy data covering nearly 100,000 patients showed a significant reduction in mortality in patients treated with remdesivir compared to the control group [62]. Trial results of remdesivir in 53 severe COVID-19 patients under compassionate use provisions showed that 36 (68%) achieved clinical improvement, and although the data were less limited, the observations of hospitalized patients treated with remdesivir were promising [63]. However, the results of a remdesivir clinical trial in China did not meet expectations [64].

3CL protease

3CL protease (3C-like protease, 3CLpro), also known as the primary protease Nsp5, can process newly-translated viral polyproteins that viral RNA was originally translated into after entering human cells. Proteases cut the polyprotein into 12 smaller proteins that will be involved in the replication of the viral RNA [65]. Rao et al [66]. used combined structure-assisted drug design, virtual drug screening, and high-throughput screening to identify new drug candidates targeting SARS-CoV-2 main protease (Mpro). The researchers first solved the crystal structure of Mpro, and then found six compounds that are potential inhibitors. Previous studies have found that the protease inhibitors lopinavir and ritonavir were effective in clinical trials, but the results of a new randomized-controlled trial showed that the drug combination of lopinavir and ritonavir worked poorly for COVID-19 inpatients [67].

Papain-Like protease (PLpro)

S-CoV2-PLpro, is a protease similar to 3CLpro that plays a role in the replication and packaging of a new generation of viruses by processing polypeptides composed of structural or non-structural proteins. In addition to its role in viral replication, it has other important functions, including the removal of ubiquitin

from host cell proteins. SCoV2-PL pro helps cut ISG15 from interferon reaction factor 3 (IRF3) and weaken the type I interferon response, which makes it a promising therapeutic target. A German team identified the naphthalene-based non-covalent inhibitor called GRL-0617 which inhibited PLpro, and found that inhibiting S CoV2-PLpro with GRL-0617 weakens the virus-induced cytopathic effect, promotes antiviral interferon pathways and reduces viral replication in infected cells [68]. Cui et al [69]. took the lead in clarifying ligand interactions of the novel coronavirus target PLpro, and solved a high-resolution 3D structure with the efficient inhibitor GRL-0617. Additionally, they also screened and evaluated the suitability of a batch of FDA approved clinical drugs potentially targeting PLpro for the treatment of SARS and MERS.

Conclusions

The integration and analysis of multi-omics data has revolutionized biology and revealed intricate interaction networks spanning different molecular levels, providing a new horizon for basic biology and disease research. Great efforts have been devoted to elucidating the correlation between multi-omics data and COVID-19 disease outcomes. A series of breakthroughs based on multi-omics methods has helped us comprehend the complexity and heterogeneity of COVID-19, as well as develop feasible diagnostic indicators and innovative agents. Here, we focused on the progress of multi-omics approaches in the study of COVID-19, especially genomics, transcriptomics, proteomics and metabolomics, in order to provide reference for the diagnosis, surveillance and clinical decision making related to COVID-19.

Highlights

- Comprehensive application of Genomics, Transcriptomic, Proteomics and Metabolomics is important in the treatment of COVID-19.
- Multi-omics analysis platforms support the diagnosis, surveillance and clinical decisions about COVID-19.
- The long-term clinical value is early detection and prevention of a COVID-10 outbreak.

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