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Review

A comprehensive review of the analysis and integration of omics data for SARS-CoV-2 and COVID-19

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Abstract

Since the first report of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in December 2019, over 100 million people have been infected by COVID-19, millions of whom have died. In the latest year, a large number of omics data have sprung up and helped researchers broadly study the sequence, chemical structure and function of SARS-CoV-2, as well as molecular abnormal mechanisms of COVID-19 patients. Though some successes have been achieved in these areas, it is necessary to analyze and mine omics data for comprehensively understanding SARS-CoV-2 and COVID-19. Hence, we reviewed the current advantages and limitations of the integration of omics data herein. Firstly, we sorted out the sequence resources and database resources of SARS-CoV-2, including protein chemical structure, potential drug information and research literature resources. Next, we collected omics data of the COVID-19 hosts, including genomics, transcriptomics, microbiology and potential drug information data. And subsequently, based on the integration of omics data, we summarized the existing data analysis methods and the related research results of COVID-19 multi-omics data in recent years. Finally, we put forward SARS-CoV-2 (COVID-19) multi-omics data integration research direction and gave a case study to mine deeper for the disease mechanisms of COVID-19.

Key words: SARS-CoV-2; COVID-19; pandemic; resources; multi-omics; integration

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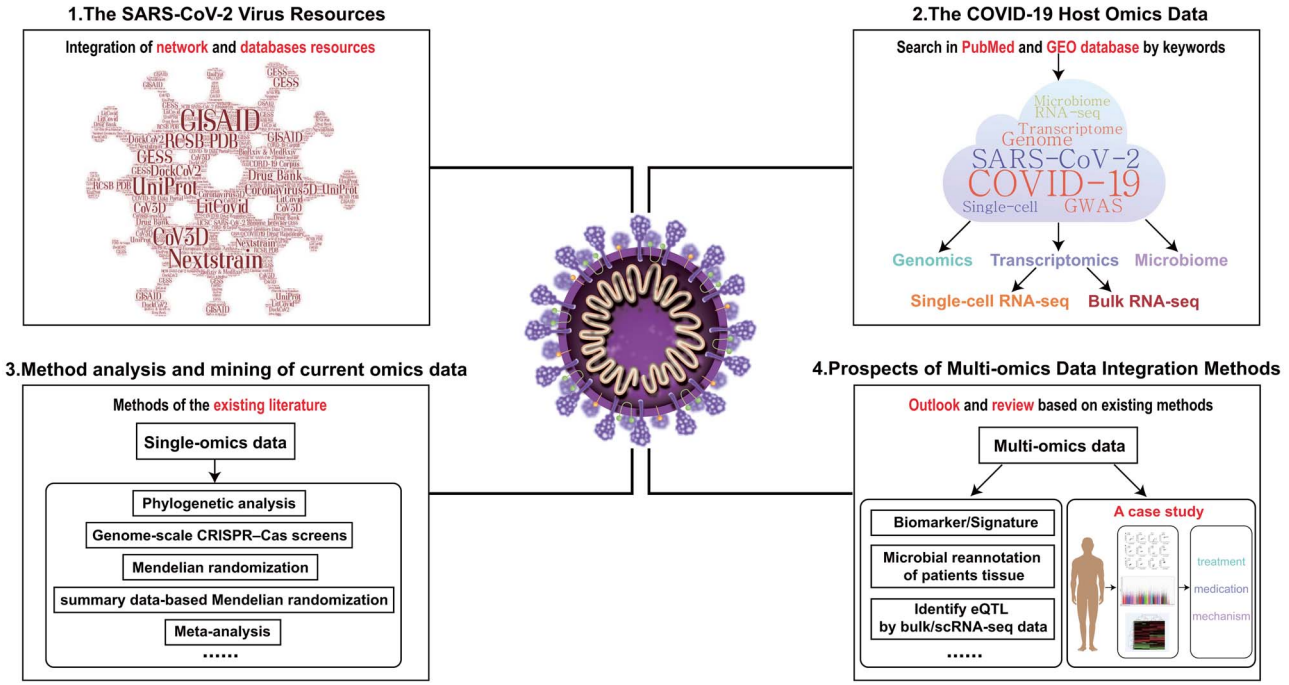

Figure 1. Graphical abstract.

Introduction

Coronaviruses (CoVs) are a highly diverse family of enveloped positive-sense single-stranded RNA viruses [1]. Severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) are two highly transmissible and pathogenic viruses that emerged in humans at the beginning of the 21st century [2], which can cause serious respiratory diseases and pose severe threats to human health. In December 2019, a case of a novel coronavirus, designated as SARS-CoV-2, was publicly reported for the first time in Wuhan, China [3]. Subsequently, it was reported worldwide and became a global pandemic disease named COVID-19, causing immeasurable harm to the world economy, human health and social order. As the third zoonotic human coronavirus of the 21st century [4–8], SARS-CoV-2 has significantly exceeded the previous two CoVs in terms of contagiousness and propagation range.

Currently, with the improvement of sequencing capability and the in-depth research on SARS-CoV-2, the omics data (genomics, transcriptomics, microbiology and potential drug information), website resources and database resources of the SARS-CoV-2 (COVID-19) have become more abundant. Due to the fast-paced nature of the pandemic and the generation of large amounts of omics data, a major challenge is not being able to integrate large amounts of data efficiently and quickly. Meanwhile, there is also still room for expansion in the research scope of omics data. The method of multi-omics data integration has the potential to gain a deeper understanding of the mechanism of COVID-19 and will be the mainstream direction of future research for SARS-CoV-2 [9].

This review briefly integrated and analyzed the existing relevant resources. Meanwhile, we conducted a more in-depth exploration of the current omics data (Figure 1). We focused on integrating multiple types of omics data as applied to research on COVID-19 and speculating about an idea for deep mining of existing multi-omics data. The purpose of this review is to make SARS-CoV-2- and COVID-19-related resources more accessible for researchers and to utilize existing resources much better.

Results

The SARS-CoV-2 virus resources

As a novel beta coronavirus, SARS-CoV-2 shares 79% genome sequence identity with SARS-CoV and 50% with MERS-CoV [10]. They all belong to the beta coronavirus genus, group 2. Since clinical cases began to appear, several teams attempted to determine the genome sequence of the causative pathogen [11]. Lu *et al*. have described the genomic structure of a seventh human coronavirus (SARS-CoV-2) and have shed light on its origin and receptor-binding properties [10]. Zhu *et al*. reported the isolation of the virus and the initial description of its specific cytopathic effects and morphology. Meanwhile, they described clinical features of pneumonia in two of these patients [12]. Wu *et al*. deposited the SARS-CoV-2 virus reference sequence in January 2020 (https://www.ncbi.nlm.nih.gov/nuccore/NC_045512) [13], which is a reference for the follow-up sequence study of SARS-CoV-2.

Functional analysis of SARS-CoV-2 sequence

The SARS-CoV-2 sequences allow us to trace the source, early spread and determine the intermediate host. Zhou *et al*. showed that 2019-nCoV was 96% identical to a bat coronavirus RaTG13 at the whole-genome level and confirmed that 2019-nCoV used the same cell entry receptor—angiotensin converting enzyme II (ACE2)—as SARS-CoV [14]. Zhang *et al*. suggested that pangolins were natural reservoirs of SARS-CoV-2-like CoVs [15]. It is essential to consider the factors driving their selection and define important mutations to understand SARS-CoV-2 variants and their risks [16]. Herein, the study of SARS-CoV-2 mutation trends in different countries and regions has become a hot research

Table 1. Prediction results of Spike protein stability of I-Mutant 3.0

Position	Reference sequence	Mutation sequence	ΔΔG	Stability prediction
439	N	K	−0.42	Neutral stability
614	D	G	−0.93	Large decrease of stability
501	N	Y	0.15	Neutral stability
484	E	K\ Q	−0.78\-0.62	Large decrease of stability
417	K	N	−0.42	Neutral stability
452	L	R	−1.85	Large decrease of stability

topic. Forster *et al*. found three central variants distinguished by amino acid changes: A, B and C, and discovered the geographical distribution of the three subtypes [17]. In addition, the replication kinetics and transmission of SARS-CoV-2 may depend on the binding affinity of spike protein to ACE2. Thomson *et al*. demonstrated that N439K spike protein had enhanced binding affinity to the human ACE2 receptor, and N439K viruses were similar *in vitro* replication fitness, causing infections with similar clinical outcomes compared to wild type [18]. Benton *et al*. observed that open conformation of the G614 spike might be responsible for the current virus' reported increased infectivity and its current predominance [19]. Hou *et al*. conducted an in-depth study on the pathogenesis and transmission ability of the D614G virus variant, finding that the D614G substitution enhanced infectivity, competitive fitness and transmission of SARS-CoV-2 in primary human cells and animal models [20] and became the dominant form circulating globally. Subsequent studies on the effects of mutations on protein functions and vaccines found that the virus variants had improved transmission capacity rather than pathogenicity [21]. Clinical data suggested that D614G alteration had no significant link with disease severity [22] and would not alter the efficacy of vaccine candidates under development currently [23, 24]. We have reached similar conclusions in previous studies [25]. In addition, N501Y contributed to increased transmission, with estimates ranging from 40 to 70% for increased transmission [26], and E484K, as well as K417N, conferred a potential immune escape to antibodies [27], which have been identified as important changes that evolved in multiple mutation lineages. Recently, a coronavirus with both E484Q and L452R mutations was discovered in India. This virus may increase infectivity and may be one of the reasons for the surge of cases in India in mid-April.

Meanwhile, three SARS-CoV-2 lineages have emerged in the UK, South Africa and Brazil. They are B.1.1.7 (501Y.V1), B.1.351 (501Y.V2) and B.1.1.28.1 (P.1), respectively. On 31 May 2021, the World Health Organization (WHO) announced that the Greek alphabet would be used to name the SARS-CoV-2 virus variant, such as the B.1.1.7 strain first discovered in the UK named 'Alpha'. In addition, the SARS-CoV-2 B.1.617 lineage was identified in October 2020 in India, which has spread to many other countries [28]. The lineage includes three main subtypes (B1.617.1, B.1.617.2 and B.1.617.3). Current research suggested that B.1.617.2, also termed the as Delta variant spread faster than other variants [29]. All these recent emergences of SARS-CoV-2 variants are causing concerns and call for several necessary protective measures [30]. Otherwise, there would be a new outbreak. The Delta variant, for example, is currently rampant worldwide, posing a huge challenge to vaccine protection and medical assistance.

Mutations in these spikes were evaluated using bioinformatics tools to analyze trends in functional changes caused by these mutations. The potential impact of these mutations on protein stability was predicted using online tools I-Mutant 3.0 [31] with support vector machines as the core algorithm. The low value of ΔΔG (<<−0.5) suggested that these mutations significantly decreased the stability of the spike protein. By comparison, the ΔΔG values of N439K, N501Y and K417N are close to zero, showing a neutral effect on protein stability (Table 1). Since the binding of ACE2 and virus spike protein affects the infectivity [32], we used PPA-Pred to evaluate the changes in the interaction caused by Spike-ACE2 binding affinity due to these mutations [33] (Table 2). The tool can analyze the change of binding affinity in dissociation free energy (ΔG) and dissociation constant (Kd), inverse ratios to protein–protein interactions and binding affinity. Except for N439K and N501Y, all the other mutations increased the binding ability and interaction of viral Spike protein to ACE2, leading to the enhancement of SARS-CoV-2 infectivity.

Integration of SARS-CoV-2 related database resources

Over time, more and more viral sequences have been produced. Therefore, we summarized the viral sequence resources (Table 3). Firstly, the GISAID is used to collect SARS-CoV-2 strains from different patients around the world. On 10 January 2020, the first virus genome and associated data were publicly shared via GISAID. As of 1 June 2021, more than 1.8 million virus strains have been deposited, submitted by laboratories across the country, including virus name, collection time, submission time, sequence length, species information, location information and laboratory information. There are multiple studies on sequence analysis supported by GISAID. In addition, several investigations assisting with these efforts are offered here, including but not limited to sequence alignments, diagnostic primers, probe coordinates, 3D protein models, drug targets and phylogenetic trees [34]. In brief, the GISAID database can provide us with a large number of high-quality data resources for sequence mutation, regional analysis and temporality analysis of virus mutation. In addition, the Nextstrain lists publicly available SARS-CoV-2 analyses that used Nextstrain from groups all over the world. The database provides the Nextclade tool to compare sequences to the SARS-CoV-2 reference sequence, assign them to clades and see where they fall on the SARS-CoV-2 tree [35]. We can see the latest global SARS-CoV-2 analysis and the geographically specific evolutionary trees of the virus. Finally, the GESS is a resource providing comprehensive analysis results based on tens of thousands of high-coverages and high-quality SARS-CoV-2 complete genomes. It allows users to browse, search and download SNVs at any single or multiple SARS-CoV-2 genomic positions, within a chosen genomic region or protein, or in a particular country/area of interest [36]. These viral sequence resources can provide us with a wealth of sequences to study.

Apart from that, we also summarized other SARS-CoV-2-related databases (Table 3). Comprehensive databases such as

Table 2. Prediction results of mutations binding affinity of PPA-Pred

Mutations	ΔG (kcal/mol)	Kd (M)	Binding affinity prediction
Reference sequence (NC_045512)	–14.36	2.96E−11	/
N439K	−14.31	3.22E−11	Decreased
D614G	−14.37	2.90E−11	Increased
N501Y	−14.26	3.48E−11	Decreased
E484K	−14.37	2.90E−11	Increased
E484Q	−14.36	2.92E−11	Increased
K417N	−14.41	2.72E−11	Increased
L452R	−14.37	2.89E−11	Increased

Table 3. Integration of resources related to SARS-CoV-2

Resources	URL	Data type
GISAID	https://www.gisaid.org/	SARS-CoV-2 Strains
Nextstrain	https://nextstrain.org/sars-cov-2/	SARS-CoV-2 Strains
GESS	https://wan-bioinfo.shinyapps.io/GESS/	SARS-CoV-2 Strains
NCBI SARS-CoV-2 Resources	https://www.ncbi.nlm.nih.gov/sars-cov-2/	SARS-CoV-2 Genome Sequencing Data
National Genomics Data Center	https://bigd.big.ac.cn/	SARS-CoV-2 Genome Sequencing Data
European Nucleotide Archive	https://www.ebi.ac.uk/ena/browser/home	SARS-CoV-2 Genome Sequencing Data
Covid-19 data portal	https://www.covid19dataportal.org/	SARS-CoV-2 Genome Sequencing Data
The UCSC SARS-CoV-2 Genome Browser	https://genome.ucsc.edu/covid19.html	SARS-CoV-2 Genome Resources
The CORD-19 corpus	https://www.semanticscholar.org/cord19	Literature about SARS-CoV-2
LitCovid	https://www.ncbi.nlm.nih.gov/research/coronavirus/	Literature about SARS-CoV-2
BioRxiv & MedRxiv	https://connect.biorxiv.org/relate/content/181	COVID-19 SARS-CoV-2 Preprints from MedRxiv and BioRxiv
Drug bank	https://go.drugbank.com/covid-19	Drug Information
DockCoV2	https://covirus.cc/drugs/	Drug Information
COVID19 Drug Repository	http://covid19.md.biu.ac.il/	Drug Information
Coronavirus3D	https://coronavirus3d.org/	chemical structure data
CoV3D	https://cov3d.ibbr.umd.edu/	chemical structure data
RCSB PDB	https://www.rcsb.org/	chemical structure data
UniProt	https://www.uniprot.org/	chemical structure data

NCBI SARS-CoV-2 resources, National Genomics Data Center, European Nucleotide Archive and COVID-19 Data Portal provide us with resources including literature, sequence and clinical resources. Literature resources, such as CORD-19 Corpus [37], LitCovid [38] and BioRxiv & MedRxiv, can provide academic articles or pre-printed journals about SARS-CoV-2 to find the latest progress in COVID-19 research. Among them, the LitCovid database puts the daily updates of COVID-19-related literature at the top for easy access by researchers. The BioRxiv & MedRxiv database is able to provide us with literature that is still under review, which can often give us important insights. Drug resources for SARS-CoV-2 such as Drug Bank [39], COVID19 Drug Repository [40] and DockCoV2 [41] provide experimental, unapproved treatments for COVID-19, potential drug targets, summary of clinical trials classified by drug, etc. The UCSC SARS-CoV-2 genome browser provides fast-tracking visualization of genome sequences and analyses apart from incorporating relevant biomedical datasets. All of these databases can give tremendous assistance for the research of SARS-CoV-2 [42]. Besides, understanding the protein chemical structure of SARS-CoV-2 is necessary for the development of structure-based therapeutics, including antibodies, antiviral compounds and vaccines. Therefore, Prates *et al.* summarized the SARS-CoV-2 proteome (reference genome NC_045512.2) and discussed the structural proteomics of SARS-CoV and SARS-CoV-2 to identify potential pathogenicity determinants [43]. Meanwhile, the Coronavirus3D [44], CoV3D [45] and RCSB PDB [46] provide researchers with COVID-19-related PDB structures, 3D visualization and analysis of SARS-CoV-2 protein structures concerning the CoV-2 mutational patterns. The UniProt provides the latest available pre-release UniProtKB data for the SARS-CoV-2 coronavirus and other viral and human entries related to the COVID-19 outbreak [47]. According to the statistics, the 2021 Nucleic Acids Research Database Issue contains 189 papers, including 7 new databases focused on COVID-19 and SARS-CoV-2 and many others offering resources for the virus studying [48]. We believe that all of the above databases provide researchers with abundant data resources, helping a lot in the fight against COVID-19.

The COVID-19 host omics data

We manually searched electronic databases, including PubMed, National Library of Medicine of the National Institutes of Health, GEO database, BioRxiv and MedRxiv preprint services operated by Cold Spring Harbor Laboratory, based on the keywords *COVID-19*, *SARS-CoV-2*, *genome*, *GWAS*, *transcriptome*, *single-cell*, *RNA-seq*, *microbiome and drug* for English-language titles and abstracts published from 1 January 2021 to 1 June 2021.

Integration of genomic data for COVID-19 patients

Studies of viral and host genetics are critical for understanding the pathophysiology of SARS-CoV-2, elucidating why

Table 4. Integration of data related to the COVID-19 host

Resources	URL	Data type
The COVID-19 Host Genetics Initiative	https://www.covid19hg.org/	Host GWAS Data
'Genomewide Association Study of Severe Covid-19 with Respiratory Failure'	www.c19-genetics.eu	Host GWAS Data
Genetic mechanisms of critical illness in COVID-19	https://genomicc.org/data	Host GWAS Data
Magellan: COVID-19 Omics Explorer	https://digital.bihealth.org/	Host Single-cell Sequencing Data
COVID-19 Cell Atlas	https://www.covid19cellatlas.org/	Host Single-cell Sequencing Data
Single cell portal	https://singlecell.broadinstitute.org/single_cell/covid19	Host Single-cell Sequencing Data
'Large-scale single-cell analysis reveals critical immune characteristics of COVID-19 patients'	http://covid19.cancer-pku.cn	Host Single-cell Sequencing Data

COVID-19 manifests differently among individuals and informing the design of new vaccines and antiviral therapeutics [49]. Therefore, we first paid attention to the genomic data of COVID-19 patients, especially the genome-wide association study (GWAS) data (Table 4), for GWAS has identified hundreds of genetic variants associated with complex human diseases and traits, providing valuable insights into their genetic architecture [50]. On 17 June 2020, an article titled 'Genomewide Association Study of Severe COVID-19 with Respiratory Failure' was published. In this work, the authors identified a gene cluster on chromosome 3 as a genetic susceptibility locus in patients with COVID-19 accompanied by respiratory failure. They also confirmed the potential involvement of the ABO blood group system [51]. Subsequent studies have shown that the risk was conferred by a genomic segment of about 50 kilobases in size, inherited from Neanderthals [52]. An article titled 'Genetic mechanisms of critical illness in COVID-19' identified and replicated new genome-wide significant associations. The authors also discovered robust genetic signals related to fundamental host antiviral defense mechanisms and mediators of inflammatory organ damage in COVID-19 [53]. Meanwhile, the COVID-19 Host Genetics Initiative was initiated to study the relationship between host genome and SARS-CoV-2 infection, aiming to explore the role of the host genome in conjunction with COVID-19 clinical and genomic variability [54]. A total of five rounds of COVID19-hg GWAS meta-analyses were registered in the web browser, including phenotype, population, total cases, total controls and data versions. This web browser will be constantly updated. The above resources allow researchers to extract the list of SNPs that may potentially modulate SARS-CoV-2 and identify genes and genetic variants (mainly SNPs) that contribute to COVID-19. Subsequently, further functional characterization and mechanism elucidation of risk SNPs and the action of the genes could be carried out. These related cohort studies provide valuable insights into probable host genetic factors influencing SARS-CoV-2 susceptibility, ACE2 expression level, pathogenicity, pathogenesis and clinical outcome.

Integration of transcriptomics data from COVID-19 patients

In addition, we also paid attention to the transcriptomics data of COVID-19 patients, consisting of single-cell RNA sequencing data and bulk RNA-sequencing data. The RNA-sequencing data has great promise and potential to enable a complete genetic map of the viruses, bacteria, host responses and even human leukocyte antigen subtypes from the sample data sources [55]. Zou *et al*. firstly made an effort in COVID-19 single-cell RNA-sequencing data mining [56]. The Magellan is a web application for displaying and analyzing next-generation sequencing data focusing on COVID-19, especially single-cell sequencing data including airway epithelium–immune cell, HBEC and lung cells. This web also supports the selection of subpopulation of cells to analyze cell types and sample distribution. The COVID-19 Cell Atlas divides the single-cell RNA sequencing data into disease donors and healthy donors for storage. Among healthy donors, the datasets are classified according to tissues/organs. The datasets from disease donors include PBMC, immunodeficiency nasal swabs, nasal epithelia, etc. [57]. The Single Cell Portal includes 48 single-cell studies relevant to COVID-19, providing us with cell numbers, literature abstracts and download links. Recently, an article titled 'Large-scale single-cell analysis reveals critical immune characteristics of COVID-19 patients' applied single-cell RNA sequencing to 284 samples from 205 COVID-19 patients to generate a large dataset including ~1.5 million single cells and controls. It created a comprehensive immune landscape, providing abundant resources for understanding the pathogenesis and designing effective therapeutic strategies for COVID-19 patients [58]. We also manually collated the single-cell RNA-sequencing datasets (Supplementary Table 1 available online at http://bib.oxfordjournals.org/) and bulk RNA-sequencing datasets (Supplementary Table 2 available online at http://bib.oxfordjournals.org/) containing the raw data from the GEO database, including lung, kidney, brain, intestine and other tissues/organs. The content of the table includes title, tissue, series accession, SRA number, platform and the size of samples. In conclusion, these data provide critical resources and essential insights in studying the mechanism of host factors.

Integration of microbiome data from COVID-19 patients

As the virus continues to be a global pandemic, accumulating evidence indicates that it can interact with the microorganisms already inhabited in the host when the virus enters the body. The interactions of the host with the microbiota are complex, numerous and bidirectional [59]. Therefore, the virus–host–microbiome interactions can yield further insights into the perturbed biological processes and their connections with disease risk factors [60]. Shen *et al*. analyzed changes in the composition of the lung microbiota in SARS-CoV-2-infected patients and found that the microbial composition of the patients and the control group were different [61]. Similarly, Fan *et al*. investigated the microbiota characteristics of the lung tissues from

deceased COVID-19 patients and found that fatal COVID-19 was associated with bacterial and fungal infections [62]. Villapol *et al*. discussed how immunomodulation could stimulate the local nasal immune response and empower the nasal microbiota to prevent SARS-CoV-2 penetration and virulence [63]. Besides, our previous work on intestinal dysbiosis of the gut microbiota in disorders and intervention certainly gave some hints about the link between SARS-CoV-2 and microorganisms [64]. We manually managed a database named gutMDdisorder, which aimed to provide a comprehensive resource for disorders and interventions in the gut microbiota. This work offers groundbreaking enlightenment for the connection between COVID-19 and microorganisms. Meanwhile, it also provides a choice about predicting roles of molecules to explore new functions of the microbiota. With development, quite a few studies have found that the gut microbiota is linked to disease severity in patients with COVID-19 [65, 66]. Zuo *et al*. and Tao *et al*. found that patients with COVID-19 had significant alterations in fecal microbiomes compared with controls, characterized by enrichment of opportunistic pathogens and depletion of beneficial commensals [67, 68]. Subsequently, Tang *et al*. demonstrated the potential correlation between intestinal bacterial populations and hematological parameters in COVID-19 patients. They also discussed the clinical significance of the correlation between changes in the significant intestinal bacteria species and COVID-19 severity [69]. Here, we summarized the data on the microorganism of SARS-CoV-2, including the gut, oral, lung and nasopharyngeal microbiome (Supplementary Table 3 available online at http://bib.oxfordjournals.org/). As in the context of COVID-19, differences in the microbiome are a neglected part of the disease. These data and the related work may help to uncover the composition of the microbiota and its metabolic products, which could determine novel microbial markers [63] for diagnosis or prognosis [70, 71] as well as patient prognosis predicting and microbiota-based therapy developing [72].

Integration of drug information from COVID-19 patients

Current research suggested that there were a large of potential approaches to pharmacologically fight with COVID-19, such as small-molecule drugs, vaccines, interferon therapies, oligonucleotides, peptides and monoclonal antibodies [73]. Considering the severity of the current epidemic, researchers are seeking to repurpose drugs that have been already approved for other diseases [74]. Remdesivir, for example, was one of the early drugs granted emergency use authorization by the US Food and Drug Administration. It shuts down viral replication by inhibiting a key viral enzyme. Several studies have demonstrated that earlier treatment with remdesivir leads to improved survival, decreased lung injury and decreased levels of viral RNA [75]. Recently, some publications have reported the potential benefit of chloroquine, a widely used antimalarial and autoimmune disease drug, in the treatment of patients infected by SARS-CoV-2 [76, 77]. Hydroxychloroquine has a similar antiviral effect to chloroquine, and researchers have tested hydroxychloroquine as a potential anti-COVID-19 drug. The experiment showed that hydroxychloroquine had antagonistic effect on SARS-COV-2 [77, 78]. Besides, favipiravir, as a purine nucleic acid analogue, has shown a better therapeutic response to COVID-19 in terms of disease progression and virus clearance [79]. And umifenovir, as an indole-based antiviral agent, has shown activity against other types of RNA and DNA viruses [80]. They are all promising antiviral drugs for reuse.

In addition, viral protein-specific monoclonal antibodies are an alternative treatment option for viral diseases. CR3022 is not only a neutralizing monoclonal antibody to SARS-CoV but also can bind to SARS-CoV-2 receptor-binding domain [81]. Recent research has found an antibody that can fight a wide range of SARS-CoV-2 variants S2H97; this could be a possible treatment option for the treatment of COVID-19 [82]. The reuse of these drugs plays a key role in the fight against the epidemic, but the adverse drug reactions may hinder the success of treatment of COVID-19 patients, which also deserves the attention of researchers. In conclusion, the integration of drug information has important implications for the fight against COVID-19. We should confirm the effectiveness of the proposed treatment in prospective trials and guide future clinical practice.

Method analysis and mining of current omics data

Given the continuous emergence of SARS-CoV-2 omics data, the previous data analysis methods can give us some inspiration, including genomics, transcriptomics and microbiomics.

Current integration of various omics data methods

Genomics is one of the most mature omics areas, focusing on identifying genetic variants associated with disease, response to treatment or future patient prognosis [83]. Phylogenetic analysis of SARS-CoV-2 strains revealed the epidemiology and multiple lineages of each country/area, such as Boston [84], northern Germany [85] and the UK [86]. Wei *et al*. and Schneider *et al*. identified host genes essential for SARS-CoV-2 infection to understand the pathogenesis and reveal novel therapeutic targets of COVID-19 by genome-wide CRISPR screens [87, 88]. Genome-scale CRISPR–Cas screens have been used to identify host factors required for virus replication, a powerful tool for probing virus–host interactions and identifying new antiviral targets [89]. Mendelian randomization (MR) is also a strategy widely applied, which utilizes genetic variants as the bridge to randomization to search for the pleiotropic/potentially causal effect of an exposure on the outcome [90, 91]. GWAS data have been used to explore the association between COVID-19 and cardiometabolic traits [92], sepsis [93], diabetes-related traits [94], etc. Meanwhile, the summary data-based MR method is used to search for genes with causal associations with certain diseases (e.g. COVID-19) by using expression quantitative trait loci (eQTL) and GWAS data [95, 96].

Transcriptomics examines RNA expression levels genome-wide both qualitatively and quantitatively [83] to study patterns of gene expression. Blanco-Melo *et al*. analyzed the transcriptional response to SARS-CoV-2 compared with other respiratory viruses by RNA-sequencing data. They proposed that reduced innate antiviral defenses coupled with exuberant inflammatory cytokine production were the defining and driving features of COVID-19 [97]. Meanwhile, some studies have also identified the immune characteristics of the respiratory tract [98], lung [99], blood [100, 101] and bronchoalveolar lavage fluid [102], highlighting the association between the pathogenesis of COVID-19 and excessive cytokine release. With single-cell RNA-sequencing data, the potential mechanisms underlying the pathogenesis of COVID-19 in tissues/organs, such as the kidney [103], bronchoalveolar [104] and blood [105], have been explored. The single-cell landscape of immunological responses in patients with COVID-19 is also a hot topic of research.

Huang *et al*. investigated the dynamic changes of blood immune response in patients with COVID-19 at different stages to reveal a dynamic landscape of human blood immune responses to SARS-CoV-2 infection [106]. Zhu *et al*. showed distinct immune response landscapes and immune response pathways of COVID-19 and influenza patients by single-cell sequencing of peripheral mononuclear cells [107]. In addition, influencing factors such as sex differences in immune responses [108], cigarette smoke and COVID-19 severity [109], the landscape in aging and COVID-19 [110], were studied in-depth by using single-cell sequencing data.

There is a growing consensus that SARS-CoV-2-induced immune abnormalities may cause infections by microorganisms [66, 111, 112], leading to several microbiome studies in COVID-19 patients. The mutual and dual interactions between microbiota and SARS-CoV-2 infections were also increasingly recognized [113]. The analysis of changes in the microbiota in COVID-19 patients may help to predict diagnosis, treatment and prognosis of COVID-19 [72, 114]. Meanwhile, the use of probiotics as adjunctive therapy in the prophylaxis and alleviation of COVID-19 symptoms is also a research direction [70, 115, 116].

Application of meta-analysis to COVID-19 omics data

Meta-analysis is a standard method for studying omics data of COVID-19, which is the quantitative and scientific synthesis of research results [117]. In recent years, meta-analysis of clinical characteristics of patients with COVID-19 was well documented [118] to identify risk factors for COVID-19 progression such as smoking [119], diabetes mellitus [120], cardiovascular metabolic diseases [121] and hypertension [122]. Multiple studies performed meta-analysis of fecal RNA from patients with COVID-19 to evaluate the prevalence of fecal SARS-CoV-2 RNA in populations of clinical characteristics, including gastrointestinal manifestations and disease severity [123, 124]. For COVID-19 genomics data, the meta-analysis of GWASs has also become a popular method for discovering genetic risk variants [125]. For example, Patrick *et al*. suggested an association between inflammatory skin conditions and higher risk of COVID-19, in which the Severe COVID-19 GWAS Group was excluded [126]. For COVID-19 transcriptomics data, for instance, Muus *et al*. assessed the cell type-specific expression of SARS-CoV-2 entry genes across 107 single-cell RNA-sequencing studies from different tissues, providing the required power to uncover age, sex and smoking associations at a single-cell resolution [127]. For microbiology data, Lansbury *et al*. found that patients in the ICU had a higher rate of bacterial co-infections than patients in mixed ward/ICU settings, and the commonest bacteria were *Mycoplasma pneumonia*, *Pseudomonas aeruginosa* and *Haemophilus influenzae* [128]. However, the proportion of bacterial co-infection was very low in mild COVID-19 patients [129, 130]. In conclusion, the meta-analysis provides researchers with a better understanding of the COVID-19 using current data.

Prospects of multi-omics data integration methods

The omics-based data can provide novel insights into COVID-19, a pandemic that has brought multi-omics studies' utility [131]. The multi-omics data integration approaches will help the fight against the epidemic and promote a better understanding of its mechanisms. Here, we reviewed some omics data methods from the existing literature and looked forward to the prospect of multi-omics data.

A summary of the application prospect of multi-omics data

The biomarkers of COVID-19 patients provide valuable resources for understanding the molecular mechanisms of host response and clinical guidance [132]. Bernardes *et al*. determined that the increase of proliferating, metabolically hyperactive plasmablasts is a feature of severe COVID-19 by longitudinal multi-omics data [133]. Chen *et al*. combined transcriptomics, proteomics and metabolomics to identify molecular markers to identify essential genes, proteins and exRNAs as potential biomarkers [134]. In addition, multiple studies have reported biomarkers that are highly associated with disease severity and progression of COVID-19, providing potential therapeutic targets and strategies [135–137].

It has been previously reported that a variety of bacteria exist in tumors [138–140]. Recently, Poore *et al*. proposed a new class of microbial-based diagnostics based on blood and tissue RNA sequencing data [141]. Next, Chen *et al*. presented a computational toolset and related resources that can quickly identify viruses and microorganisms from sequencing data [142]. Meanwhile, the gut microbiome has been determined to have multiple effects on biology, including the transformation process, progression and response therapies [143]. SARS-CoV-2 can cause gastrointestinal symptoms in the early stages of the disease [63], and bacterial and fungal infections are common complications of viral pneumonia [144]. Some studies have also revealed that lung microbiota is altered and correlated in critically ill patients [145, 146]. Therefore, we hypothesized that the microbiome in the tissues of COVID-19 patients may also change. This view requires multi-omics analyses of tissue and blood sample data from COVID-19 patients. The above content is a further expansion of the existing data (Figure 2A).

The studies of eQTL can explain the regulatory mechanisms and illuminate the genetics of gene expression [147]. Several studies have developed various methods and pipelines to identify eQTL landscapes using RNA-sequencing data or single-cell RNA-sequencing data. For example, Gillies *et al*. described the eQTL landscape in these functionally distinct kidney structures by individuals with nephrotic syndrome [148]. Zhernakova *et al*. systematically identified context-dependent eQTL using a hypothesis-free strategy in whole blood [149]. Recently, Deelen *et al*. constructed an approach to identify genetic variants that affect gene-expression levels by invoking genotypes from public RNA sequencing data [150]. Meanwhile, Van der Wijst *et al*. identified cell type-specific cis-eQTLs and co-expression QTLs to identify genetic variants that could affect regulatory networks using single-cell RNA-sequencing data [151]. Compared with RNA-seq data, single-cell sequencing data can be more precise by observing specific cells' regulatory relationships [152]. We speculated that in the context of COVID-19, the eQTL landscapes generated from bulk RNA-sequencing data or single-cell RNA-sequencing data have great potential to provide insights into disease mechanisms. Apart from that, we can also build a database such as GTEx [153] and study the genetic mechanisms of tissues in disease states (Figure 2B).

In addition, we have noticed that multi-omics data studies for COVID-19 have emerged over the past years. Therefore, we systematically integrated these articles from COVID-19 multi-omics studies in this section. For example, Su *et al*. conducted a comprehensive analysis of the clinical measurements, immune cells and plasma multi-omics data from COVID-19 patients representing all levels of disease severity [154]. They identified a major shift between mild and moderate disease. Meanwhile,

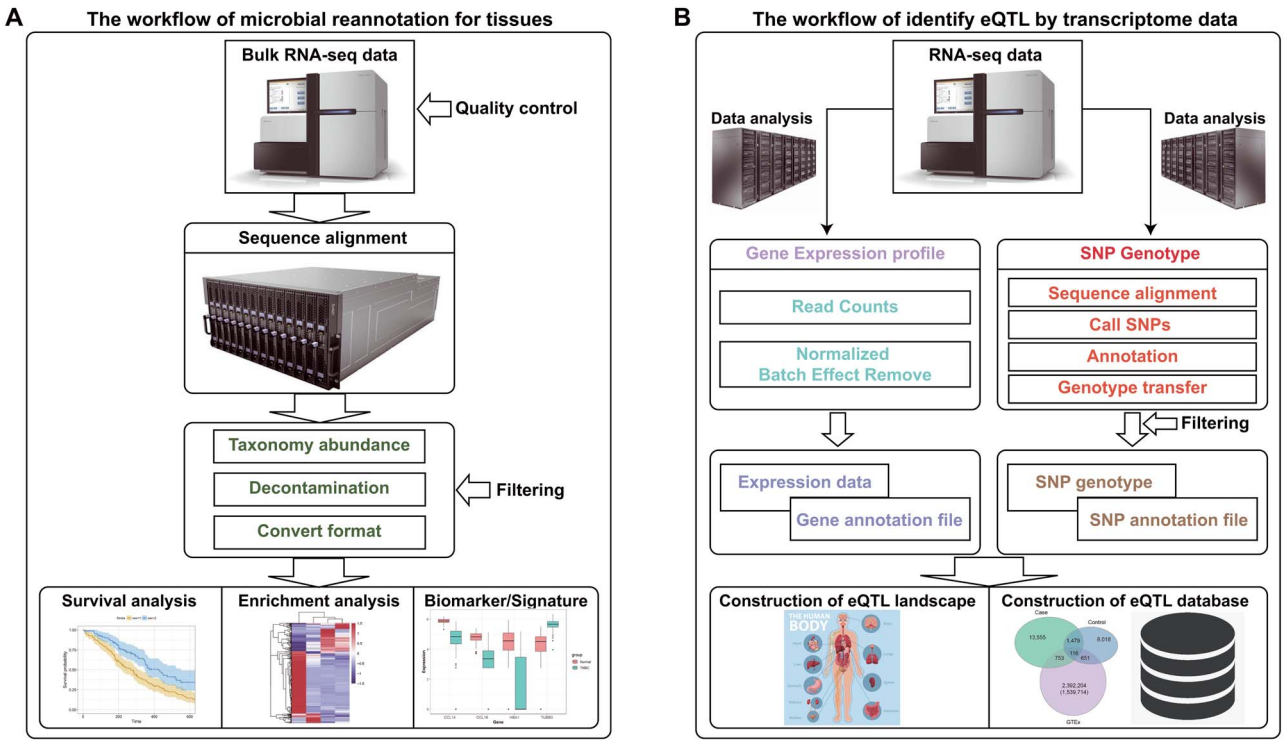

Figure 2. Microbial reannotation and identification eQTL workflow.

they also demonstrated that moderate disease may provide the most effective environment for therapeutic intervention. This work could be valuable in terms of interventions for COVID-19. Besides, using interactome, proteome, transcriptome and bibliome data, Barh *et al.* presented the biological events associated with SARS-CoV-2 infection and identified several candidate drugs against COVID-19 [155]. On the other hand, Singh *et al.* argued that the multi-omics approaches offered various tools and strategies for identifying potential therapeutic biomolecules for COVID-19, and they explored the available multi-omics approaches [156]. In addition, Stephenson *et al.* also used a multi-omics data approach of single-cell transcriptome, surface proteome, and T and B lymphocyte antigen receptor analysis, highlighting the coordinated immune response that contributes to the pathogenesis of COVID-19 and revealing discrete cellular components that can be targeted for treatment [157].

In general, the methods of multi-omics data analysis are critical for researchers to better understand the underlying pathogenesis of COVID-19 and potential therapeutic strategies. Meanwhile, we can also observe that multi-omics data analysis will contribute to the fight against COVID-19.

Practical application of multi-omics data: a case study

Recently, Kang *et al.* determined an effective method of the fatal inflammatory response [Cytokine release syndrome (CRS)] that has been overactivated in patients with severe COVID-19 [158]. They investigated 91 CRS patients with sepsis, acute respiratory distress syndrome (ARDS) or burns. They found that the expression of IL-6, IL-8, IL-10 and MCP-1 increased and are positively correlated with the expression of plasminogen activator inhibitor-1 (PAI-1, also known as SERPINE1, related to the more severe pneumonia, which is a common cause of death in COVID-19 patients [159, 160]). Finally, they found tocilizumab, a human monoclonal antibody, can block IL-6 signal transduction to reduce the expression of SERPINE1, which was helpful in the treatment of severe respiratory complications in CRS and COVID-19. However, they did not explore other important cytokines and serpin family genes.

For the study of Kang *et al.*, multi-omics analysis can get more comprehensive results. Therefore, we investigated the expression of other vital cytokines and serpin family genes using single-cell RNA-sequencing data (Supplementary Table 1 available online at http://bib.oxfordjournals.org/) as a case study [161]. These data profiled 44 721 peripheral blood mononuclear cells from seven COVID-19 patients (2 Asian, 1 Black, 2 Hispanic/Latino, 2 White, aged from 20 to 80, and 4 of 7 had ARDS) and six healthy controls (5 White, 1 Asian, aged from 36 to 49). We found significantly different expressions of other important cytokines (IL32, IL7R, IL2RB, IL6ST, IL17RA, IL4R, IL-8, IL6R, ILF3, IL13RA1, IL10RA) and serpin family genes (SERPINA1, SERPINB1, SERPINF1, SERPINB10, SERPING1) in multiple immune cell types (Table 5), which were defined by know cell type-specific gene markers [161]. Among these inflammatory cytokines, the significant increase of IL-8 in plasma samples of COVID-19 patients has been reported several times. In contrast, Kang *et al.* found an increasing trend but fail to reach statistical significance [3, 162]. Serum IL-17RA was also increased significantly in COVID-19 patients with low severity [163]. In addition, IL-6R has been deemed as a critical target for treating COVID-19 patients [164]. Among these serpin family genes, serum levels of SERPINA1 and SERPING1 [165] significantly increase in COVID-19 patients [165, 166]. The SERPINB1 plays an essential role in regulating innate immune response [167], inflammation and cellular homeostasis, which is highly consistent with Kang *et al.*'s conclusion.

In addition, Kang *et al.* did not investigate the associations between COVID-19 and these cytokines, which prompted us to

Table 5. Differentially expressed cytokines and serpin family genes in immune cell types

Gene	P_value	avg_logFC	Cell type
IL32	0	0.39116507	CD8m T
IL7R	2.076E−168	0.58233013	CD8m T
IL2RB	2.1665E−94	0.27327977	CD8m T
IL32	7.5077E−66	0.27681885	CD8m T
IL7R	0	1.24712557	CD4m T
IL32	0	0.36835828	CD4m T
IL6ST	2.784E−199	0.25042649	CD4m T
IL17RA	0	0.47849297	CD14 monocyte
IL7R	0	0.69516049	CD4n T
IL6ST	0	0.45541719	CD4n T
IL4R	4.318E−206	0.39605514	B cell
IL17RA	2.273E−297	0.3208715	CD14 monocyte
IL-8	3.603E−241	0.26306012	CD14 monocyte
IL-8	0	0.56951826	CD14 monocyte
IL17RA	2.929E−287	0.33161521	CD14 monocyte
IL17RA	0	0.59001037	CD14 monocyte
IL-8	0	0.41184786	CD14 monocyte
IL6R	2.874E−167	0.28400176	CD14 monocyte
IL2RB	1.578E−130	0.34297959	Natural killer cell
IL32	2.9642E−77	0.26221845	Natural killer cell
IL2RB	0	0.81123381	Natural killer cell
IL32	3.8326E−98	0.38554833	Proliferative lymphocytes
ILF3	4.8531E−46	0.25042985	Proliferative lymphocytes
IL6ST	4.5439E−49	0.41042519	Platelet
IL6ST	1.5327E−69	0.41731725	IFN-stim CD4 T
IL13RA1	1.342E−278	0.47076776	Dendritic cell
IL6R	3.4988E−98	0.38272268	Dendritic cell
IL7R	0	1.52928531	gd T cell
IL32	3.3531E−78	0.37223253	gd T cell
IL10RA	7.4066E−13	0.3224205	CD16 monocyte
SERPINA1	0	0.89156779	CD14 monocyte
SERPINB1	0	0.68221653	CD14 monocyte
SERPINB1	3.8282E−39	0.5163943	SC & eosinophil
SERPINA1	1.0565E−51	0.42889468	Neutrophil
SERPINB1	1.2303E−31	0.40771692	Neutrophil
SERPINF1	0	1.10146911	pDC
SERPINB10	0	0.36560529	Developing neutrophil
SERPINB1	4.8577E−71	0.74696649	Developing neutrophil
SERPING1	2.137E−109	0.44113965	CD16 monocyte
SERPINA1	0	0.83001985	CD16 monocyte

investigate their observations further [168]. Therefore, we used two sets of GWAS data (summarized data of severe COVID-19 accessed from a GWAS of 1610 severe patients and 2205 controls in Italian and Spanish (Table 4) [51]. Summarized data of circulating cytokines were obtained from a GWAS on 8293 Finnish individuals [169]) for multi-omics data analysis. We used genetic instrumental variables to explore the risk of COVID-19 on the cytokines level by two-sample MR analysis [170], which has been applied for identifying the risk factors of COVID-19 [93].

This case study found several differentially expressed cytokines and serpin family genes between COVID-19 patients and healthy controls in multiple immune cell types. Among these genes, serum levels of IL-8, IL-17RA, SERPINA1 and SERPING1 have been reported to be related to the CRS and COVID-19. Meanwhile, we determined that COVID-19 can reduce the levels of IL-8, IL-10 and MCP-1. In general, we used multi-omics data to further explore the relevant mechanisms of CRS in patients with severe COVID-19 and provide a more comprehensive supplement to the work of Kang *et al*.

Discussion

Since the COVID-19 pandemic outbroke in December 2019, more than 180 million people worldwide have been infected. It spread across all continents (https://covid19.who.int/) and has emerged as a public health threat. Thus, COVID-19 was declared a pandemic by the WHO in March 2020 [171]. COVID-19 has significant impacts on the global economic infrastructures, social governance and cultural development. However, there are several vaccines and effective COVID-19-specific pharmaceutical interventions in clinical use. Over time, the omics data resources of SARS-CoV-2 will undoubtedly increase substantially. How to use existing resources to further deepen the expansion of current data is a question worthy of discussion.

In addition, the challenge of how to fully exploit COVID-19-related omics data and bring all of these findings and approaches together to make clinical transformation lies ahead [172]. Therefore, this review collated various network resources, host genomics data, transcriptomics data, microbiome data and drug information. We hope that the integration of these

resources will facilitate researchers in data extraction and SARS-CoV-2 (COVID-19) analysis. Meanwhile, we reviewed the current approach to the study of omics data in the hope of providing new insights into the extension of existing research. Finally, we focused on the integration of multi-omics data for COVID-19 hosts and presented an analysis case. Currently, there are various tools and methods publicly available for the integration of multi-omics datasets of SARS-CoV-2 (COVID-19) to derive meaningful insights. The multi-omics methods are used to resolve urgent questions such as immune suppression in the early stage of COVID-19 disease [173], inter-patient and intra-patient heterogeneity of pulmonary virus infection [174], virus–host interactions [175] and host response [176]. These problems are indicators for severity diagnosis and therapeutic target [177]. Meanwhile, there is also a challenge of integrating current and future SARS-CoV-2 related data more efficiently and standardly, which would greatly facilitate the struggle against this new pathogen [178].

With the rapid evolution and transmission of SARS-CoV-2, the COVID-19 epidemic has become a clinical threat facing ordinary people and medical staff worldwide. To be sure, COVID-19 will not be eradicated in a short period and may become a long-term epidemic that co-exists with humans [179, 180]. The omics data research of SARS-CoV-2 (COVID-19) still has a long way to go before an effective antiviral therapy can be developed and vaccinations can be administered universally. There is no doubt that the integration of multi-omics data has unparalleled advantages in the fight against COVID-19 [181].

Consent for publication

Not applicable.

Key Points

- Comprehensive summary of SARS-CoV-2 (COVID-19) omics data.
- Review of current omics data methods.
- Analysis of the integration direction of multi-omics data.
- Integration and practical application of SARS-CoV-2 (COVID-19) multi-omics data prospects.

Supplementary data

Supplementary data are available online at https://academic.oup.com/bib.

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