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Application of Omics and Bioinformatics Technologies in Response to COVID-19 Pandemic

Abebe Mengesha Aga[1,2], Adugna Abdi Woldesemayat[2]

[1]*Armauer Hansen Research Institute, Addis Ababa, Ethiopia*
[2]*Addis Ababa Science and Technology University, Department of Biotechnology, Addis Ababa, Ethiopia*

The medical biotechnology community has undertaken significant endeavors to gain a comprehensive understanding of SARS-CoV-2's biology and pathogenesis mechanisms. Omics approaches and technologies have been widely employed in the fight against SARS-CoV-2. Since the onset of the virus outbreak, researchers have demonstrated how recent omics and bioinformatics technological advancements have contributed to the diagnosis, vaccine development, treatment, and control of disease transmission. Studies conducted since the outbreak have been collected and summarized, with a focus on bioinformatics approaches and their contribution to controlling this pandemic. Developments and advanced omics technology in connection to the COVID-19 pandemic have been analyzed. The multi-omics technology, which offers various strategies in identifying potential diagnostics, therapeutics, studies of variants of concern, and drug repurposing approaches, has been assessed. Pandemic response has seen the application of multi-omics and pan-genomics approaches, including genomics, metabolomics, transcriptomics, proteomics, epigenomics, clustered regularly interspaced short palindromic repeats (CRISPR) technology, host-pathogen interactions, artificial intelligence, and machine learning in various research areas. Additionally, bioinformatics and mathematical modeling have played a significant role in disease control. The use of smart technologies to control virus transmission and predict patients' health conditions and treatment outcomes has also been crucial. Transcriptome analysis has emerged as a major application, contributing to the generation of new knowledge on viral sequences and intracellular signaling pathways that regulate viral infection and pathogenesis mechanisms. The sequencing of the virus has paved the way for the use of omics technologies and an integrative technique in combating the pandemic. In general, the advancement of omics technology during this pandemic has been fascinating and has contributed a significant role to the science of health biotechnology in general and omics and bioinformatics in particular.

Keywords*: bioinformatics, coronavirus, COVID-19, omics, SARS COV-2*

Introduction

Coronaviruses are an assemblage of sizable, enveloped viruses that possess single-stranded, positive-sense ribonucleic acid (RNA). These viruses have the potential to induce a variety of respiratory illnesses in humans, ranging from mild common colds to severe acute respiratory syndrome (SARS).[1] There exist four genera of

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Corresponding Author:
Abebe Mengesha Aga
Armauer Hansen Research Institute, ALERT Compund Zenebework
Jimma Road, Addis Ababa 1005, Ethiopia
e-mail: agagurmu@yahoo.com

Cell and Biopharmaceutical Institute

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coronaviruses, with beta-CoV comprising five sub-genuses, namely embevovirus, sarbecovirus (which encompasses SARS-CoV), merbecovirus (which includes MERS-CoV), nobecovirus, and hibecovirus. SARS-CoV-2 has been classified as a member of the beta coronavirus family, belonging to the same species as SARS-CoV and MERS-CoV.[2] As coronaviruses can infect a variety of animals, SARS-CoV and MERS-CoV show the potential to cross species barriers.

The characterization of the SARS-CoV-2 spike protein reveals that it initially attaches to the receptor ACE2 of SARS-CoV and is expressed in both the upper and lower respiratory tracts of humans before developing in lung as the disease progresses. Unlike other currently recognized coronaviruses, which cause mild upper respiratory tract infections and only rarely pneumonia in elders, neonates, and immune-compromised patients, SARS-CoV-2 causes severe lower respiratory tract illness that leads to pneumonia.[3,4] The disease caused by the SARS-CoV-2 virus is still affecting the world population.[1,2] The transmission patterns of the SARS-CoV-2 virus suggest that it has a high propensity for person-to-person transmission and may exhibit greater transmissibility than its predecessor, SARS-CoV.[5]

Direct RNA sequencing, coupled with a high-resolution map of the SARS-CoV-2 utilizing sequencing-by-synthesis (SBS) and transcriptome analysis, has the capacity to generate RNAs encoding unknown open reading frames (ORFs) and at least 41 potential RNA modification sites.[6] This study underscores the significance of transcriptomics as a valuable tool in the study of SARS-CoV-2, enabling the identification of new therapeutic targets and the generation of pertinent information related to the viral genome. The Global Initiative on Sharing All Influenza Data (GISAID) has played a significant role in this case by submitting over 12.2 million SARS-CoV-2 genomes. Additionally, public information has supported the development of genomic analysis tools, vaccines, and diagnostic tests for epidemiological surveillance of the virus. These efforts have been documented in various studies.[2,6-8] This procedure is designed to oversee the emergence of novel virus variants of significance and facilitate the investigation of viral evolution and dissemination throughout the pandemic era.

The initiation of SARS-CoV-2 infection occurs through the binding of the virus to the angiotensin-converting enzyme 2 (ACE2) receptor on the host cell. The identification of the expression pattern of this receptor across various cells and tissues has been a subject of interest, as evidenced by recent studies.[3,9,10] This virus-host interaction prompts a cascade of biological events, which includes the formation of vesicles, enzyme activation/repression, host molecule recruitment, and synthesis of viral components. Integrated multi-omics studies provide an unbiased approach to investigating the host-virus interaction, which is the basis for diagnostic, therapeutic, and vaccine development.[11,12]

Approach in COVID-19 pandemic response

The utilization of emerging omics technologies has played a significant role in comprehending the COVID-19 disease and has aided in facilitating the pandemic response. The pivotal roles of omics-based analysis in COVID-19 disease have contributed to providing comprehensive insights into various aspects of the disease. Figure 1 provides an overview of the omics and bioinformatics approach in response to the COVID-19 pandemic.

Omics-based technologies, including genomics, transcriptomics, proteomics, and metabolomics, have played a crucial role in addressing the challenges presented by the COVID-19 pandemic. The rapid sequencing of the SARS-CoV-2 genome has allowed for the swift development of diagnostic tools and has informed research on the virus's structure and origin. Additionally, transcriptomic studies have provided valuable insights into the host's response to the virus and the interactions between the virus and human cells. Proteomic investigations have led to the identification of potential therapeutic targets and biomarkers associated

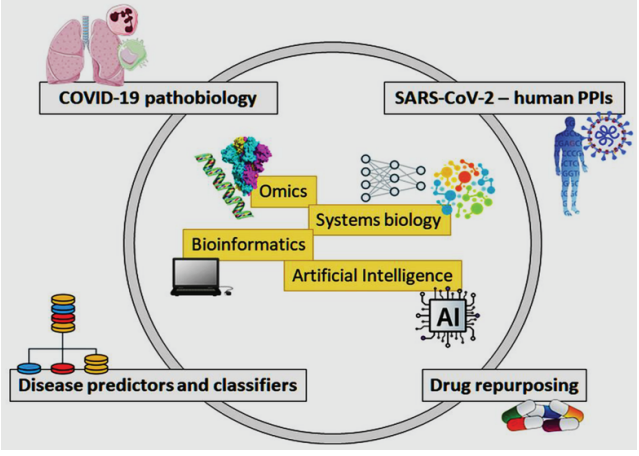

Figure 1. Omics-based technologies application to COVID-19 pandemic response.[13] (Adapted from MDPI).

with disease severity. Furthermore, metabolomics has shed light on the metabolic changes occurring in affected patients, offering further insights for potential therapeutic approaches. Integrated multi-omics analyses, supported by advanced bioinformatics, have provided a comprehensive understanding of the virus's impact on human physiology, guiding the development of interventions and treatments.

Application in COVID-19 diagnosis

In contrast to proteomics, the utilization of lipids as a pretreatment method for samples is a direct and remarkably sensitive approach for detecting SARS-CoV-2 infection and assessing the severity of COVID-19. One study demonstrated this, revealing a positive correlation between triglycerides and free fatty acids and the severity of COVID-19 in an untargeted metabolomics investigation of COVID-19 plasma.[13] Further examined alterations in triglyceride structure in individuals with diverse severity profiles and identified multiple triglycerides that accurately discriminate severe COVID-19 disease states.[14]

The development of a sensitive and focused detection tool is crucial for controlling the transmission of SARS-CoV-2 and providing prompt treatment to halt potential illness progression.[15] While reverse transcription polymerase chain reaction (RT-PCR) is currently the gold standard for SARS-CoV-2 diagnosis, its accuracy is impacted by various factors, and it may not detect viruses in some samples. Enzyme-linked immunosorbent tests are frequently used for SARS-CoV-2 detection, but they may take up to three weeks to produce antibodies against the viral particle.

Proteomic methodologies utilizing mass spectrometry have emerged as a promising adjunctive technique for the diagnosis of COVID-19. Through targeted proteomic screening, potential viral peptide targets for SARS-CoV-2 detection have been identified, and a protein-based microarray has been developed to enable high throughput assessment of proteome-wide antibody responses. Mass spectrometry also has been employed to directly detect viral peptides or proteins in nasopharyngeal epithelial swabs, respiratory tract samples, and gargle solutions with exceptional sensitivity.[16,17] These approaches offer quick and sensitive diagnostic testing for SARS-CoV-2 infection.

Application in vaccine development

The past decade has seen advances in biotechnology and computational analysis, which have produced vast amounts of new data and given hope for accelerating prophylaxis, therapeutics, and diagnostics developments for particular diseases.[18,19] With the aid of omics and bioinformatics technology, virtually every illness and clinical study area has seen an explosion in the amount of data generated. Several vaccines have been developed to control COVID-19 rapid transmission.[20,21] An in-depth understanding of the molecular mechanisms and related transitions of the COVID-19 disorders is provided by computational analysis of the varied omics data that is currently accessible.[22] Significant advancements have been made in the field of extracting patterns from extensive data sets through the utilization of clinical data management, genome and proteome analysis, next-generation sequencing data mining, as well as machine learning and deep learning algorithms.[23,24]

The omics technology provides the collective techniques that aid in examining the many molecules' functions and roles in the cells that make up an organism. Genomic, transcriptomic, proteomic, and metabolomic studies fall under this category. These methods play a big part in developing vaccines and reusing medicines. The primary use of omics technologies is to identify and validate all gene products present in a particular biological sample. Omics analysis has been heavily used in drug discovery and evaluation of their efficacy and toxicity. These high-throughput technologies have been helpful in describing gene/protein expression profiles and their intricate relationships to available SARS-CoV-2 therapy choices.[25,26] The powerful omics approaches seem to be helping researchers and medical professionals further grasp SARS-CoV-2 pathophysiology for a better knowledge of disease processes and diagnosis because of its enormous potential.[27]

In order to determine biomarkers indicative of vaccine effectiveness and tolerability, evaluate and track the dynamics of COVID-19 cases, manage genomic surveillance, and understand cellular transcriptomics responses, omics technologies must be applied to vaccinations. The investigation of many human and viral factors is necessary for the personalized and prescriptive vaccination. The use of multi-omics-based techniques, which combine data from genomes, proteomics, metabolomics, and metagenomics with artificial intelligence and machine learning models, is linked to the development of a universal vaccination (Figure 2).[28] This will be resolved once we are able to recognize and track SARS-CoV-2 mutations, find novel viral variations, comprehend the genetic make-up of the individual, and

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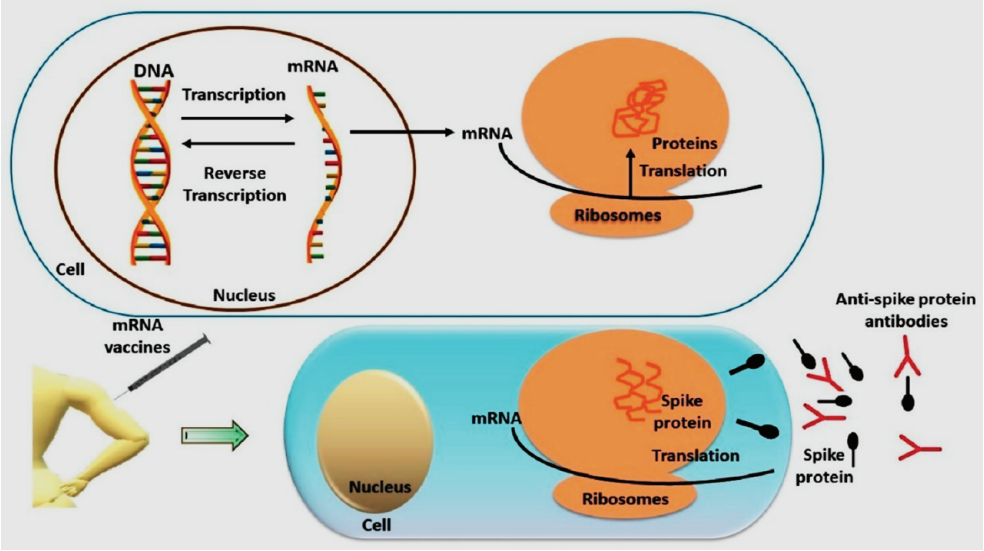

Figure 2. mRNA-based COVID-19 vaccine development process.[29] (Adapted from MDPI).

comprehend the molecular host response to vaccination.[29,30] In addition, new omics and bioinformatics techniques are used to study vaccine immunogenicity, efficacy, and safety.

Application in SARS-COV-2 variant study

According to many studies, compared to the mutations observed in influenza and HIV, the typical SARS-CoV-2 virus undergoes a relatively modest accumulation of one to two single nucleotide mutations in its genome per month.[1] Contrary to most RNA viruses, coronaviruses have a novel exoribonuclease (ExoN) encoded in their genomes, suggesting that many errors are corrected during replication.[30-32] This is thought to be the reason why SARS-CoV-2 appears to be mutating more slowly.

Due to its high infection rate, SARS-CoV-2 is known to have a high mutation rate.[33] When compared to a reference sequence of the virus isolated from Wuhan or a sequence found from the USA during 2020 isolated from the initial outbreak, a mutation of the SARS-CoV-2 virus is a change in the genetic sequence.[26] A study revealed that a 655Y spike polymorphism in the gamma and omicron current variation of concern is a crucial factor in the transmission of the SARS-CoV-2 virus and the sickness itself.[34] Through an increased cleavage of the S protein, animal models show that mutation is linked to an improvement in viral adaptability to a variety of hosts.[35,36] Using omics data from many sources, problems like forecasting patient outcomes and finding new biological targets can be addressed.

The rapid and unexpected emergence of the COVID-19 pandemic has sparked an unprecedented race to comprehend, combat, and manage the spread of the SARS-CoV-2 virus. This challenge extends beyond traditional diagnostics and treatment, infiltrating the realm of high-resolution molecular investigations. In this pursuit, the potential of multi-omics approaches has been swiftly acknowledged and harnessed. By combining genomics, proteomics, transcriptomics, metabolomics, and other omics disciplines, a more comprehensive understanding of viral pathogenesis, host-virus interactions, and downstream effects has been achieved. Researchers explore how the integration of multi-omics-based molecular strategies has strengthened the global response to the COVID-19 pandemic as summarized in Figure 3.

To investigate the complex characteristics of SARS-CoV-2 from various perspectives, a high-throughput omics technology technique will be helpful. Thus, multi-omics and subsequent integrated analyses offer a chance to comprehend SARS-CoV-2, providing a thorough comprehension of pathophysiological heterogeneity in COVID-19 patients. A multi-omics strategy to study applications in investigating mutations, host responses, infectious biology, transmission traits, and candidate drug development.

Another study report states that the D614G mutation of virus types from the Republic of South Africa, Britain, Northern Ireland, Denmark, and has sparked interest and concern over the impact of viral modifications leading to various pathogenic outcomes. The initial SARS-CoV-2 strain discovered in China was replaced by this D614G mutation caused by a change in the gene encoding the spike protein in late January 2020.[35,37,38] The virus now propagating around the world is mostly this mutant type. Studies on human

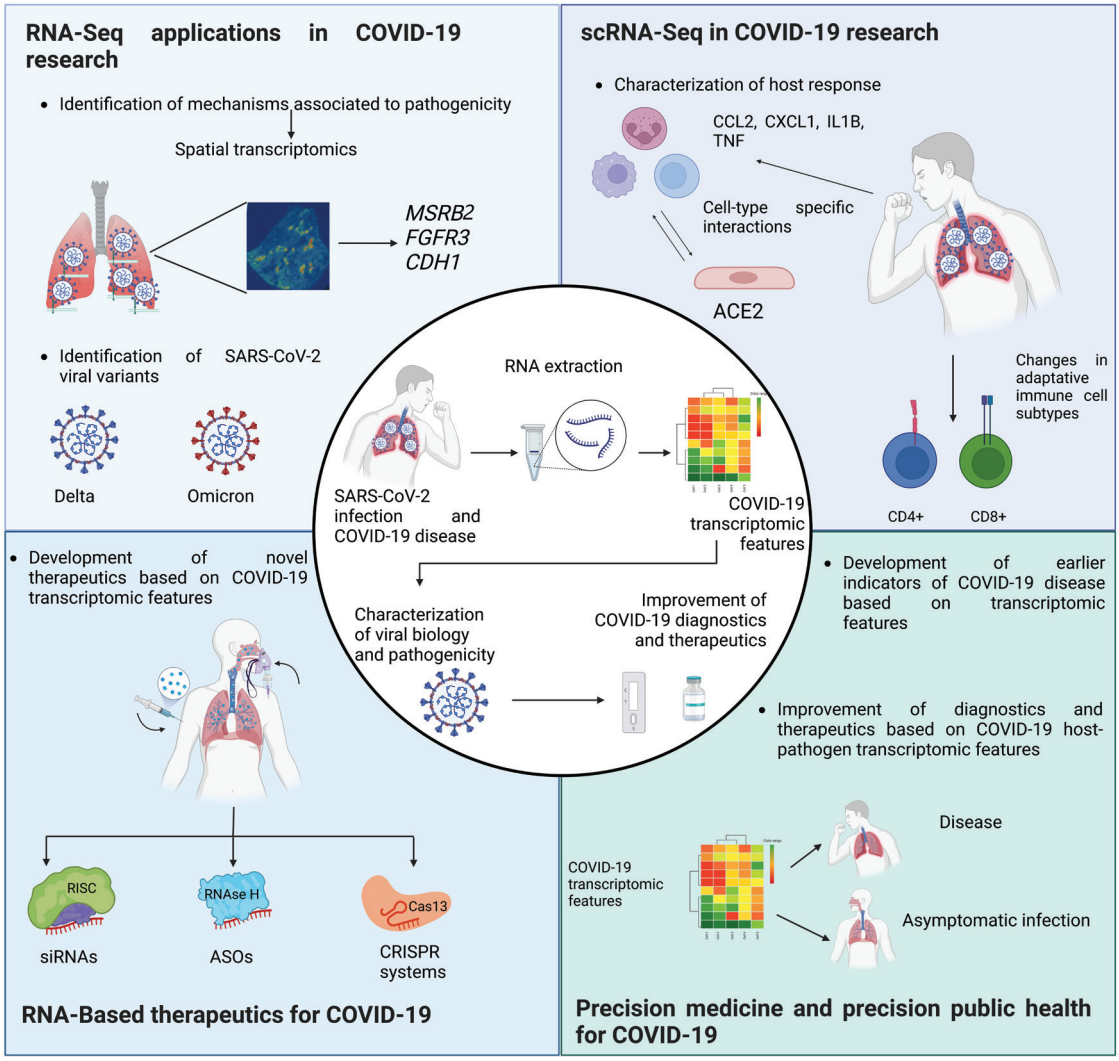

Figure 3. Applications of the multi-omics integration-based molecular approaches.[6] (Adapted from MDPI).

respiratory cells and in animals have shown that the virus strain with the D614G substitution considerably increases the virus's ability to infect and spread when compared to the original virus strain.[35]

The multiomics approach is employed to obtain a more comprehensive analysis of the pathogenesis mechanism in patients by integrating data from various 'omics' sources, including genomics, transcriptomics, proteomics, metabolomics, and others. By simultaneously analyzing datasets from these diverse sources, researchers strive to attain a more thorough comprehension of the biological systems under investigation. The combination of these multiple layers of molecular data facilitates a clearer and more exhaustive depiction of the intricate interactions taking place within cells and tissues.

Transcriptomics

In contrast to proteomics, the pre-treatment of samples with lipids represents a straightforward and highly effective approach for the detection of SARS-CoV-2 infection and the assessment of COVID-19 severity.[14] Recent untargeted metabolomics studies have demonstrated a positive association between triglycerides and free fatty acids and the severity of COVID-19. Furthermore, specific triglycerides have been identified as precise discriminators of severe disease states.[15]

In light of the pressing requirement for precise and targeted detection methodologies to manage the spread of SARS-CoV-2, timely diagnosis is imperative for timely intervention and prevention of disease progression. Although RT-PCR continues to be the benchmark for SARS-

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CoV-2 diagnosis, its efficacy is influenced by multiple factors and may not identify viruses in specific samples, such as urine. Enzyme-linked immunosorbent assays are commonly employed for SARS-CoV-2 detection, but they may necessitate up to three weeks to generate antibodies against the viral particle.

At present, proteomic methodologies utilizing mass spectrometry are being employed for diagnostic testing of SARS-CoV-2. Targeted proteomic screening is utilized to identify potential viral peptide targets for detection. Additionally, a protein-based microarray has been developed to expedite the discovery of potential diagnostic and therapeutic targets for COVID-19. Mass spectrometry has exhibited exceptional sensitivity in detecting the SARS-CoV-2 N protein in diverse samples, including nasopharyngeal epithelial swabs, respiratory tract samples, and gargle solutions.[17,18] Thus, proteomics has emerged as a promising supplementary diagnostic method for COVID-19, offering a direct means of identifying viral peptides or proteins.

Single-Cell Transcriptomics Study

In light of the past global pandemic, single-cell RNA sequencing (scRNAseq) has emerged as a valuable tool for gaining a deeper understanding of COVID-19 infection. Research has demonstrated that the scRNAseq technique is capable of identifying complex and rare cell populations, uncovering regulatory connections between genes, and tracking the progression of numerous cell lineages.[39-41] Recent advancements in spatial approaches have enabled the combination of spatial position of transcriptomic data proof with cellular barcodes, resulting in enhanced throughput to identify the origin of transcripts from hundreds of thousands of cells. The high-throughput and low-depth paradigm is a widely employed approach in experiments utilizing the genomics chromium platform. This platform is capable of detecting 500-1500 genes per primary cell.[42,43] The utilization of scRNAseq has yielded significant findings regarding the synchronized reaction to SARS-CoV2 viral infections at the individual cell level. This technology has proven to be indispensable in the identification of novel biomarkers for the diagnosis and prognosis of SARS-CoV-2 infections.[44]

Next-Generation Sequencing

RNA-seq is a highly adaptable instrument that can be employed to explore a range of RNA-related subjects, including gene fusion detection, expression, splicing, and gene structure. The progressions in RNA-seq technology, such as direct RNA-seq, long read detection, spatial omics, and the creation of novel computational tools for transcriptome quantification and assembly, have facilitated a thorough comprehension of transcriptome biology in biomedical research.[45] In the management of the COVID-19 pandemic, the utilization of second and third generation sequencing (STGS) technology has become indispensable in the identification of novel variations of concern and in the prevention of further transmission of the disease. Additionally, STGS has enabled the characterization of variants of interest (VOIs) and variants of concern (VOCs), thereby enabling the prioritization of monitoring and viral research efforts.

In order to bolster genomic surveillance efforts, SARS-CoV-2 genomes have been submitted to worldwide platforms, and mechanisms have been implemented to identify potential VOIs or VOCs on a global scale. GISAID has been instrumental in advancing and streamlining the sharing of genetic information pertaining to COVID-19. Presently, GISAID houses 12.2 million complete SARS-CoV-2 genome sequences, with over 100,000 supplementary sequence data being added daily through the use of STGS platforms. Illumina, Oxford Nanopore, Ion Torrent, and Pacific Bioscience are the primary platforms used for sequencing, with Illumina producing 75%, Oxford Nanopore producing 23%, Ion Torrent producing 1%, and Pacific Bioscience producing 1% of the sequences.[46] The Illumina platform, which employs short reads ranging from approximately 36-151 bp, offers numerous advantages. These include the capacity to sequence a high number of samples per run (up to 3072 on the NovaSeq6000 with coverage of 300-600) and a dependable bioinformatic analysis workflow.[47] Conversely, the Oxford Nanopore platform exhibits the capability to sequence extended reads of up to 20 kilobases and has the ability to directly sequence viral RNA.

Genomic Mutation Analysis

As the COVID-19 pandemic persists, recently identified variants of SARS-CoV-2 have demonstrated a growing number of mutations, suggesting viral evolution that is adaptive in nature. The efficacy of currently approved COVID-19 vaccines against the emerging SARS-CoV-2 variant S protein remains unknown, as these vaccines were primarily developed for the original S protein of the

virus. Therefore, it is crucial to obtain sufficient SARS-CoV-2 genomes for genomic monitoring in order to track the mutations, evolution, and adaptation of this virus.[48,49] Several efforts have been made to achieve real-time genomic surveillance of this virus.

The emergence of new strains of the SARS-CoV-2 virus is attributed to heritable mutations. Research has demonstrated that SARS-CoV-2 has the ability to utilize all ACE2 proteins as cell entrance receptors, with the exception of mouse ACE2.[41] During virus entry, the SARS-CoV-2 virus interacts with cells via its highly changeable spike (S) protein, which is composed of the S1 and S2 subunits. The S1 subunit's receptor binding domain (RBD) directly mediates virus attachment and entry, while the S2 subunit's fusion peptide (FP) promotes membrane fusion.[50] Although S protein mutations are rapidly increasing during the SARS-CoV-2 pandemic, the majority of mutations are either lost or infrequently repaired at the site of transmission, with little shared diversity remaining among variations.[51] Several mutations of SARS-CoV-2 were identified in epidemic strains during the initial stages of the pandemic. These mutations include H49Y on the S1 N-terminal domain (NTD) originating from China, G476S on the RBD originating from Washington, USA, and S943P on FP originating from Belgium.[52] More mutations, including several well-known mutations that have spread globally, are being discovered as the COVID-19 pandemic progresses.

The coupling of RBD to ACE2 is facilitated by the mutation of the C-terminal domain 2 (CT2) expressed as D614G (G614), which results in an open conformational state of the S protein. Additionally, the D614G mutation in the S protein has greater virulence and transmission potential. Among circulating variations, D614G mutations have demonstrated a selective advantage of larger viral loads, younger patient age, and reinfection.[53] Studies show that the N439K mutation on the S protein's receptor binding motif can moderately increase the protein's affinity for the ACE2 receptor and can result in resistance to a number of neutralizing monoclonal antibodies and some polyclonal sera from individuals recovering from infection.[30,54,55]

A comparative analysis of the structural genes of SARS-CoV-2 and other CoVs revealed that the sequence of the E gene exhibited the highest degree of evolutionary conservation among 200 SARS-CoV-2 isolates.[48,56] Based on a phylogenetic tree analysis, it has been determined that the E and M gene sequences of SARS-CoV-2 and NC014470 CoV exhibit a close relationship and are classified within the same branch.[57] The SARS-CoV-2 isolates exhibited a diverse range of E gene and M gene sequences, which were comparable to those observed in typical CoVs that infect alternative hosts. The KJ481931 CoV's M gene sequence's overall diversity was comparable to that of SARS-CoV-2 and CoVs that infect other organisms.[58] This data can greatly benefit our understanding of the origins and intermediate hosts of SARS-CoV-2.

Pathogenesis study

The life cycle of SARS-CoV-2, being an RNA virus, is heavily dependent on the host cell machinery. Consequently, infection with SARS-CoV-2 leads to significant alterations in the transcriptomes of host cells. Transcriptomic analysis offers a means of investigating the cellular mechanisms that underlie risk factors, pathophysiology, and potential therapeutic targets for SARS-CoV-2 infection. Furthermore, the use of transcriptome analysis in various clinical samples can aid in elucidating the mechanisms that contribute to tissue damage and comorbidities associated with COVID-19. The SARS-CoV-2 isolates exhibited a diverse range of E gene and M gene sequences, which were comparable to those observed in typical CoVs that infect alternative hosts. A multitude of interferon, cytokine, and immune-related genes were observed to exhibit upregulation, such as chemokine C-X-C motif ligand (CXCL)5, CXCL12, chemokine C-C motif ligand 2 (CCL)2, CCL4, CXCL10, interferon induced with helicase C domain (IFIH)1, interferon induced protein (IFI)44, interferon-induced protein with tetratricopeptide repeats (IFIT)1, and interleukin (IL)6, IL10. Conversely, metabolic pathways or housekeeping genes, including ribosomal protein L (RPL)41, RPL17, solute carrier family 25 member 6 (SLC25A6), calmodulin I (CALM1), and tubulin alpha-1A chain (TUBA1A), were found to be downregulated.[59]

Understanding Patients' Immune Response

Several investigations have revealed the presence of permanently increased T-cells and monocytes, as well as reduced antiviral responses and inappropriate inflammatory responses, in patients with COVID-19.[60,61] SARS-CoV-2 infects alveolar macrophages, which then produce a chemoattractant for T cells, activating them. Subsequently, the T-cells produce interferon, which stimulates the production of inflammatory cytokines from alveolar macrophages, including T cell chemoattractant, leading to

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further T-cell activation.[61] In this cycle, circulating follicular helper T-cells are associated with moderate disease, while severe disease is characterized by clonally enlarged cluster of differentiation 8 ($CD8^+$) T-cells and an elevated ratio of $CD8^+$ effector T-cells to effector memory T-cells.[52]

Susceptible factors for disease severity

Numerous investigations have confirmed that ACE2 serves as the receptor for SARS-CoV-2 viral entry into host cells, while transmembrane protease serine 2 (TMPRSS2) prepares the S protein for viral entry. Transcriptomics-based omics experiments have yielded significant findings regarding severe COVID-19 risk factors. One of the contributing factors is the simultaneous expression of ACE2 and TMPRSS2 in various tissues, including but not limited to the pulmonary and extrapulmonary regions, as well as the maternal-fetal interface, salivary glands, and the granulosum of the skin. This co-expression presents a potential threat of systemic tissue damage and suggests the likelihood of vertical and contact transmission of the disease.[62]

Elevated expression of ACE2 and TMPRSS2 was observed in the lung epithelial cells of COVID-19 patients who were either moderately or critically unwell in response to IL13 and interferon signals. The upregulation of ACE2 and TMPRSS2 resulted in a heightened manifestation of clinical inflammatory lung injury and respiratory insufficiency. The involvement of pathways linked to inflammation, such as toll-like receptor (TLR)4, C-C chemokine receptor type (CCR)1, CCR5, C-X-C chemokine receptor type 6 (CXCR6), mammalian target of rapamycin (mTOR), mitogen-activated protein kinase (MAPK)/MAPKK/protein kinase B, inhibitor of nuclear factor κB kinase/nuclear factor κB (NF-κB), and ferroptosis pathways, has been noted.[11]

Infected epithelial cells with SARS-CoV-2 exhibit hyperactivated intrinsic blood coagulation cascades and suppressed plasminogen activation systems, increasing the likelihood of developing various coagulopathies in the lung and distal organ systems. The major regulators of extrinsic coagulation cascade signaling, including coagulation factors von Willebrand factor (VWF) and a disintegrin and metalloproteinase with a thrombospondin type 1 motif member 13 (ADAMTS13), are potential therapeutic targets for COVID-19-associated coagulopathies.[63] The levels of microtubule-associated proteins 1A/1B light chain 3B (LC3B) and p62/SQSTM1, which are degraded by lysosomes, have been identified as indicators of severe illness that necessitates hospitalization for supplementary oxygen therapy.[64,65] Furthermore, smoking and lung cancer have been found to be associated with increased levels of ACE2 and TMPRSS2 expression, thereby increasing the susceptibility to SARS-CoV-2 infection. In addition, preexisting dysregulation of viral infection-associated genes, including proven and hypothesized entry receptors and priming proteases, has been observed in AT2 cells, which may facilitate SARS-CoV-2 infection in COVID-19 patients with chronic lung injury.[14]

Proteomics in emerging pandemic study

Proteomics, which is the comprehensive study of proteins, has proven to be an invaluable tool in the face of emerging pandemics. As a crucial component of omics-based technologies, proteomics provides valuable insights into the structure and function of viral proteins, thereby facilitating the identification of potential therapeutic targets and biomarkers. By utilizing techniques such as mass spectrometry, researchers can decipher host-virus protein interactions, laying the foundation for novel therapeutic strategies. Additionally, proteomic analysis can identify biomarkers indicative of disease severity or progression, thereby aiding in patient management and prognostication.
Proteomics is currently being extensively used to research and create new treatments for various diseases. Based on the method of application, the application of proteomics in the COVID-19 pandemic was split into two components. In the first, it is used directly in the characterization of viruses, for the diagnosis of pathogens, for the discovery of mutations, and for posttranslational modifications. The second objective pertains to monitoring the impact of infection on host cells at the protein level. This includes the identification of potential therapeutic targets, comprehension of pathologic processes and immunogenicity, disclosure of the antiviral mechanism of drugs, and detection of biomarkers for tracking and predicting the progression of disease.[3,66]

Proteome sequence and prognosis factors

To effectively implement preventive measures and tailored interventions, particularly for critically ill patients, it is imperative to identify the disease courses of COVID-19. In pursuit of this objective, researchers have conducted numerous proteome investigations on various samples to discover useful biomarkers that can accurately predict COVID-19 illness trajectories. Plasma proteins have

emerged as potential biomarkers for assessing the severity of COVID-19 patients' condition through the analysis of plasma proteomics. IL6 has been found to be significantly correlated with COVID-19 severity, and cytokines associated with IL6-mediated proinflammatory signaling have been identified as key COVID-19 biomarkers. Proteomic analyses of exosomes and plasma samples have yielded insights into the cytokine profiles associated with disease progression. Specifically, the cytokines C-reactive protein (CRP), lactate dehydrogenase (LDH), procalcitonin (PCT), serum amyloid A (SAA), antiglobulin test (AGT), IL12, pentraxin-related protein (PTX)3, immunoglobulin lambda variable 3-19 (IGLV3-19), basonuclin zinc finger protein (BNC)2, and cytoskeleton-associated protein (CKAP)4 have been found to exhibit significant upregulation or downregulation as the disease advances. Although certain cytokines necessitate additional validation, they hold potential as potential markers of disease progression and mortality.[15]

The application of targeted proteomic technology has been employed to examine serum samples in correlation with the extended recovery prognosis of individuals afflicted with SARS-CoV-2. The findings reveal that biochemical and inflammatory pathways continue to be disrupted even following the resolution of SARS-CoV-2 infections for an extended duration. In order to assess the efficacy of treatment and monitor the recuperation progress of COVID-19 patients, it is imperative to identify valuable prognostic biomarkers.[15] Additionally, it should be noted that the prognostic markers and predictors used to categorize COVID-19 severity share many similarities, necessitating further characterization of these variables.[9]

Potential therapeutic target study

In order for healthcare systems to effectively administer interventions for COVID-19, it is imperative to ascertain the pathophysiology and potential therapeutic targets of the virus. Researchers have made numerous attempts and found numerous promising therapeutic targets using the current proteomics technique.[66] The first of these studies' three main approaches is to look for cellular-level antiviral targets. The second step entails the creation of a protein-protein interaction network through a direct analysis of the proteomics of diverse tissue samples obtained from COVID-19 patients. The third step involves the amalgamation and scrutiny of the proteome data that has already been published, with the aim of identifying further targets that exhibit high efficacy and low toxicity.[67] A recent investigation employed proximity proteomics to assemble a comprehensive list of 2422 human proteins that were in close proximity to 17 distinct SARS-CoV-2 viral proteins. The findings of this study provide valuable insights into the pathogenicity of SARS-CoV-2 and identify potential targets for therapeutic intervention.[14,68] A549 cells expressing ACE2 and infected with SARS-CoV-2 were subjected to proteomic analysis, revealing significant disruption of multiple antiviral pathways.

A proteomics and bioinformatics study have revealed a strong association between SARS-CoV-2 and complement protein C3, apolipoprotein A1 (APOA1), amyloid precursor protein (APP), epidermal growth factor (EGF), and other targets. These targets could be useful for both diagnostic and therapeutic purposes. In numerous proteomics investigations, the complex protein seed of APOA1 has been identified as a prominently important differentially expressed protein. The researchers conducted a comprehensive analysis of proteomics data, including a direct proteome analysis of SARS-CoV-2 infected sample sets. Through impact pathways analysis and network analysis of the available proteomics data, they were able to confirm the role of inflammatory responses and identify changes in proteins involved in chromosomal segregation during mitosis. Notably, the widely distributed bromodomain-containing protein RIPK1 and the tissue-specific receptor expression boosting protein 5 were identified as promising therapeutic targets.[5]

Amino Acid Metabolism Study

As per research findings, SARS-CoV-2 infection has the potential to impact a significant number of amino acid metabolism pathways, including those that rely on branched chain amino acids (BCAAs), aromatic amino acids, and gluconeogenic amino acids.[3] Tryptophan can also be converted to nicotinamide adenine dinucleotide (NAD) via the Kynurenine pathway in addition to the tryptophan/5-hydroxytryptamine pathway. Arginine plays a crucial role in regulating the activation of host immune cells and safeguarding against viral pathogen invasion. In individuals afflicted with COVID-19, a multitude of metabolites implicated in arginine metabolism exhibit anomalous levels.[68,69] The metabolomics profiling of critically ill COVID-19 patients admitted to the ICU was conducted with the aim of identifying potential diagnostic or prognostic biomarkers in blood. The results of the study revealed

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elevated kynurenine levels, as well as decreased levels of arginine, sarcosine, and lysophosphatidylcholines.[3] In a separate instance, it was demonstrated that the metabolism of arginine was linked to inflammatory cytokines and adverse outcomes in patients with COVID-19.

COVID-19 Associated with Lipid and Glucose Metabolism

Lipid and glucose metabolism are closely related, and some metabolites from either pathway can be transformed into the other. The pathogenesis of COVID-19 is comprehensively elucidated through a molecular perspective, wherein SARS-CoV-2-induced metabolic reprogramming plays a crucial role in affecting lipid metabolism, glycolysis, and the tricarboxylic acid (TCA) cycle.[15] The involvement of lipid is evident in every stage of viral replication and invasion, and COVID-19 patients manifest a remarkable alteration in lipid, lipid mediators, and associated metabolic pathways.[19]

Antiviral repurposing for the treatment of COVID-19

When it is challenging to develop and execute a new pharmacological target, previously designed antiviral medications can be used to combat newly discovered viruses through drug repurposing or repositioning. In response to the COVID-19 pandemic, a multitude of pharmaceutical treatments have been repurposed and established for clinical trial evaluation. While certain medications have undergone satisfactory clinical testing, others have yet to undergo randomized controlled trials (RCTs). In a pandemic outbreak, drug repurposing aids in the quick finding of medicines with a known safety profile.[70] Due to observed inefficiency, safety issues, and positive results in COVID-19 patients, several of the chosen medications were eliminated. Based on recent research, it has been found that 79.5% of the proteins encoded in SARS-CoV-2 share genetic similarities with other SARS-CoVs. This discovery has opened up the possibility of repurposing previously prescribed medications for the treatment of this virus, as well as the development of broad-spectrum antivirals.[71] Pharmacological agents, including protease inhibitors, neuraminidase inhibitors, corticosteroids, antibiotics, and antifungal agents, have been recognized as potential treatments that specifically target the RNA-dependent RNA polymerase (RdRp). These agents are utilized in various medical conditions, such as high procalcitonin levels, hospital-acquired pneumonia, ventilator-acquired pneumonia, and pneumocystis pneumonia. Additionally, anticoagulants and other therapies that disrupt the renin-angiotensin system (RAS) are currently being researched.[72]

Corticosteroids

Corticosteroids have emerged as a highly effective repurposing treatment for mitigating the severity and mortality of COVID-19. Notably, dexamethasone and methylprednisolone have demonstrated positive outcomes in regulating dysregulated immune responses and hypotension, resulting in a significant reduction in mortality rates during the late stages of the disease. This is particularly crucial as cytokine storms, which can cause damage to multiple organs, are a common occurrence during this phase.[48,73] In a separate investigation, it was observed that patients who presented with acute respiratory failure and exhibited indications of fever and hypoxia experienced a noteworthy amelioration in their symptoms and a reduction in latency upon administration of methylprednisolone, as compared to those who did not receive the medication.[28] Additionally, dexamethasone has exhibited a decrease in mortality and ventilation duration in acute respiratory disease (ARD) patients, although additional data and research are necessary to further substantiate these findings.

Nucleoside Analogues

The nucleoside analogues presently recognized for their efficacy against COVID-19 are analogues of guanine, adenosine, or cytidine. These analogues are specifically targeted towards RdRp with the aim of impeding the synthesis of viral RNA. Remdesivir, Favipiravir, and Galidesivir are the medications that have undergone RCTs. Remdesivir acquired an emergency use license from the FDA since it was found that patients who needed oxygen had a lower recovery time with just 11 days recovery time as opposed to the group of patients who received the placebo, which was 15 days recovery time.[74] The native adenosine triphosphate's competitive integration into the lengthening polynucleotide chain is inhibited by this medication. Furthermore, the clinical recovery rate of individuals who received the medication was observed to be 7 days, which was significantly shorter than those who were administered umifenovir. Additionally, the RCT conducted a comparative analysis between the administration of Favipiravir alone and the administration of Favipiravir in combination with Nafamostat Mesylate, with regards to the latency period for fever and cough relief.[75]

Protease Inhibitors

The process of repurposing has been employed in the treatment of COVID-19 through the utilization of certain protease inhibitor medications that possess the ability to impede the maturation of crucial proteins in the viral life cycle. Research on drug-enzyme binding has indicated that twenty protease inhibitors may interact with the primary SARS-CoV-2 protease.[76] Protease inhibitor medications have therefore been chosen as a contender utilizing computational bioinformatics techniques.

Antibiotic and Antifungal Agents

Only in the case of procalcitonin are antibiotics administered because of the potential for hospital- or ventilator-associated pneumonia. Teicoplanin's ability to potently prevent the virus' entry into the cell during study trials demonstrated its efficacy in the treatment of COVID-19.[77] Similar to azithromycin, ventricular myocardium cells' time spent repolarizing showed cardiac damage. Doxycycline also appears to reduce COVID-19-related anosmia and respiratory symptoms, according to a study.[78]

Study biomarkers

The technology of metabolomics, particularly the Nuclear Magnetic Resonance (NMR) spectroscopic technique, offers comprehensive qualitative and quantitative insights into a diverse array of metabolites present in a given sample. Additionally, the Mass Spectrometry (MS) technique, when coupled with either Liquid Chromatography (LC-MS) or Gas Chromatography (GC-MS), enables the detection and quantification of thousands of metabolites with exceptional sensitivity and specificity. One metabolomics study has revealed that various molecules linked to glucose and lipid metabolism can serve as biomarkers for monitoring COVID-19 illness.[3] The study analyzed serum samples from COVID-19 patients and identified combinations of metabolites, including D-fructose, citric acid, and 2-palmitoyl-glycerol, which exhibit a decline in concentration with the severity of the disease. These metabolites can be utilized to detect the presence of SARS-CoV-2 in COVID-19 patients.

Disturbance of Lipid and Glucose Metabolism

The infection caused by SARS-CoV-2 has a close association with metabolic control and physiological processes within the body. In patients with critical COVID-19, cytokine release syndrome (CRS) is the primary factor responsible for multiorgan injury and mortality throughout the pathogenesis.[59] The discovery of a strong correlation between proinflammatory cytokines and chemokines and reprogrammed host metabolism in serum samples of COVID-19 patients has led to the suggestion that metabolic modulation could be a viable treatment option for fatal CRS. This therapeutic approach, based on a deeper understanding of the disease, offers a fresh perspective for treating deadly CRS caused by SARS-CoV-2 infection.[25]

The accumulation of lactate in large amounts has been observed in severe COVID-19 patients using both untargeted and targeted metabolomic approaches. Even in the recovery group whose SARS-CoV-2 PCR test is negative, lactate accumulation is still evident, indicating a significant disturbance in energy metabolism. Furthermore, aberrant quantities of TCA cycle metabolites such as glucose, lactate, and pyruvate are present during COVID-19. This underscores the strong connection between the clinical processes of COVID-19 illnesses and the TCA cycle and related metabolic pathways.[59,79]

Conclusion

Omics technologies are highly effective methods for rapidly generating insights into both reemerging and emerging infectious diseases. Extensive efforts have been devoted to investigating the relationship between COVID-19 illness outcomes and multi-omics data. Through a range of multi-omics-based developments, the complexity and heterogeneity of COVID-19 have been better understood, leading to the creation of improved drugs and diagnostic indicators. The development of multi-omics methods, encompassing genomes, transcriptomics, proteomics, and metabolomics, is critical to COVID-19 research, as they provide a valuable resource for clinical decision-making regarding illness diagnosis and surveillance. Applications in monitoring of SARS-CoV-2 sequences, mutations, and variants are conducted with great scrutiny to detect any potential uncontrolled outbreaks. Similarly, comprehensive methodologies that incorporate transcriptomics, proteomics, and metabolomics are employed in tandem to unravel the pathogenesis of COVID-19, thereby enabling the identification of infected individuals and the development of efficacious treatments. Consequently, the multi-omics approach has played a pivotal role in generating intricate disease maps and identifying pathogenic pathways that

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underlie the emergence of disease phenotypes and outcomes. The multi-omics method is also instrumental in advancing research into unexplored facets of the disease, such as the processes underlying COVID-19's long-term effects, neurological involvement, and Kawasaki-like COVID-19 inflammatory syndrome.

Authors Contribution

AMA, AAW were involved in concepting the topic of the manuscript. AMA prepared the manuscript draft, and all authors took parts in giving critical revision of the manuscript.

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