A COMPREHENSIVE REVIEW ON THE MULTIFACETED INTERACTIONS BETWEEN HOST IMMUNITY AND VIRAL PATHOGENESIS IN COVID-19

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ABSTRACT

The Corona Virus Disease (COVID-19) pandemic has presented unparalleled challenges, marked by a wide array of clinical presentations spanning from asymptomatic carriage to severe respiratory compromise and multi-organ dysfunction. It is crucial to comprehend the intricate interplay between host immunity and viral pathogenesis to elucidate disease mechanisms and guide therapeutic strategies. This review delves into the multifaceted interactions between host immunity and viral pathogenesis in COVID-19, with a particular focus on the impact of host factors such as age, sex, comorbidities, and genetic predisposition on disease severity. Utilizing state-of-the-art methodologies, including multiomics approaches, has yielded an expansive molecular portrayal of COVID-19, furnishing innovative perspectives on host immune reactions, viral pathogenicity, and disease advancement. Establishing standardized methodologies for data analysis and interpretation while concurrently addressing ethical considerations and promoting interdisciplinary collaboration are crucial steps in advancing our comprehension of COVID-19 pathogenesis. Despite obstacles like complexities in data integration, this review highlights the imperative of persistent endeavors in deciphering the complex interactions between hosts and pathogens to alleviate the global health ramifications of COVID-19.

Keywords: COVID-19, HPI, ACE2, Multiomics, Host immunity, Viral proteins

INTRODUCTION

The Corona Virus Disease (COVID-19) pandemic stands as a paramount global health crisis of recent times, profoundly affecting millions worldwide and resulting in substantial morbidity and mortality. This pandemic is attributed to Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), a member of the coronaviridae family [1, 2]. The coronaviridae family encompasses a broad spectrum of viruses capable of inducing respiratory, gastrointestinal, and neurological ailments in both humans and animals. Within the COVID genus, a diverse array of viruses is recognized for eliciting respiratory illnesses in humans, spanning from mild common colds to SARS and Middle East Respiratory Syndrome (MERS). Nonetheless, none have exhibited the extensive global repercussions witnessed by COVID-19, precipitated by SARS-CoV-2 [3, 4]. COVID-19 presents unparalleled challenges to public health due to its high transmissibility and diverse symptomatic range, spanning from asymptomatic cases to severe respiratory distress. The severity of COVID-19 exhibits considerable variation among individuals, influenced by factors such as age, underlying health conditions, and immune status. While some individuals manifest mild symptoms or remain asymptomatic, others progress to severe pneumonia, Acute Respiratory Distress Syndrome (ARDS), and multi-organ failure, resulting in elevated morbidity and mortality rates [5].

The multifactorial mechanisms governing this variability in disease severity entailed intricate interactions between the host immune response and viral pathogenesis. Understanding the dynamics of Host-Pathogen Interactions (HPI) is pivotal in elucidating the complexities of COVID-19 and devising effective management strategies [6].

The host possesses an inherent evolutionary capacity to enhance its defense mechanisms against viral invasion, primarily through innate and adaptive responses. Innate responses encompass swift cytokine production aimed at combating viral infections. Conversely, adaptive responses, including antibody and cell-mediated immune reactions, necessitate time to materialize but are instrumental in eliciting virus-specific immune defenses [7]. These innate and adaptive immune mechanisms have evolved over extensive periods of evolution. By elucidating the intricate molecular underpinnings of HPI, researchers can pinpoint shared targets for therapeutic intervention and devise innovative strategies to modulate the host immune response, thereby constraining viral replication. Comprehending the intricate interplay between host factors and viral pathogenesis is paramount for devising personalized treatments customized to the unique immune profiles and disease progressions of individual patients [6, 8].

The methodology involved conducting a thorough literature search across bibliographic databases, including PubMed, Google Scholar, Web of Science, and Scopus, encompassing both review articles and research papers published between 2019 and 2023. A comprehensive set of keywords, including "Cov2", "coronavirus," "host-pathogen interaction (HPI)," "ACE2," and "covid" were utilized for efficient search results. Searches were refined iteratively to ensure coverage, with screening based on titles and abstracts followed by full-text review to select relevant publications.

This review endeavors to delve into the multifaceted interactions between host immunity and viral pathogenesis in the context of COVID-19, exploring the latest advancements in our comprehension of HPI.

Basic virology of SARS-CoV-2

Coronaviruses represent a category of enveloped, positive-sense, single-stranded RNA viruses recognized for their role in precipitating respiratory ailments in humans. The genome of SARS-CoV-2 spans approximately 30,000 nucleotides and encompasses numerous structural and non-structural proteins pivotal for viral replication and assembly [2, 3]. Grasping the intricacies of the structure, genome arrangement, and replication cycle of SARS-CoV-2 is imperative for unraveling its pathogenesis and formulating efficacious interventions against COVID-19.

Structure and genome of SARS-CoV-2

SARS-CoV-2, the etiological agent responsible for COVID-19, belongs to the coronaviridae family, a group of enveloped, positive-sense, single-stranded RNA viruses. Its genome spans approximately 30,000 nucleotides and encodes numerous structural and non-structural proteins pivotal for viral replication and assembly. The genome encompasses 14 Open Reading Frames (ORFs), with ORF1a and ORF1b responsible for encoding the viral replicase polyproteins pp1a and pp1ab, respectively. These polyproteins undergo cleavage into individual Non-Structural Proteins (nsps) by viral proteases,
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including the Main Protease (Mpro) and Papain-Like Protease (PLpro). Among the structural proteins of SARS-CoV-2 are the Spike (S), Envelope (E), Membrane (M), and Nucleocapsid (N) proteins. The S protein of SARS-CoV-2 facilitates viral entry into host cells through its binding affinity with the Angiotensin-converting Enzyme 2 (ACE2) receptor situated on the host cell surface. This interaction is primarily mediated by the Receptor-Binding Domain (RBD) localized within the S1 subunit of the S protein. Subsequently, the S protein undergoes proteolytic cleavage by host cell proteases, including TMPRSS2 and cathepsins, to facilitate membrane fusion and enable viral entry (fig. 1).

Viral entry mechanism into the host cell

The initial stage of viral entry entails the binding of the SARS-CoV-2 S protein to the ACE2 receptor present on the surface of host cells. This binding event induces conformational alterations in the S protein, leading to the exposure of the fusion peptide located within the S2 subunit. Following this, host cell proteases, such as TMPRSS2, catalyze the proteolytic cleavage of the S protein, thereby priming the virus for membrane fusion [9]. The fusion peptide then integrates into the host cell membrane, facilitating the fusion between viral and cellular membranes and subsequent release of the viral genome into the cytoplasm of the host cell. Moreover, endocytosis-mediated entry pathways have been implicated in the infection of SARS-CoV-2, whereby the virus is internalized into host cells within endosomal vesicles [9, 10]. This mechanism entails the interaction between the S protein and cell surface receptors, such as ACE2, resulting in the internalization of the virus-receptor complex into endosomes.

Subsequent acidification of the endosomal compartment induces conformational alterations in the S protein, facilitating membrane fusion and the subsequent entry of the virus into the cytoplasm of the host cell [10] (fig. 1).

Replication cycle of the virus

Upon entry into the host cell, the viral genomic RNA functions as a template for the translation of viral replicase proteins, which include nsps originating from ORF1a and ORF1b. These nsps assemble into the viral Replicase Complex (RC), which is responsible for catalyzing the replication and transcription of the viral genome [11]. This process results in the production of full-length genomic RNA and a series of subgenomic RNAs (sgRNAs). The sgRNAs encode viral structural and accessory proteins crucial for viral assembly and release. Notably, viral RNA synthesis occurs within double-membrane vesicles (DMVs) derived from host cell membranes during replication [12]. These double-membrane vesicles (DMVs) act as replication compartments, providing a protected environment where viral RNA synthesis occurs without interference from the host cell’s innate immune responses.

The newly synthesized viral genomic RNA and sgRNAs are subsequently encapsulated into viroparticles by the viral nucleocapsid protein (N) and assembled at the Endoplasmic Reticulum-Golgi Intermediate Compartment (ERGIC). Ultimately, mature virions are released from the host cell either through exocytosis or budding from the plasma membrane, facilitating the dissemination of infection to adjacent cells and tissues [13].

IFNs play a pivotal role in inhibiting viral replication and dissemination by inducing an antiviral state in neighboring cells. Additionally, innate immune cells such as macrophages, dendritic cells, and Natural Killer (NK) cells are recruited to the infection site, where they contribute to viral clearance through phagocytosis and cytotoxicity [15]. Macrophages produce inflammatory cytokines such as Interleukin-6 (IL-6) and Tumor Necrosis Factor-Anti (TNF-α), which coordinate the recruitment and activation of other immune cells. NK cells recognize and eliminate virus-infected cells through the release of cytotoxic granules containing perforin and granzymes [16] (fig. 2).

Nonetheless, SARS-CoV-2 has evolved mechanisms to evade and manipulate the innate immune response. The virus hampers the production of IFNs by disrupting the activation of transcription factors, including Interferon Regulatory Factors (IRFs) and Nuclear Factor-Kappa B (NF-kB). Additionally, certain SARS-CoV-2 proteins, such as Nsp1 and Nsp3, counteract the host’s antiviral defenses by...
targeting critical signaling pathways associated with innate immunity [14, 15].

Adaptive immune response to the virus

The adaptive immune response against SARS-CoV-2 involves the orchestrated activation of B cells and T cells, pivotal in eradicating the virus and conferring long-lasting immunity. B cells are responsible for generating antibodies that target and neutralize viral antigens, notably the SARS-CoV-2 spike protein [15]. These antibodies hinder viral entry into host cells by impeding the interaction between the virus and its cellular receptor, ACE2. Concurrently, T cells play a crucial role in eliminating virus-infected cells and regulating immune responses. CD4+ T helper cells coordinate the adaptive immune reaction by stimulating B cells and cytotoxic CD8+ T cells (fig. 2) [16].

A robust adaptive immune response is crucial for effectively combating SARS-CoV-2 infection and resolving COVID-19. However, certain individuals may encounter dysregulated immune responses characterized by excessive inflammation and tissue damage, which can lead to severe disease manifestations like ARDS and multi-organ failure. Remarkably, SARS-CoV-2 has evolved strategies to evade detection and elimination by the adaptive immune system [17]. The virus diminishes the expression of Major Histocompatibility Complex (MHC) molecules on infected cells, thereby hindering antigen presentation and T-cell recognition (fig. 2). Furthermore, specific SARS-CoV-2 proteins, such as the nucleocapsid protein (N), hinder the activity of T cells and impede their effector functions, thus fostering viral persistence and immune evasion [15].

Immune evasion strategies employed by the virus

SARS-CoV-2 employs diverse immune evasion strategies to circumvent detection and elimination by the host immune system. One notable strategy involves the suppression of IFN signaling, a pivotal step in initiating an antiviral response [18]. Certain SARS-CoV-2 proteins, such as Nsp1 and Nsp3, hinder the production of type 1 IFNs by impeding the activation of crucial signaling pathways, including the IRF3 pathway (fig. 2) [19]. Furthermore, SARS-CoV-2 has been observed to disrupt antigen presentation and T-cell recognition by reducing the expression of MHC molecules on infected cells. This downregulation of MHC molecules impedes the ability of infected cells to display viral antigens to T cells, thereby hindering effective immune surveillance and response. This impedes the capacity of infected cells to present viral antigens to T cells, enabling the virus to evade immune surveillance and establish persistent infection [20]. Additionally, certain SARS-CoV-2 proteins, like the nucleocapsid protein (N), have been identified to directly hinder the activity of T cells and compromise their effector functions. This encompasses the suppression of T cell proliferation and cytokine production alongside the induction of T cell apoptosis. Through its interaction with T cells, SARS-CoV-2 can dampen the adaptive immune response, thereby promoting viral persistence [21].

Host factors influencing disease severity

Numerous host factors contribute to the spectrum of COVID-19 severity, encompassing demographic features like age and sex, as well as underlying health conditions and genetic susceptibilities. Comprehending these factors holds paramount importance for risk assessment, tailoring treatment modalities, and crafting precise interventions aimed at ameliorating disease severity and enhancing clinical prognosis [22]. Through deciphering the intricate dynamics between host factors and disease trajectory, scientists strive to unveil innovative therapeutic targets and approaches for addressing severe manifestations of COVID-19.

Demographic and health factors influencing COVID-19 severity

Age, sex, and underlying health conditions, often referred to as comorbidities, are pivotal determinants of COVID-19 severity. Advanced age consistently emerges as a notable risk factor for severe disease outcomes and mortality [23]. Elderly individuals frequently exhibit compromised immune systems and a higher prevalence of comorbidities such as hypertension, diabetes, and cardiovascular disorders, which collectively contribute to adverse clinical trajectories [24]. Furthermore, sex-based distinctions in COVID-19 severity are evident, with males exhibiting a propensity towards more severe disease manifestations and heightened mortality rates compared to females. The underlying reasons for this divergence are multifaceted, potentially encompassing variations in immune responses, hormonal influences, and lifestyle elements [25].

Comorbidities, encompassing conditions like obesity [26], chronic lung disease [27], kidney disorders [28], and immunosuppression [29], correlate with heightened susceptibility to COVID-19 manifestations. These underlying health ailments impede both immune and respiratory functionalities, rendering individuals more prone to complications such as ARDS and multi-organ dysfunction [30]. Moreover, socio-economic determinants, inclusive of healthcare accessibility, living standards, and occupation, exert notable influence on disease severity. Individuals hailing from marginalized communities and economically disadvantaged backgrounds often exhibit heightened healthcare services and exhibit elevated prevalence rates of comorbidities, thereby amplifying disparities in COVID-19 outcomes [31, 32].

Genetic susceptibility to severe COVID-19

Genetic factors significantly influence an individual’s susceptibility to severe COVID-19. Through Genome-Wide Association Studies (GWAS), numerous genetic variants linked to heightened risk of severe disease outcomes have been identified, particularly within genes governing immune regulation and host-viral interactions [33, 34]. Notably, variants within the gene encoding the ACE2 receptor, pivotal for SARS-CoV-2 entry, have emerged as relevant determinants. Variants affecting ACE2 expression or function may modulate viral entry and replication kinetics, thereby impacting disease severity [35].

Similarly, genetic variations in genes encoding components of the immune system, including cytokines and Human leukocyte Antigen (HLA) genes, can influence immune responses to SARS-CoV-2 and contribute to disease severity [36]. Variants associated with dysregulated cytokine responses, such as elevated levels of proinflammatory cytokines like IL-6, are correlated with an increased risk of cytokine storm and severe respiratory complications. Moreover, host genetic factors may affect vaccine efficacy and the occurrence of adverse reactions to SARS-CoV-2 vaccines [37]. Understanding the genetic determinants of COVID-19 severity can facilitate risk stratification and personalized treatment approaches, thus enhancing disease management.

Immunological factors affecting disease outcomes

Immunological factors play a pivotal role in determining disease outcomes in COVID-19. Dysregulated immune responses, characterized by excessive inflammation and cytokine release, contribute to the pathogenesis of severe manifestations such as ARDS and multi-organ failure [38, 39]. Severe COVID-19 cases often exhibit an exaggerated immune response known as a cytokine storm, marked by elevated levels of proinflammatory cytokines, including IL-6, TNF-α, and Interleukin-1β (IL-1β), which cause tissue damage and systemic complications. Conversely, impaired immune responses, such as T cell dysfunction and lymphopenia (reduced lymphocyte count), are also linked to severe COVID-19 (fig. 2) [40]. Dysfunction of cytotoxic CD8+T cells, critical for viral clearance, can lead to prolonged viral replication and disease progression [41].

Moreover, pre-existing immune dysregulation, encompassing autoimmune conditions and immunodeficiency disorders, can predispose individuals to severe COVID-19. Patients with autoimmune diseases like rheumatoid arthritis and systemic lupus erythematosus may experience exacerbations of their underlying conditions during COVID-19 infection, potentially resulting in worse clinical outcomes [42].

Viral factors influencing disease severity

The severity of COVID-19 is influenced by several viral factors, encompassing viral load dynamics, the emergence of Variants of
Genetic capacity and specific viral elements contributing to cytokine storm and hyperinflammation [43]. Understanding the intricacies of these viral factors is imperative for anticipating disease outcomes, informing clinical management decisions, and devising targeted interventions to alleviate disease severity.

**Viral load concern**

The viral load, referring to the amount of virus present in an infected individual, plays a pivotal role in determining the severity of COVID-19. Elevated viral loads consistently correlate with more severe clinical outcomes, including an increased likelihood of respiratory failure and mortality [44]. The initial viral load upon exposure, along with the subsequent kinetics of viral replication within the host, significantly influence the progression of the disease. Research indicates that individuals with severe COVID-19 typically exhibit higher viral loads in respiratory specimens, such as nasopharyngeal swabs and bronchoalveolar lavage fluid, compared to those with mild or asymptomatic disease [45]. Furthermore, prolonged viral shedding, characterized by persistent detection of viral RNA in respiratory samples, is more prevalent among patients with severe disease and is associated with prolonged symptom duration and higher mortality rates [46].

The association between viral load and disease severity highlights the critical need for early detection and monitoring of viral replication in individuals with COVID-19 [44]. Quantitative assessments of viral load, such as determining Reverse Transcription Polymerase Chain Reaction (RT-PCR) cycle threshold values, hold significant prognostic value and inform clinical management strategies, including the initiation of antiviral treatments and the timing of hospital discharge. Moreover, individuals with higher viral loads pose a greater risk of transmitting the virus to others, underscoring the importance of promptly identifying and isolating infectious individuals to curb the spread of COVID-19 within communities [47].

**Variants of concern and their impact on pathogenesis**

The emergence of VOCs has sparked apprehension regarding their potential impact on the pathogenesis and severity of COVID-19 [48]. VOCs, characterized by distinct mutations in the viral genome, may display altered transmissibility, virulence, and immune evasion capabilities compared to the original strain of SARS-CoV-2. Notably, several VOCs, including the Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), and Delta (B.1.617.2) variants, have been linked to heightened disease severity and increased mortality rates in specific demographics [49]. These variants harbour mutations primarily within the spike protein, particularly in the Receptor-Binding Domain (RBD), potentially enhancing viral affinity for the ACE2 receptor and facilitating cellular entry. Furthermore, VOCs may demonstrate resistance to neutralization by antibodies generated post-natural infection or vaccination, thereby diminishing the efficacy of existing therapeutics and vaccines [50]. Of note, the Delta variant, in particular, has been associated with breakthrough infections in vaccinated individuals, prompting the development of booster doses to bolster immunity against emerging variants [51].

**Viral contributions to cytokine storm**

The phenomenon known as cytokine storm, characterized by the dysregulated and excessive release of proinflammatory cytokines, is a hallmark of severe COVID-19, contributing significantly to tissue damage, multi-organ failure, and unfavorable clinical outcomes. Viral factors, encompassing specific viral proteins and genetic variations, play a pivotal role in instigating and perpetuating cytokine storms and hyperinflammation among COVID-19 patients [52]. Notably, the SARS-CoV-2 spike protein, particularly the S1 subunit housing the RBD, possesses the capacity to directly stimulate immune cells and provoke the production of proinflammatory cytokines such as IL-6 and TNF-α. Moreover, viral proteins like the nucleocapsid protein (N) and Nsp1 have been implicated in modulating host immune responses and fostering the release of cytokines [53] (fig. 2).

Genetic variations within the viral genome, particularly mutations found in the ORF3a and ORF7a genes, have been linked to heightened cytokine production and increased disease severity among COVID-19 patients. These genetic alterations have the potential to bolster viral replication and intensify host immune responses, thereby triggering exaggerated inflammatory reactions and the onset of cytokine storm [54, 55]. Moreover, viral elements implicated in immune evasion, such as the inhibition of IFN signaling, can compromise host antiviral defenses and foster hyperinflammation. Notably, proteins encoded by SARS-CoV-2, such as Nsp1 and Nsp3, disrupt crucial signaling pathways integral to innate immunity, thus resulting in dysregulated cytokine responses and exacerbating inflammatory pathology [56].

**Interplay between host and pathogen**

**Immunopathology**

The dysregulated production of proinflammatory cytokines, known as cytokine responses, is pivotal in the immunopathology associated with severe COVID-19 [38]. Upon viral invasion, the host immune system initiates a response characterized by the release of cytokines, including IL-6, TNF-α, and IL-1β, among others [40, 41]. In severe cases, this dysregulation can culminate in a hyperinflammatory condition termed cytokine storm. This excessive immune activation contributes to tissue damage, multi-organ dysfunction, and unfavorable clinical outcomes. Moreover, cytokine storm is closely linked to the development of ARDS, a severe complication characterized by extensive lung inflammation in COVID-19 patients [52]. The dysregulated cytokine responses observed in severe cases of COVID-19 are believed to arise from a combination of viral factors and host immune dysregulation. SARS-CoV-2 infection triggers the activation of innate immune sensors, such as TLRs and RLRs, leading to the production of proinflammatory cytokines. Additionally, viral proteins such as the nucleocapsid protein (N) and Nsp1 have been implicated in modulating host immune responses and promoting cytokine release [57] (fig. 2).

**Role of renin-angiotensin system (RAS)**

The Renin-Angiotensin System (RAS) is a fundamental regulatory pathway crucial for maintaining blood pressure, fluid balance, and inflammatory responses. ACE2, a pivotal component of the RAS, acts as the cellular receptor facilitating the entry of SARS-CoV-2 into host cells [58]. Upon binding to ACE2, SARS-CoV-2 leads to the downregulation of ACE2 expression, resulting in disrupted RAS signaling and imbalanced levels of angiotensin II (Ang II). This dysregulation in COVID-19 is characterized by heightened production of Ang II and activation of the Angiotensin Type 1 Receptor (AT1R), ultimately culminating in increased vascular permeability, inflammation, and tissue damage (fig. 2). The inflammation mediated by Ang II is intricately linked to the development of acute lung injury and ARDS, severe complications often observed in COVID-19 patients [59]. Furthermore, dysregulated RAS signaling may exacerbate endothelial dysfunction, thrombosis, and cardiovascular complications in individuals affected by COVID-19 [60]. Understanding the intricate interplay of the renin-angiotensin system in COVID-19 pathogenesis is pivotal for devising targeted therapeutic interventions to mitigate severe outcomes associated with the disease.

**Impact of host genetics**

Host genetics significantly influence individual susceptibility to viral infections and the severity of diseases like COVID-19. Genetic variations in crucial host factors, including genes encoding viral receptors, immune response pathways, and antiviral defence mechanisms, play pivotal roles in determining the outcome of viral encounters. For instance, genetic alterations within the ACE2 gene, responsible for encoding the cellular receptor utilized by SARS-CoV-2, may impact the virus's ability to bind and enter cells, thereby shaping an individual’s vulnerability to infection [61]. Similarly, gene variations governing innate and adaptive immune responses, such as TLRs, cytokines, and HLA genes, can significantly influence immune reactions to SARS-CoV-2 and affect disease severity. Additionally, host genetic factors can also affect how individuals respond to therapeutic interventions, including antiviral medications and vaccines. Understanding these genetic variations is essential for the development of personalized therapeutic approaches to mitigate the impact of SARS-CoV-2 infections on public health.

predispositions is essential for developing personalized approaches to combat COVID-19 effectively [62]. Comprehending the impact of host genetics on both susceptibility to COVID-19 and the severity of its associated outcomes is paramount for identifying individuals at heightened risk and devising personalized treatment regimens. Incorporating host genetic data into clinical protocols holds promise for enhancing risk assessment and refining therapeutic strategies for COVID-19 patients.

Fig. 2: Interaction of coronavirus with host proteins

Each stage of viral replication, including attachment and entry, translation of viral replicase, genome transcription and replication, translation of structural proteins, and virion assembly and release, relies on host factors. These interactions may induce changes in cellular structure and function, triggering host stress responses, autophagy, cell death, and innate immune processes. This illustration elucidates the molecular mechanisms through which SARS-CoV manipulates host cell death pathways, innate immune responses, translation, intracellular signalling, regulatory pathways, and cell-cell junctions. (Image has been generated with Reactome Pathway)

Vaccines and their impact on hps

Gaining insight into the influence of vaccines on host-pathogen interactions is imperative for comprehending immune protection mechanisms and formulating robust vaccination strategies. Vaccines stimulate a comprehensive immune response, activating both innate and adaptive immunity to confer durable protection against pathogens [63]. Incorporating an understanding of host-pathogen interactions into vaccine design and development holds substantial promise for bolstering vaccine effectiveness and tackling the obstacles presented by emerging variants of concern [64].

Vaccines are meticulously engineered to emulate the presence of a pathogen, such as a virus or bacterium, while avoiding disease manifestation, prompting the immune system to recognize and memorize the pathogen’s characteristics. This recognition enables the immune system to mount a swift and vigorous response upon subsequent encounters with the actual pathogen. For instance, in the context of SARS-CoV-2, the virus responsible for COVID-19, vaccines like the Pfizer-BioNTech and Moderna mRNA vaccines [65], as well as the Johnson and Johnson viral vector vaccine [66], have been developed to target the virus’s spike protein, a crucial component for viral entry into host cells. By focusing on the spike protein, these vaccines trigger the production of neutralizing antibodies and activate T cells, furnishing protection against SARS-CoV-2 infection. The influence of vaccines on host-pathogen interactions has been thoroughly examined across different experimental models, including murine models of pulmonary tuberculosis induced by Mycobacterium tuberculosis [67]. Studies have indicated that vaccination can impact the prevalence of more virulent strains within the lungs of vaccinated subjects, underscoring the intricate dynamics between the host’s immune response and the pathogen. Furthermore, the impact of vaccinated hosts on the population structure of microorganisms has been elucidated, particularly in the context of “imperfect vaccines,” which function by attenuating the growth rate of a microorganism rather than entirely preventing infection and transmission to new hosts [67].

Transcriptomics, a field of study focusing on the analysis of RNA transcripts, has proven invaluable in elucidating the intricate dynamics of host-pathogen interactions. By examining the gene expression profiles of host cells during severe SARS-CoV-2 infection and following vaccination, researchers have gained crucial insights into the human body’s immune response [68, 69]. This comprehensive understanding is pivotal for tracking the evolution of viruses like SARS-CoV-2 and evaluating the implications of emerging variants of concern. Armed with this knowledge, scientists can tailor next-generation vaccines and vaccination strategies to effectively combat the evolving landscape of infectious diseases.

Multi-omics in studying hps

The amalgamation of multi-omics data has enabled the discernment of prospective therapeutic targets, the formulation of diagnostic markers, and the elucidation of the intricate interactions between the virus and the host. These advanced technologies, characterized by their high-throughput nature, have furnished a holistic comprehension of the molecular terrain of SARS-CoV-2 infection, the host’s immune reaction, and the pathophysiological underpinnings of COVID-19 [70].

Genomics and transcriptomics in COVID-19

Metagenome sequencing stands as a pivotal high-throughput genomics methodology for swiftly identifying emerging pathogens and accurately diagnosing COVID-19. This approach directly extracts
genetic information from environmental samples, laying the groundwork for comprehensive microbiota sequencing. For instance, in a study conducted by Lin et al., 310 clinical samples from 248 COVID-19 patients underwent metagenome sequencing, revealing the presence of SARS-CoV-2 in 98.7% of the samples. Moreover, a multiomics investigation integrated proteomics, metabolomics, phosphoproteomics, and exometabolome analyses to thoroughly delineate the host responses provoked by SARS-CoV-2 infection in human lung epithelial cells [71]. The research delineated the activation of the Hippo signaling pathway, perturbations in metabolic pathways, and immune pathways in reaction to SARS-CoV-2 infection. Furthermore, it pinpointed various prospective therapeutic targets, encompassing the Hippo signaling pathway [71, 72], the interferon signaling pathway [73], and the NF-kB pathway [74].

The COVID-19 Host Genetics Initiative has convened the human genetics community to collate, exchange, and scrutinize data aimed at unraveling the genetic underpinnings of COVID-19 susceptibility, severity, and prognosis [75]. By amalgamating genomics data, investigators have pinpointed potential genetic predisposing factors linked to severe COVID-19, including variants in the human leukocyte antigen (HLA) genes [76] and the IFN-induced transmembrane protein-3 gene [77].

Proteomic and metabolomics

The exploration of proteomics and metabolomics has proven pivotal in delineating the intricate proteomic and metabolic shifts elicited by SARS-CoV-2 infection. These investigations have unveiled a comprehensive spectrum of alterations, shedding light on changes in immune responses, fatty acid metabolism, amino acid metabolism, and other critical pathways. For instance, in a study conducted by Wang et al., the proteomic and metabolomic profiles associated with the immune response were scrutinized in individuals vaccinated with an inactivated SARS-CoV-2 vaccine. The findings underscored the impact of COVID-19 infection on pathways linked to arginine biosynthesis, alanine, aspartate, and glutamate metabolism, as well as glycine, serine, and threonine metabolism. Furthermore, the investigation demonstrated notable alterations in various pathways after vaccination with the inactivated SARS-CoV-2 vaccine, encompassing vitamin B6 metabolism, biosynthesis of unsaturated fatty acids, and phenylalanine metabolism, among others [78].

Proteomic analysis has unveiled aberrations in the extracellular matrix [79], immunity [80], and homeostasis [81] among COVID-19 survivors in comparison to healthy individuals. Elevated levels of specific proteins associated with inflammation and immune response, such as IL-6, CRP, and ferritin, were observed in COVID-19 patients [82].

Additionally, metabolic investigations have delineated notable changes in the immune response [83], fatty acid metabolism [84], and amino acid metabolism [85] among individuals afflicted with COVID-19. Further, the abnormal metabolite profile offers insights into the dysregulated biological pathways, contributing valuable understanding to the pathogenesis of COVID-19. For instance, a study by Vakil et al. highlighted specific metabolites, such as cytosine and inosine-3′-acetic acid, which exhibited differential expression, predominantly distinguishing between COVID-19-positive and negative patients alongside other metabolites. Another study delved into the potential utility of saliva and plasma metabolomic profiles as a means of risk stratification among COVID-19 patients. The investigation revealed that severe cases of COVID-19 correlate with dysregulated innate immunity, lymphopenia, cytokine storm, and altered metabolite profiles [86]. These observations hold substantial importance in tailoring personalized diagnostic and therapeutic interventions, ultimately enhancing patient prognosis. Through the analysis of multiomics data across various infection stages, researchers can pinpoint disease progression biomarkers, prognosticate patient outcomes, and customize treatment approaches. The integration of multiomics data harbors the potential to drive the advancement of personalized diagnostic and therapeutic methodologies, thereby fostering enhanced patient outcomes.

CONCLUSION

The COVID-19 pandemic has posed a significant challenge, manifesting across a spectrum of clinical presentations from asymptomatic cases to severe respiratory compromise and multi-organ dysfunction. Host-related variables such as age, gender, underlying health conditions, and genetic predisposition contribute to the diverse severity observed in patients, underscoring the necessity for personalized medicine strategies in patient care. The integration of advanced methodologies such as multiomics has yielded a holistic understanding of the molecular dynamics of the disease, unveiling novel insights into host immune reactions, viral pathogenesis, and disease evolution. Moving forward, the future of COVID-19 research entails integrating longitudinal multiomics data to capture the temporal dynamics of host responses, establishing standardized multiomics methodologies for data analysis and interpretation, and exploring novel therapeutic strategies targeting host-pathogen interactions. Nevertheless, challenges such as complexities in data integration, ethical considerations, and the imperative for interdisciplinary collaboration persist as obstacles to furthering our comprehension of COVID-19 pathogenesis.

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REFERENCES


COVID patients to elderly patients: a comparison with young and middle pathogenesis and therapeutic implications

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