Interactions of SARS-CoV-2 & Variants with Cellular Components

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Given the global scale of the COVID-19 pandemic and the health emergency it has caused, it is crucial to understand the impact of SARS-CoV-2 and its mutations. Here, we comprehensively review SARS-CoV-2 interactions with host cells, describe SARS-CoV-2 variants, assess impact of their protein mutations and enumerate databases with SARS-CoV-2 host-pathogen interaction data.

Keywords: SARS-CoV-2 ; SARS-CoV-2 Mutants ; Host Pathogen Interactions ; Proteins ; miRNA ; Innate Immunity

1. Introduction

The outbreak of Coronavirus Disease 2019 (COVID-19) is caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). The virus was first detected in the city of Wuhan, China, around December 2019 [1]. Due to the exponential rise in COVID-19 infections across countries, COVID-19 was declared a pandemic by the World Health Organization (WHO) on 11 March 2020 [2]. COVID-19 has caused a global health crisis, infecting over 191 million individuals with over 4 million deaths as of June 2021 (https: //www.worldometers.info/coronavirus/, accessed 30 June 2021).

SARS-CoV-2 is among the largest RNA viruses, ranging from 26-32 kilobases, and comprises two large open reading frames (ORF1a and ORF1b) [3][4]. The two ORFs translate into replicase polypeptides (pp1a and pp1b) that form the non-structural proteins essential for viral replication [5][6]. The complete assembly of SARS-CoV-2 is aided by the structural proteins (spike (S), envelope (E), membrane (M), and nucleoprotein (N)). [6].

RNA viruses demonstrate rapid evolution due to a high mutation rate which is a million times higher than the host mutation rate [7][8]. The high mutation rate in SARS-CoV-2 is attributed to the enormous genome variability that enabled it to the escape host immune response and antiviral therapeutics. The evolving nature of SARS-CoV-2 has resulted in several new strains of the virus across the world, including highly infectious B.1.1.7/Alpha (UK), B.1.351/Beta (South Africa), B. 1.1.28/Gamma (Brazil), B.1.617.2/Delta (India), and C.37/Lambda (South America) variants [9][10][11][12][13]. Multiple studies have reported that rapidly evolving new strains of SARS-CoV-2 exhibit decreased susceptibility to antiviral therapeutics and escape neutralization by vaccine-induced humoral immunity in the host [14][15][16]. The evolution has urged for the need to dissect the molecular features in the virus that enhance its infectious capacity and modulates host cells through direct and indirect interactions in various cellular components. Several studies on sequence variation in the SARS-CoV-2 genome have also identified an abundance of mutations in the spike protein of the virus that enables its entry into the host cell [17][18][19][20][21][22].

2. SARS-CoV-2 Interactions with Host Cellular Components

Various structural, non-structural, and accessory proteins interact with host cellular components to regulate the biological processes [23]. Several host RNA molecules such as small nuclear RNA (snRNA), 18s rRNA, and the 7SL RNA component of the signal recognition particle (SRP) are shown to interact with SARS-CoV-2 [24]. The E protein binds to BRD proteins and disrupts BRD binding with histones [25][26]. E and M proteins are also found in cellular compartments involved in intracellular tracking (Golgi apparatus, ER, ERGIC) [27][28]. The N protein interacts with host factors RNA factors to protect genome from nucleases and pattern recognition proteins [29]. Non-structural proteins interact with snRNAs and signal recognition proteins [30].

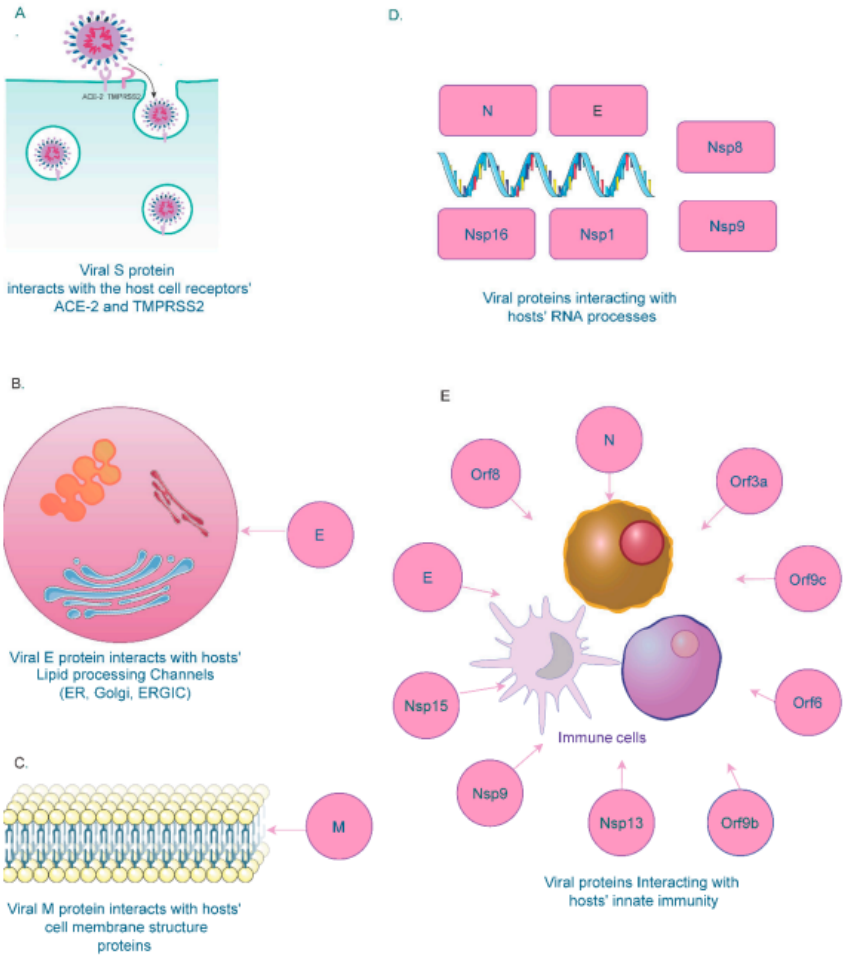

Figure 1. SARS-CoV-2 Interactions with Host Cellular Components.

2.2. SARS-CoV-2 Interactions with Host Immune System

Various viral structures have been identified to interact with several components of the host innate immune system. Several of the viral non-structural proteins (Orf6, Orf9, Nsp13, and Nsp15) targets proteins of the IFN pathway, resulting in a dysregulated immune response [31][32][33]. Viral E and ORF8 proteins also promote high cytokine levels; cytokine storms marked by hyperactive inflammatory response are associated with severe COVID-19 cases and poor outcomes [34][35]. Depletion of cellular nucleic acid binding proteins is also associated with higher viral titers [36].

3. SARS-CoV-2 Interactions with Host RNA-Binding Proteins & microRNAs

SARS-CoV-2 modulates the host immune response by suppressing these signaling pathways to support the viral life cycle and propagate infection. Experimental and computational studies indicate multiple host RBPs have direct and specific binding to the SARS-CoV-2 RNA genome. miRNA profiling experiments and computations also find miRNA with binding sites in SARS-CoV-2 ORFs and 5′ and 3′ UTRs also modulate mRNAs of proteins associated with viral entry [37]. Sequestration of miRNA on the viral genome could also enhance viral replication and suppress the host immune response[38][39].

Table 1. Interaction between SARS-CoV-2, human RBPs, and microRNAs.

Interactions between SARS-CoV-2, Human RBPs, and miRNAs	Technique Used
332 SARS-CoV2–host protein–protein interaction	AP-MS
309 host proteins interaction with SARS-CoV-2 RNA	ChIRP-MS
Host RAB2A, RAB7A, and RAB10 interaction with both viral RNA and protein	CRISPR Cas-9-based perturbation
25 human RBPs targeting SARS-CoV-2 viral RNA	RBP motif-based in silico prediction
104 human proteins directly and specifically bind to SARS-CoV-2 RNAs	RAP-MS
288 host miRNAs predicted to bind SARS-CoV-2 (ORF1ab, N, S, 5′-UTR, and 3′-UTR)	Bioinformatic prediction algorithms and miRNA profiling

Interactions between SARS-CoV-2, Human RBPs, and miRNAs	Technique Used
479 human miRNAs could target various SARS-CoV-2 genes (S, E, M, N, Orf 1ab, 3a, 6, 7, 8, and 10)	Machine learning-based miRNA prediction
22 miRNAs could bind throughout the length of the SARS-CoV-2 viral genome	Computational approach using FIMO

4. SARS-CoV-2 Protein Mutations & Impact

We evaluate reported and predicted synonymous, nonsynonymous, insertion, and deletion mutations in SARS-CoV-2 proteins. Many mutations occur in the spike (S) and nucleocapsid proteins (N) and ORF1ab polyprotein, which are vital for viral cellular entry, structure and replication. Several non-synonymous mutations (S N354D, N R203K) alter protein secondary structure and solvent accessibility [40][41] . Moreover, some mutations may be linked to changes in virus transmissibility and antigenicity.

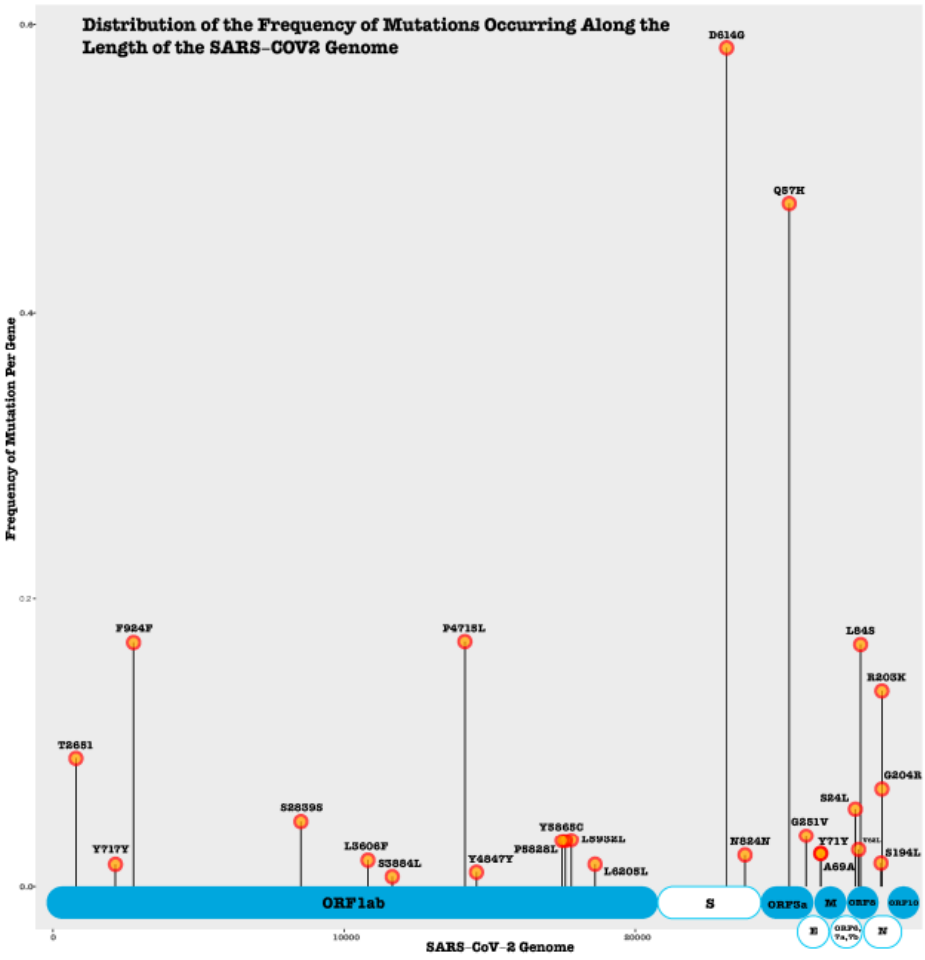

Figure 2. SARS-CoV-2 Protein Mutation.

5. Database Resources for SARS-CoV-2 Host-Pathogen Interactions

Several databases provide SARS-CoV-2 Host-Pathogen Interaction (HPI) data including protein–protein, protein–RNA and RNA–RNA interactions. We identify eight public-available databases covering at least one of these interaction types: SARS-3D, VirHostnet, BioGRID, IntAct, Human Proteome Atlas, Intomics, Protein Data Bank and STRING-DB. We also note six other databases well poised to accomodate SARS-CoV-2 HPI data.

Table 2. Publicly available databases containing at least one of the SARS-CoV-2 HPI types.

Database	Interaction(s)	URL	Description
SARS-3D	Protein–protein	http://sars3d.com (accessed on 30 June 2021)	3D protein models predicted using genome data

Database	Interaction(s)	URL	Description
VirHostNet	Protein–protein	http://virhostnet.prabi.fr (accessed on 30 June 2021)	Interactions between SARS-CoV-2 and human proteins
BioGRID (curated dataset)	Protein–protein	https://thebiogrid.org/project/3 (accessed on 30 June 2021)	Curated coronavirus dataset with 22,223 interactions over 110 proteins
IntAct	Protein–protein and protein–RNA	https://www.ebi.ac.uk/intact/query/annot:%22dataset:coronavirus%22 (accessed on 30 June 2021)	Over 4400 binarized SARS-CoV-2–human molecular interactions
Human Proteome Atlas	Protein–protein	https://www.proteinatlas.org (accessed on 30 June 2021)	Summary of tissue and cell expression patterns of human proteins interacting with SARS-CoV-2
Intomics	Protein–protein	https://www.intomics.com/covid19/?utm_source=intomics&utm_medium=linkedin&utm_campaign=covid19 (accessed on 30 June 2021)	PPI network based on transcriptional response in human SARS-CoV-2-infected cells
Protein Data Bank	Protein–protein	https://www.rcsb.org/news?year=2020&article=5e74d55d2d410731e9944f52&feature=true (accessed on 30 June 2021)	Protein–protein complex crystal structures (i.e., S—ACE2 complex)
STRING-DB	Protein–protein	https://string-db.org/cgi/covid.pl (accessed on 30 June 2021)	Protein–protein interaction network with 332 virus-interacting human proteins

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