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Mini-review on Evolutionary Dance between Innate Host Antiviral Pathways and SARS-CoV-2

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Abstract

Coronaviruses have been circulating in the human population for thousands of years and the human immune system is ineffective in fighting them. However, the innate immune response is a promising avenue for therapeutics against SARS-CoV-2 and other emerging viruses. Deficiencies in innate immune signalling are associated with poor outcomes in SARS-CoV-2 patients, emphasizing the need to understand and harness these mechanisms in the fight against the virus. Innate antiviral strategies range from the direct inhibition of viral components to reprograming the host's own metabolic pathways to block viral infection. The current knowledge of the innate immune signaling pathways triggered by the SARS-CoV-2 with a focus on the type I interferon response, as well as the mechanisms by which SARS-CoV-2 impairs those defenses.

Keywords: SARS-CoV-2; COVID-19 pandemic; Innate immunity; ISGs; Interferon pathways

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the etiologic agent of coronavirus disease 2019 (COVID-19). As a pandemic virus, SARS-CoV-2 has attracted extensive research attention. As a member of the Coronaviridae family of viruses, SARS-CoV-2 has many structural, pathological, and epidemiological features that overlap with other infectious viruses [1]. The latter observation has allowed notably advanced investigational starting points, thus further contributing to the explosion of scientific discovery. In The Evolutionary Dance between Innate Host Antiviral Pathways and SARS-CoV-2, our group sought to summarize the existing understanding of the unique features of SARS-CoV-2 and COVID-19, how the innate immune system detects SARS-CoV-2; the mechanisms by which SARS-CoV-2 disrupts innate immune responses; and the interferon-stimulated genes specific to SARS-CoV-2 infection [2]. Here, we provide a brief synopsis of this review. We hope that the scientific and medical communities harness our insights as a foundation for developing new techniques and therapeutics to combat SARS-CoV-2 and other emerging viruses.

Literature Review

Unique properties of SARS-CoV-2

SARS-CoV-2 falls into the same betacoronavirus genus as the highly pathogenic SARS-CoV-1 and MERS-CoV, as well as the milder HCoV-OC43 and HCoV-HKU1 [3]. However, SARS-CoV-2 carries differences in genome organization and protein structure that may significantly contribute to the enhanced infectiousness of the virus and the additional symptoms of COVID-19 [4,5]. Moreover, the differing mechanisms by which SARS-CoV-2 interferes with host immune responses may help to explain the apparent pathogenic and epidemiologic differences of SARS-CoV-2 and COVID-19. For example, the gastrointestinal and neurological symptoms of COVID-19, the ineffectiveness of many existing antiviral therapeutics against SARS-COV-2, the higher incidence of asymptomatic SARS-CoV-2 infections, the morbidity, and mortality observed in acute COVID-19 infection, and the appearance of Multi-Inflammatory Syndrome (MIS) may all be attributed to the unique properties of SARS-CoV-2 [6].

Innate immune detection of SARS-CoV-2

The two main Pattern Recognition Receptors (PRRs) that detect SARS-CoV-2 Pathogen-Associated Molecular Patterns (PAMPs) are Toll-Like Receptors (TLRs) and Retinoic Acid-Inducible Gene 1 (RIG-1)-Like Receptors (RLRs), especially on the involvement of TLR2, TLR3, TLR4, and TLR7 in SARS-CoV-2 detection by the innate immune system [7]. TLR2, which generally recognizes viral proteins, recognizes SARS-CoV-2 viral Envelope (E) protein; multiple lines of evidence suggest an important role of TLR2 in SARS-CoV-2 antiviral defense [8,9]. TLR3, which generally recognizes transient viral double-stranded RNA intermediates during replication, may affect mortality due to SARS-CoV-2 infection [10]. TLR4, a cell membrane-bound PRR known to recognize various PAMPs, is a likely factor responsible for the cytokine storm phenomenon observed in severe cases of COVID-19 [11-13]. TLR7, an endosomal receptor that generally recognizes viral single-stranded RNA, may also hold an important role in the antiviral defense against SARS-COV-2, as suggested by an apparent relationship between aberrant TLR7 and severe COVID-19 [14].

RIG-1 and Melanoma Differentiation-Associated Gene 5 (MDA-5) are the main RLRs in detecting SARS-CoV-2. RIG-1 generally recognizes short viral RNA molecules, and MDA-5 favorably binds double-stranded RNA molecules during viral replication. The binding of substrate RNA by RLRs triggers a signaling cascade involving Mitochondrial Antiviral Signaling Proteins (MAVS) that ultimately results in the transcription of Interferon Type I (IFN-I) and Interferon Type III (IFN-III), which subsequently upregulate the expression of specific Interferon-Stimulated Genes (ISGs) [7]. Although the binding of RIG-1 and MDA-5 to their respective SARS-CoV-2 targets has been demonstrated, the consequent antiviral effects have not been readily observed. Timing of interferon responses and host age may be important factors in RLR-mediated control of SARS-CoV-2 infections [15].

The role of SARS-CoV-2 proteins in disrupting innate immune responses

The SARS-CoV-2 genome consists of a 5'-cap, ORF1ab, S (spike protein), ORF3, E (envelope protein), M (outer membrane glycoprotein), ORF6, ORF7, ORF8, N (nucleocapsid protein), ORF10, and a 3'-polyA tail. ORF1ab, which utilizes -1 Programmed Ribosomal Frame shifting (PRF) in the translation of numerous viral proteins from a single template, encodes sixteen Non-Structural Proteins (nsp1-16), and the remaining Open Reading Frames (ORFs) encode one or two accessory proteins each nsp3 and nsp5 are responsible for the post-translational cleavage of the remaining individual NSPS. SARS-CoV-2 has adapted secondary functions for many of these proteins to subvert host immune responses. Here, we provide an abridged overview of the extensive list of functions of the SARS-CoV-2 structural proteins; the S, M, and N proteins have notable roles in disrupting innate immune responses. As the primary virulence factor of the virus, the S protein directly mediates cell invasion and even interferes with host cell translation to limit the antiviral response [16]. The S1 domain, which projects outward and is exposed to host antibodies, is hypervariable, leading to novel variants with advantages in establishing infection and evading the immune system. The M protein, which binds the N protein during viral assembly, interacts with multiple host factors involved in interferon signaling cascades, including RLR signaling, resulting in an anti-IFN activity [17]. The M protein also interferes with the expression of ISGs *via* ubiquitin-dependent modulation of RLR and NF-κB pathways [18,19]. Additionally, the N protein interferes with RLR pathways and ISG expression [20,21].

Nearly every SARS-CoV-2 nsp has one or many roles in disrupting innate immune responses. For example, beyond its function in redirecting host machinery toward viral mRNA synthesis, nsp1 suppresses the expression of host proteins, including TLRs [22]. Along with their primary function in processing the viral polyprotein, nsp3 and nsp 5 disrupt innate immune responses through cleavage, de-ubiquitination, and de-ISGylation [23,24]. Nsp1, nsp2, nsp3, nsp6, nsp 7, nsp12, nsp13, nsp14, and nsp15 are each known to disrupt different stages of IFN signaling *via* interactions with Interferon Regulatory Factor 3 (IRF3) and/or other pathways components [20,22,25-27]. Other nsps, such as nsp8 and nsp9, interfere with protein and nuclear trafficking *via* interactions with signal recognition particle RNA (7SL and others) and nucleoporins (e.g., NUP62), thereby disrupting innate immune functions [26,28]. Interestingly, nsp10 and nsp14 work together to affect translation and limit the expression of ISGs through exonuclease activity, and nsp14 and nsp16 work together to cap viral mRNA to avoid recognition and degradation by host innate immune responses [25,28].

Many accessory proteins encoded by ORFs other than ORF1ab also have roles in innate immune disruption. Some of these accessory proteins, such as ORF3b, ORF4a, ORF5, ORF6, ORF8, and ORF9b, have actions similar to those of nsps, especially in limiting IFN and NF-κB pathways *via* interaction with IRF3 and other pathway components [20,29]. ORF3a and ORF6 are notable for interfering with the actions of STAT1/2, limiting ISG activation in IFN-stimulated cells [20,30]. Other ORF accessory proteins have unique roles, like ORF3a, which can bind a ubiquitin ligase involved in innate immune signaling, and ORF7a, which has been shown to activate mitogen p38 [31].

Discussion

Interferon stimulated genes

Recognition of components of SARS-CoV-2 by TLRs and RLRs induces IFN-I and IFN-III; IFNs then regulate a subset of ISGs specific to SARS-CoV-2 infection and host cell type [32]. Together, IFNs and ISGs reprogram host metabolic pathways to respond to infection. However, negative feedback controls are necessary to stabilize the hyperinflammatory state often presented in severe COVID-19 cases.

ACE2: SARS-CoV-2 binds ACE2 in epithelial cells of the trachea, bronchi, alveoli, and other tissues. ACE2 is an important regulator of blood pressure, fluid-electrolyte balance, and vascular leakage, so decreased ACE2 availability due to binding by viral particles has been implicated as a potential factor in severe COVID-19 pathology. As an ISG, ACE2 stimulation by IFNs would theoretically serve as a potential virulence mechanism by increasing accessibility to viral particles [33,34]. However, this theory remains speculative as IFN-induced ACE2 does not appear to enhance viral replication [35].

ISG15: When stimulated by IFN-I, ISG15, a ubiquitin-like protease, is conjugated to viral proteins in an antiviral process called ISGylation [36]. SARS-CoV-2 papain-like protease (PLpro; nsp3) can de-ISGylate proteins, thereby increasing the levels of free (unconjugated) ISG15, inducing the production of cytokines, and ultimately resulting in the aberrant inflammatory responses observed in severe COVID-19 [37].

IFIT: As their name suggests, IFN-induced proteins with Tetratricopeptide Repeats (IFITs) are cytosolic proteins known to be highly induced upon activation of the IFN-I signaling pathway. IFITs contain Tandem Tetratricopeptide Repeats (TPRs), influencing various biological functions [38]. Broad antiviral activity by IFITs has been observed against infection by several viruses. The SARS-CoV-2 infection has been shown to induce IFITs in human epithelial lung cell lines, suggesting potential antiviral functions.

IFITM: Interferon-Induced Transmembrane Proteins (IFITMs) are small proteins that exhibit antiviral activity by changing the mechanical features of cell membranes [39]. The effectiveness of each IFITM family member in inhibiting viral infection depends on the infecting virus, although broad protection by IFITM3 has been demonstrated against several enveloped viruses [40]. The observed inability of IFITMs to inhibit SARS-CoV-2 infection has resulted in doubts about IFITMs antiviral role against coronaviruses, but conflicting findings may be due to artificial testing conditions [41].

Nonetheless, an association between a particular IFITM3 variant and severe symptoms of COVID-19 has been observed [42].

LY6E: Variable expression of Lymphocyte antigen 6 complex, locus E (LY6E) has been observed following infection by different viruses. In various cell types, LY6E expression has been observed to promote infection by several viruses [43]. However, LY6E-expressing cell lines have been observed to resist infection by numerous coronaviruses, including SARS-CoV-2 [44].

ZAP: Zinc-Finger Antiviral Protein (ZAP) can recognize CpG dinucleotides in viral RNA, thereby targeting RNAs for exosome-mediated degradation. ZAP isoforms produced by alternative splicing, which contain an identical N-terminal RNA binding domain, carry diverse and distinct antiviral functions. The long ZAP isoform (ZAP-L), which possesses a C-Terminal Poly (Adp-Ribose) Polymerase (PARP) domain containing a CaaX-box motif that facilitates interaction with cofactors, appears to have more potent antiviral activity against SARS-CoV-2, even though the short ZAP isoform (ZAP-S) is more strongly induced by activation of the IFN-I signaling pathway [45]. It can impair the PRF utilized by SARS-CoV-2 to produce viral proteins. ZAP-S also appears to function in the negative feedback loop that regulates IFN-I and IFN-III expression, suggesting its importance in controlling post-viral infection cytokine storms. However, SARS-CoV-2 has appeared to develop the ability to suppress CpG dinucleotides to avoid ZAP-mediated viral RNA degradation [46]. Resistance to ZAP has been observed in many other viruses, so ZAP antiviral activity does not appear universal.

OAS/RNAse L system: Polymorphisms in the Oligoadenylate Synthase (OAS) family of proteins have been associated with severe COVID-19. Upon detecting viral dsRNA in the cytosol, OAS generates 2'-5'-linked oligoadenylate second messengers to activate Latent Ribonuclease (RNAse L) to degrade viral RNA [47].

BST2: Bone marrow stromal antigen 2 gene encodes tetherin (Bst-2), a lipid raft-associated protein that can prevent the viral infectious spread by tethering mature virions to the cell surface. Although Bst-2 can restrict SARS-CoV-2 virion release, the virus has developed countermeasures such as S protein-mediated targeting of Bst-2 to lysosomal degradation [48]. The Bst-2-mediated restriction of SARS-CoV-2 spread is likely dependent on N-terminal glycosylation and the transmembrane domain.

CH25H: Cholesterol-25-hydroxylase (CH25H) converts cholesterol to 25-hydroxycholesterol (25HC) and is, therefore a critical element in cholesterol homeostasis. However, CH25H has recently been identified as an ISG expressed during SARS-CoV-2 infection. CH25H and 25HC have broad antiviral activity against various viruses, including SARS-CoV-2. Numerous mechanisms of CH25H/25HC antiviral activity have been proposed and investigated [49]. 25HC inhibits multiple stages of the viral life cycle, and both the expression of CH25H and the serum concentration of 25HC are elevated during SARS-CoV-2 infection. 25HC may inhibit viral-host membrane fusion, possibly by altering membrane curvature. When conjugated with 25HC, EK-1 can block the formation of six-Helix Bundles (6HB), a structure that promotes S protein-mediated viral-host membrane fusion. 25HC activates Acyl-Coa Cholesterol Acyltransferase (ACAT), thereby promoting the depletion of cholesterol accessible to the cell membrane and Liver X Receptor (LXR), activating the transcription of genes involved in cholesterol export [50]. Finally, 25HC inhibits inflammatory cytokines like IL1β, suppressing the uncontrolled activation of inflammatory responses. In general, inhibiting lipid biosynthesis through activation of IFN-I pathways ultimately establishes an antiviral state, particularly by influencing the composition and structure of cell membranes [51].

FASN: Fatty Acid Synthase (FASN) might more aptly be deemed an interferon-inhibited or deactivated gene. It is involved in synthesizing the fatty acid palmitate (C16:0), and thus influences the composition of fatty acids in cell membranes [52]. Because optimal membrane fluidity is required for viral infection, FASN is necessary for optimal viral growth, and inhibition of FASN, which results in the impairment of protein palmitoylation and neutral lipid synthesis, can impact viral infection at multiple stages of the viral life cycle, including cell entry, replication, and budding [53]. Specifically, SARS-CoV-2 utilizes distinct spherical organelles built from vesicular membranes as viral replication factories and palmitoylates multiple proteins during infection. Pharmaceutical inhibition of FASN has been shown to block SARS-CoV-2 replication, limit infection, and improve survival (in mice) [52].

Conclusion

The human population has likely been exposed to coronaviruses for thousands of years, with the first human coronavirus, HCoV-229E, being discovered in the 1960s. Despite this, the human immune system is unable to mount a prolonged and efficacious response against coronaviruses, leading to the emergence of new variants that can evade current vaccines and monoclonal antibodies. However, the innate immune response, which has evolved over hundreds of millions of years to defend against pathogens, remains a promising avenue for therapeutics against SARS-CoV-2 and other emerging viruses. Studies have demonstrated that deficiencies in innate immune signaling are associated with poor clinical outcomes in SARS-CoV-2 patients, highlighting the importance of understanding and harnessing these mechanisms in the fight against the virus.

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Author Contributions

All authors contributed to the study and manuscript writing. Lulan Wang and Nathaniel A. Sands wrote the manuscript. All authors have revised and approved the final draft of the paper.

Conflict of Interest

The authors declare no conflict of interest.

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