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Review Article

Host's innate immune response to SARS-CoV-2 infection—Current understanding and trends

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Abstract

The COVID-19 pandemic, which began in 2019 due to SARS-CoV-2, remains a global health crisis, especially as new variants emerge that could trigger widespread outbreaks again. While various aspects of SARS-CoV-2 infection warrant attention, the antiviral innate immune response is a crucial area of focus. Understanding how viruses evade host defenses is vital for developing effective vaccines and therapies. SARS-CoV-2 targets key components of the innate immune system for its survival, and this interference with the host immune system is central to the virus's ability to cause disease. However, the specific mechanisms by which the innate immune response counteracts SARS-CoV-2 infection have not been fully clarified. This review examines key elements of the antiviral innate immune response to SARS-CoV-2 infection, concentrating on viral evasion strategies and potential therapeutic targets.

Keywords: Innate immunity, SARS-CoV-2, COVID-19, viral proteins, Host immunity, MiRNA

Innate Immune Response and SARS-CoV-2 Infection

The innate immune response is the body's first defense mechanism and is activated within minutes to hours of viral entry. Upon detection of the virus, pattern recognition receptors (PRRs) trigger signaling cascades that produce interferon (IFN) and proinflammatory cytokines [1,2]. These responses aim to suppress the virus by inhibiting various stages of its lifecycle. However, SARS-CoV-2 has evolved to evade these responses, causing delays in immune activation, which can lead to severe consequences such as hyperinflammation and cytokine storms [2,3]. SARS-CoV-2 replication induces a delayed interferon response that is regulated by MDA5 and LGP2 in lung epithelial cells [4]. The resulting delayed immune response contributes to disease severity and is characterized by the overactivation of the immune system and tissue damage [2,5]. Dysregulation of the innate immune system plays a significant role in severe COVID-19, in which the balance between pro- and anti-inflammatory responses is disrupted. This leads to excessive inflammation and organ damage, particularly of the respiratory tract, also known as Acute-Respiratory-Distress Syndrome (ARDS) [6]. A clear understanding of the interplay between viral factors and host innate immunity is critical for developing effective treatments and vaccines [7].

Key Mechanisms of Innate Immune Response

Several stages of the innate immune response can be targeted to block SARS-CoV-2. These stages include virus recognition, interferon response, cytokine and chemokine production, natural killer (NK) cell activity, complement system activation, dendritic cell function, and viral evasion strategies.

Virus recognition and interferon response

Viral RNA is recognized by PRRs in epithelial cells, macrophages, and dendritic cells (DCs), which activate signaling pathways [1]. This results in the production of type I and III IFNs, which limit viral replication [4]. However, SARS-CoV-2 delays IFN responses to gain a replication advantage.

Cytokine and chemokine production

Infected cells release proinflammatory cytokines (e.g., IL-6, IL-1β, and TNF-α) and chemokines (e.g., CXCL10 and CCL2), which recruit immune cells to the infection site. In severe cases, dysregulated cytokine production leads to a cytokine storm that causes tissue damage and ARDS [2,3].

NK cells and viral clearance

NK cells recognize and eliminate infected cells. However, NK cell dysfunction has been observed in severe COVID-19 cases, impairing viral clearance [7]. Unconventional NK cell subsets, such as the CD56-and CD16+ population, may also emerge during infection, reflecting chronic immune activation or exhaustion and contributing to immunopathogenesis [30].

Complement activation

The complement system enhances viral phagocytosis and inflammation. However, its overactivation contributes to tissue damage and thrombosis in severe cases [7].

Dendritic cells and antigen presentation

DCs present viral antigens to T Cells, linking innate and adaptive immunity. However, SARS-CoV-2 may impair DC function and delay adaptive responses [7].

Viral host-immune evasion mechanisms

SARS-CoV-2 employs several mechanisms to evade or modulate the innate immune system. Some of the common ones are:

Inhibition of interferon signaling: SARS-CoV-2 cleverly avoids detection by turning off interferon (IFN) signaling, which is essential for early immune defense. Viral proteins such as Nsp1, Orf6, and Orf3b function as disruptors. Nsp1 inhibits the cell's ability to produce new proteins, including those necessary for the IFN response. Orf6 sequesters key signaling proteins within the nucleus, preventing them from functioning correctly. Orf3b directly suppresses IFN production itself. By turning off this critical communication pathway, the virus effectively hides from the immune system, gaining a crucial advantage to replicate and spread (**Table 1**).

Delayed pattern recognition receptor (PRR) activation

The virus cleverly evades detection by delaying the activation of PRRs. These cellular sensors commonly identify foreign molecules, such as viral RNA. SARS-CoV-2 accomplishes this by adding host-like chemical modifications, including N6-methyladenosine (m6A), to its RNA. This process, known as "molecular mimicry," causes the viral RNA to resemble the host's RNA, preventing sensors like TLR7 and RIG-I from recognizing it as a threat. This delay allows the virus extra time to establish infection before the immune system responds effectively, leading to initial unchecked replication.

Complement system antagonism

SARS-CoV-2 actively disrupts the complement system, a crucial part of the innate immune response that eliminates pathogens. The virus employs various tactics to interfere with this system. For example, the spike (S) protein and other viral elements can attach to and sequester essential complement proteins, preventing their assembly into the membrane attack complex (MAC), which functions to puncture and destroy infected cells. Additionally, the virus hijacks host-derived complement regulators to its surface, enhancing its resistance to complement-mediated attack. By neutralizing this key immune defense, the virus secures its survival and ongoing replication within the host [7].

Epigenetic silencing

Coronaviruses have evolved the ability to tamper with host epigenetic machinery to interfere with immune-sensing pathways to evade host immune response, thereby enhancing their replication and pathogenesis post-entry. SARS-CoV-2 utilizes epigenetic mechanisms. Silencing to dampen the host's immune defenses and to improve its replication. Central to this process is the viral non-structural protein 1 (Nsp1) (**Table 1**) (3G), which hijacks the host's epigenetic system to suppress genes vital for the antiviral response, especially those involved in interferon (IFN) signaling. Nsp1 specifically increases the levels of Histone 3 Lysine 9 dimethylation (H3K9me2), a mark linked to gene repression (**Table 1**). This modification effectively silences immune-related genes, blocking the host cell from producing antiviral proteins and thereby aiding the virus in replicating silently [40].

Role of SARS-CoV-2 Proteins in Modulation of the Host's Innate Immunity

SARS-CoV-2 proteins play crucial roles in modulating the host's innate immune response, with different proteins targeting various aspects of the host defense mechanisms. Understanding how these proteins help the virus evade immune responses is key to the development of therapeutic strategies. For instance, the membrane (M) glycoprotein acts as a negative regulator by interacting with MAVS (mitochondrial antiviral-signaling protein), impairing its ability to recruit downstream factors such as TRAF3, TBK1, and IRF3, thus attenuating antiviral responses [14]. The nucleocapsid (N) protein plays a dual role: suppressing type I interferon signaling at low doses but promoting it at higher doses by interacting with TRIM25, affecting the nuclear translocation of IRF3, STAT1, and STAT2 [15,17] (**Table 1**). Other SARS-CoV-2 proteins, such as Nsp6, Orf6, and Orf8, inhibit type I interferon responses at different stages (**Table 1**). Orf6 blocks STAT1 and STAT2 nuclear translocation and suppresses IRF3- and TNF-α-induced NF-κB activation, whereas Orf8 inhibits these pathways after STAT1/2 translocation [16] (**Table 1**). Several structural and non-structural proteins, including Orf3a, Orf6, Orf8, and the main protease, further inhibit interferon signaling [18,19]. Nsp14 targets type I IFN receptors for lysosomal degradation, Orf3a prevents autophagosome-lysosome fusion, and Orf7a interferes with autophagosome acidification [20] (**Table 1**). A key distinction of SARS-CoV-2 is that Nsp15 is less efficient at antagonizing IFN signaling compared to orthologs in related coronaviruses like SARS-CoV and MERS-CoV [20] (**Table 1**). This difference is attributed to specific amino acid changes that weaken its endoribonuclease activity, making it less effective at degrading host mRNAs that are critical for mounting an IFN response. This multi-pronged approach allows SARS-CoV-2 to evade and suppress host immune defenses, thereby contributing to pathogenicity. These insights reveal potential therapeutic targets and suggest that type II and III interferons may be more effective against SARS- CoV-2 owing to the weaker suppression of these pathways by the virus [20]. Understanding these mechanisms highlights new avenues for treatment aimed at enhancing the host immune response.

Table 1. The table below presents SARS-CoV-2 viral proteins that impede innate immune responses, detailing their functions and key references. It emphasizes the various interconnected approaches used by SARS-CoV-2 proteins to thwart the host's innate antiviral defenses, especially the interferon (IFN) pathways.

Viral Protein	Function in Innate Immune Subjugation	Key References
NSP1 (Non-structural protein 1)	Shuts down host protein translation by binding to the 40S ribosomal subunit, thereby blocking host immune functions including interferon (IFN) and antiviral gene expression. It also induces host mRNA degradation and modulates signaling pathways (e.g., calcineurin/NFAT, ATF2/c-Jun, IRF3, IRF7, NF-kappa-beta, STAT-1).	[41–43]
NSP3 (Papain-like protease, PLpro)	Acts as a de-ubiquitinase and deISGylase, removing ubiquitin and ISG15 (Interferon-Stimulated Gene 15) modifications from host proteins. This interferes with innate immune signaling, particularly by cleaving ISG15 from IRF3 and MDA5, and blocking TLR-7 signaling by removing K63-linked polyubiquitination of TRAF3 and TRAF6. Can also directly cleave IRF3.	[22,44–46]
NSP5 (3C-like protease, 3CLpro/Mpro)	Cleaves viral polyproteins but also contributes to immune evasion. Can cleave the N-terminal of RIG-I, rendering it inactive. Promotes MAVS ubiquitination for degradation. Suppresses nuclear translocation of phosphorylated IRF3. Can cleave NEMO.	[44,47,48]
NSP6	Complexes with NSP3 and NSP4 to form double-membrane vesicles (DMVs) where viral replication occurs, effectively shielding the replication machinery from host pattern recognition receptors (PRRs). Also inhibits IFN-β production by targeting IRF3 and STAT1/STAT2 phosphorylation.	[42,49]
NSP8	Interacts with MDA5 to inhibit the phosphorylation of IRF3 and TBK1, thereby downregulating antiviral immune responses. It may interfere with K63-linked polyubiquitination of MDA5 and MAVS recruitment.	[49]
NSP10	Acts as a cofactor for NSP16, aiding in RNA capping, which helps the viral RNA evade recognition by RIG-I and MDA-5.	[42]
NSP12	While primarily the RNA-dependent RNA polymerase (RdRp), it has been implicated in inhibiting MDA5-dependent Type I interferon induction.	[41]
NSP13 (Helicase)	Interacts with TBK1 and inhibits TBK1/IRF3 activation, thereby disrupting IRF3-directed signal transduction.	[42,47]
NSP14	Possesses guanine-N7-methyltransferase activity, mimicking the 5'cap structure on viral RNA, which helps evade PRR recognition. Also involved in RNA proofreading.	[42]
NSP15 (Endoribonuclease)	Processes viral RNA and limits the formation of dsRNA intermediates, which are potent PRR activators. Interacts with RNF41, an E3 ligase associated with IRF3 activation.	[42]
N (Nucleocapsid protein)	Interferes with the interaction of TRIM25 and RIG-I, suppressing RIG-I ubiquitination. Also suppresses phosphorylation and nuclear translocation of STAT1 and STAT2. Can be ISGylated, but the virus has mechanisms (e.g., PLpro) to remove this tag.	[42,45,50]
M (Membrane protein)	Signaling molecules (TRAF3, TBK1, IRF3) interacts with TBK1 and KPNA6 to hinder nuclear translocation of IRF3, reducing IFN production.	[42,47,51]
ORF3a	Suppresses STAT1 phosphorylation via upregulation of SOCS1. This is also implicated in inducing apoptosis, which can contribute to tissue damage and immune dysregulation.	[42]
ORF3b	Prevents the nuclear translocation of IRF3, thus antagonizing IFN function. Notably, its C-terminal contains a nuclear localization signal (NLS).	[42,47]
ORF6	Acts as a potent interferon antagonist by directly binding to the Nup98-Rae1 complex, thereby blocking nuclear import of STAT1, STAT2, and IRF3. This prevents the activation of IFN-stimulated genes (ISGs).	[42,47,52]
ORF8	Can reduce the nuclear translocation of IRF3 and suppress the type I interferon response, potentially through interaction with HSP90B1. It is also involved in downregulating MHC-I expression.	[47]
ORF9b	Suppresses type I interferon (IFN-I) responses through association with TOM70, a mitochondrial protein crucial for MAVS activation. It also interrupts K63-linked ubiquitination of NEMO.	[42,47,53]

Host Gene Expression Interference

Furthermore, SARS-CoV-2 manipulates host gene expression by targeting master regulators known as microRNAs (miRNAs). These single-stranded non-coding RNAs play a crucial role in regulating innate immune and inflammatory responses [24]. During SARS-CoV-2 infection, miRNAs control the human innate immune response by regulating granulocytes, macrophage activation and polarization, and neutrophil extracellular trap formation [24]. Interestingly, SARS-CoV-2 has evolved to encode its miRNA, which produces two isoforms in infected cells. These virus-encoded miRNAs target the 3'-untranslated region (UTR) of interferon-stimulated genes, repressing their expression and potentially aiding the virus in evading the interferon-mediated immune response [25,26]. This mechanism highlights the complex interplay between viral and host miRNAs in modulating innate immune responses.

Given their regulatory role in immune response, miRNAs hold significant potential as therapeutic targets for COVID-19. Several studies have shown that host miRNAs can target different sites in the SARS-CoV-2 RNA, constraining the production of essential viral proteins [27]. Moreover, miRNAs exhibit lower toxicity, increased immunogenicity, and greater diversity compared to protein- and plasmid-DNA-based therapeutic agents [27]. Novel miRNA delivery strategies, such as EDV™ nano-cells, demonstrate promise for targeting lung tissue in the treatment of SARS-CoV-2 infection [27]. Additionally, dietary polyphenolic compounds may protect against SARS-CoV-2 infection by modulating the expression of host cell miRNAs [28]. These findings suggest that miRNA-based therapies could be valuable approaches for combating COVID-19 and other future pandemics.

Latest Trends in Innate Immune Response to SARS-CoV-2 Infection

From the discussion in this review, it is clear that the innate immune response to SARS-CoV-2 infection involves complex interactions between the virus and the host's first line of defense. Recent studies have revealed several key trends in the field. The innate immune response plays a crucial role in shaping the adaptive immune response toward a protective phenotype. However, SARS-CoV-2 can exploit and subvert the immune response, leading to an excessive inflammatory reaction, which is among the leading causes of disease severity and mortality in COVID-19 patients [29,30]. The latest trends in the innate immune response to SARS-CoV-2 highlight the delicate balance between protective immunity and inflammation. Understanding these mechanisms, including cellular, genomic, and non-coding miRNAs, is crucial for the development of targeted therapies and interventions to mitigate the severity of COVID-19 and improve patient outcomes [31,32]. In particular, the components of host innate immunity during SARS-CoV-2 infection, focusing on how the virus evades immune detection and how this knowledge can inform therapeutic strategies, are highly relevant. Key strategies include:

Viral evasion of innate immunity

PRR recognition: SARS-CoV-2 evades detection by PRRs such as RIG-I and MDA5, impairing the host's ability to mount a rapid antiviral response. Recent research has shown that the virus delays the release of type I interferons (IFNs), allowing it to replicate before the immune system can act effectively.

Interferon suppression: The virus uses proteins like Orf6, Orf8, and Nsp1 to block the IFN pathway at different stages. For instance, Orf6 prevents the nuclear translocation of STAT1 and STAT2, which are essential for activating antiviral responses. Recent research on Omicron subvariants (e.g., JN.1, KP.2) shows that mutations in proteins like Orf6 and the N protein improve their ability to inhibit IFN signaling, aiding in greater immune evasion (**Table 1**).

Cytokine dysregulation: SARS-CoV-2 triggers an overproduction of pro-inflammatory cytokines (cytokine storm) while suppressing antiviral IFNs, thereby contributing to severe COVID-19 in some cases, accompanied by ARDS.

Novel immune mechanisms and pathways

MicroRNAs (miRNAs): Recent studies have shown that SARS-CoV-2 modulates host miRNAs to fine-tune the immune response. For example, some miRNAs regulate inflammatory cytokine production, whereas others influence the expression of interferon-stimulated genes (ISGs).

Complement system: There is growing evidence of SARS-CoV-2's ability to manipulate the complement system, contributing to inflammation and tissue damage in severe cases of COVID-19. Understanding how the virus interacts with the complement pathways is a new area of research.

Emerging therapeutic strategies

Interferon therapies: Given the virus's ability to evade type I IFN responses, researchers have investigated the use of type II (IFN-γ) and type III (IFN-λ) interferons. These interferons may circumvent viral evasion tactics, thereby reducing viral replication.

Targeting viral proteins: New strategies involve targeting viral proteins such as Nsp6, Nsp14, and Orf6, which inhibit interferon signaling. Drugs designed to prevent these proteins from interacting with host immune components are currently under development.

Antiviral monoclonal antibodies: These antibodies can neutralize SARS-CoV-2 before it binds to host cells and boost innate immunity. Additionally, Fc-enhanced antibodies are being studied to improve immune cell functions like phagocytosis and complement activation.

Host cell receptor inhibitors: Blocking ACE2 and TMPRSS2, the main entry points for the virus, remains the focus of current trials. However, it is important to recognize that other possible entry pathways exist and should also be considered. Small-molecule inhibitors and monoclonal antibodies that block these pathways are being developed to lower infection rates.

Immune modulators: Researchers are exploring medications that can modulate the overactive immune response (e.g., corticosteroids and IL-6 inhibitors) to prevent cytokine storms in severe COVID-19 cases without suppressing antiviral defenses.

Next-generation vaccines

Current research on vaccines focuses on enhancing innate immune memory (trained immunity), whereby innate immune cells such as macrophages and NK cells become more effective upon re-exposure. These vaccines aim to prepare the innate immune system for a swift response against future SARS-CoV-2 variants. Overall, the latest trends emphasize the complex interplay between

viral evasion mechanisms and the host's innate immune response. Strategies targeting viral proteins, boosting interferon responses, and modulating host receptors present promising avenues for preventing infection and improving COVID-19 outcomes.

Unique features of SARS-CoV-2

About the latest trends in innate immunity concerning SARS-CoV-2 infection, it is essential to understand what is unique about SARS-CoV-2 in its interaction with the host innate immune system, which separates it from all other viruses that infect humans. This virus employs several distinctive strategies to evade and antagonize the host's innate immune response, setting it apart from other viruses. For example, the membrane (M) glycoprotein acts as a negative regulator by interacting with MAVS, impairing its recruitment of downstream factors, such as TRAF3, TBK1, and IRF3, thus weakening antiviral responses [14]. The nucleocapsid (N) protein plays a dual role in suppressing type I interferon signaling at low doses but promotes it at higher doses through TRIM25, affecting the nuclear translocation of IRF3, STAT1, and STAT2 [15,17]. Proteins such as Nsp6, Orf6, and Orf8 inhibit type I interferon responses at various stages. Orf6 blocks STAT1/STAT2 nuclear translocation and suppresses IRF3- and TNF-α-induced NF-κB activation, whereas Orf8 inhibits signaling after STAT1/2 translocation [16] (**Table 1**). Other proteins like Orf3a, Orf6, Orf8, and the main protease inhibit interferon signaling [18,19] (**Table 1**). Nsp14 degrades type I interferon receptors, Orf3a prevents autophagosome-lysosome fusion, and Orf7a interferes with autophagosome acidification [20]. This multipronged approach enables SARS-CoV-2 to evade and suppress host immune defenses, thereby contributing to its pathogenicity. These findings suggest that types II and III interferons may be more effective against SARS-CoV-2 due to their weaker suppression of these pathways [20] (**Table 1**).

Future Investigations

Despite significant advancements in understanding the interaction between SARS-CoV-2 and the innate immune system, several areas warrant further exploration. These include the virus's evasion of PRR detection, modulation of miRNAs, and unique interactions with the complement system. Additional research is needed to fully elucidate these mechanisms and develop targeted therapies that modulate the immune response without causing harm. Furthermore, the long-term effects of SARS-CoV-2 on innate immunity require further investigation to better prepare for future pandemics [37,38]. Discrepancies in research findings on immune responses highlight the urgent need for a global effort to standardize research methodologies, from sample collection to data analysis, to ensure reproducibility and comparability across studies.

The effectiveness of viral evasion strategies is not uniform across all individuals. Host factors such as genetics, age, and comorbidities significantly influence the innate immune response and disease outcomes. Future studies should focus on how these variables modulate the virus's ability to evade immunity, which could pave the way for personalized medicine approaches.

Conclusion

Understanding the complex interactions between SARS-CoV-2 and the host innate immune system is critical for developing effective treatments and vaccines. SARS-CoV-2's ability to evade early immune detection, suppress interferon signaling, and manipulate host gene expression differentiates it from other viruses. Targeting these viral strategies presents promising avenues for therapeutic development to mitigate the severity of COVID-19 and enhance patient outcomes.

Declaration

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