Review
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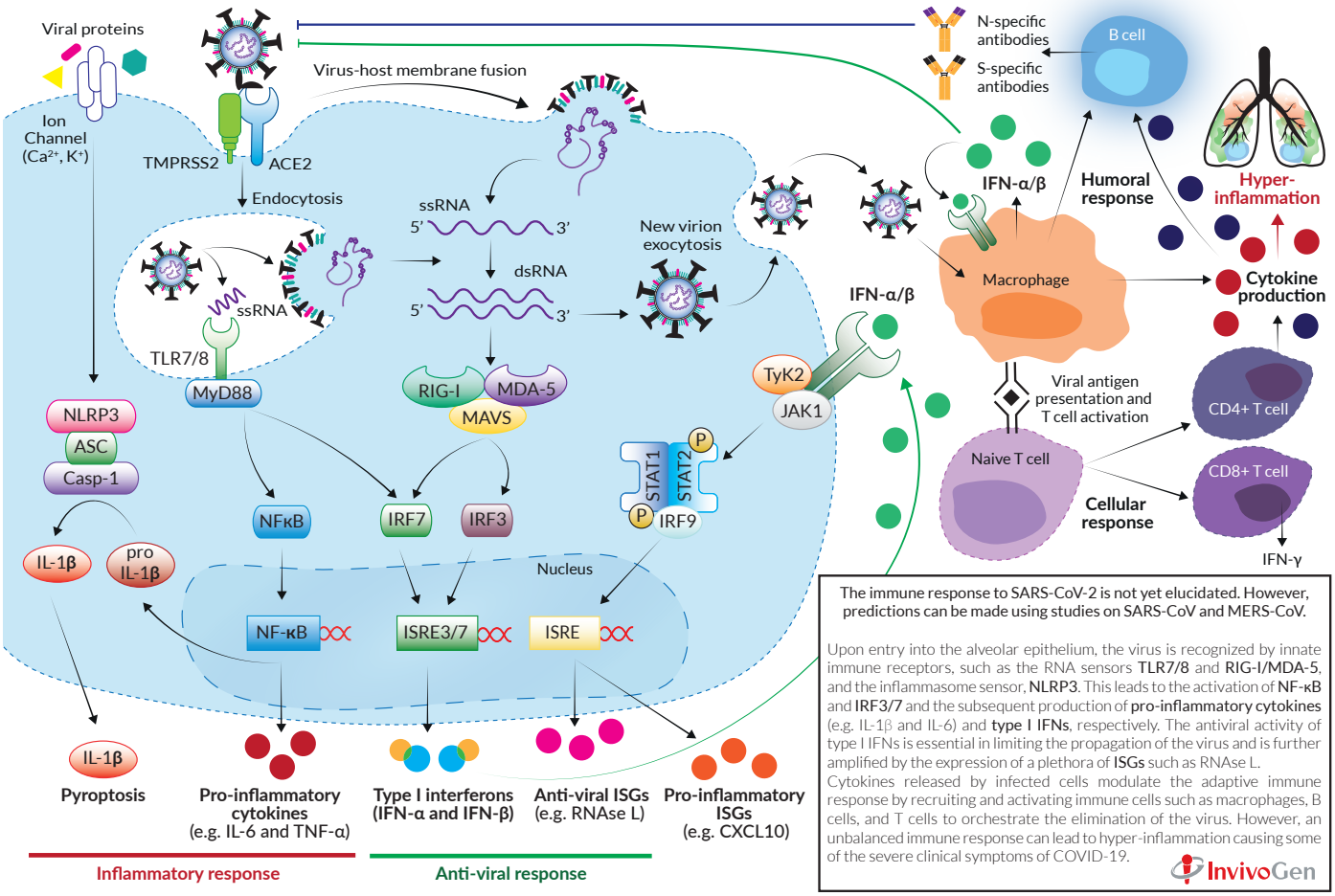
Spotlight on COVID-19
Predicted immune responses

Predicted immune responses to SARS-CoV-2

The ongoing COVID-19 pandemic is caused by a novel β-coronavirus, named "SARS-CoV-2" by the International Virus Classification Commission. Genetic and clinical data are rapidly emerging and suggest strong similarities with two previous highly pathogenic human β-coronaviruses, SARS-CoV and MERS-CoV. SARS-CoV-2 shares approximately 79% and 50% sequence identity with SARS-CoV and MERS-CoV, respectively [1], similar cell entry mechanisms [2], and the propensity to induce hyper inflammation in severe cases [3]. Currently, there is very limited knowledge of the host immune response to SARS-CoV-2. However, based on the accumulated clinical and experimental data on these previous viruses, predictions can be made on how the host immune system may deal with this virus and how the virus may evade such host responses [4].

Predicted host immune responses to SARS-CoV-2



The immune response to SARS-CoV-2 is not yet elucidated. However, predictions can be made using studies on SARS-CoV and MERS-CoV.

Upon entry into the alveolar epithelium, the virus is recognized by innate immune receptors, such as the RNA sensors **TLR7/8** and **RIG-I/MDA-5**, and the inflammasome sensor, **NLRP3**. This leads to the activation of **NF-κB** and **IRF3/7** and the subsequent production of **pro-inflammatory cytokines** (e.g. IL-1β and IL-6) and **type I IFNs**, respectively. The antiviral activity of type I IFNs is essential in limiting the propagation of the virus and is further amplified by the expression of a plethora of **ISGs** such as RNAse L.
Cytokines released by infected cells modulate the adaptive immune response by recruiting and activating immune cells such as macrophages, B cells, and T cells to orchestrate the elimination of the virus. However, an unbalanced immune response can lead to hyper-inflammation causing some of the severe clinical symptoms of COVID-19.

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VIRAL RECOGNITION BY THE INNATE IMMUNE SYSTEM

The first line of defense against viral infection comprises a set of pattern recognition receptors (PRRs), including Toll-like receptors (TLRs) and RIG-I-like receptors (RLRs) that recognize the RNA viral genome and its replication intermediates. Evidence suggests that upon entry into the alveolar epithelium, the virus is sensed by the endosomal single-stranded (ss)RNA sensor, TLR7/8, and the cytosolic double-stranded (ds)RNA sensor, RIG-I/MDA-5. Upon recognition, these sensors recruit the adaptor proteins, MyD88 and MAVS, respectively, and induce downstream signaling. Ultimately, this leads to the activation of the transcription factors, IRF3/7 and NF-κB, and the subsequent production of type I interferons (IFN-α and IFN-β) and proinflammatory cytokines (e.g. IL-6 and TNF-α), respectively [5]. Additionally, the virus is thought to activate the inflammasome sensor, NLRP3, resulting in the secretion of the highly inflammatory cytokine IL-1β and the induction of pyroptosis, an inflammatory form of cell death. Indeed, SARS-CoV has previously been shown to induce the formation of the NLRP3 inflammasome through the action of viral proteins such as the E and 3a proteins [6,7]. Still, our understanding of the viral recognition mechanisms is far from being fully elucidated.

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TYPE I IFN RESPONSE

Induction of the type I IFN response is essential in limiting the propagation of the virus within the host during the early phases of the disease. Type I IFNs mediate direct antiviral effects that limit viral replication and modulate the innate and adaptive immune responses. They bind to their receptor, which is expressed on a number of different cells including macrophages, and activate the JAK/STAT signaling pathway. This signaling leads to the formation of the STAT1/2/IRF9 complex and the induction of a plethora of IFN-stimulated genes (ISGs), such as the anti-viral enzyme RNAse L, and the pro-inflammatory chemokine CXCL10 [8, 9].

Many viruses, including SARS-CoV and MERS-CoV, have developed multiple strategies to evade the antiviral response orchestrated by type I IFNs [10]. These evasion strategies include:

- **Avoidance:** The virus shields itself or its byproducts from host recognition. SARS-CoV and MERS-CoV hide viral intermediate products (e.g. dsRNA) within double-membrane vesicles (DMVs) during the replication process [11,12].
- **Suppression of IFN induction:** Viral proteins may actively inhibit the host sensor machinery or its downstream signaling molecules to prevent the initiation of IFN expression. MERS-CoV membrane (M) and nsp4a are known to suppress RIG-I-induced activation of IRF3 and MDA-5 activation, respectively [13,14]. Furthermore, the viral protease, PLpro, has been shown to have deubiquitinase (DUB) activity in the infected cell, as well as inhibitory activity against IRF3 activation in both SARS-CoV and MERS-CoV [15-17].
- **Suppression of IFN signaling:** Viruses can block the IFN signaling cascade directly. SARS-CoV nsp1 and nsp6 have been shown to block the phosphorylation of STAT1 and the translocation of the STAT1/2/IRF9 complex, respectively, preventing the activation of an antiviral state within the infected cell and the enhancement of the IFN response [18,19].

Downregulation of the host IFN response, either directly by the virus or by other indirect means, can cause an unbalanced production of pro-inflammatory cytokines and infiltration of inflammatory cells leading to a more severe form of COVID-19.

IMMUNOPATHOLOGY OF SARS-CoV-2

The immunopathology of COVID-19 greatly resembles that seen in SARS and MERS infections. Recent studies found that increased cytokine levels (e.g. IL-6, IL-10, and TNFα) and lymphopenia (significantly reduced CD4+ and CD8+ T cells) correlate with disease severity of COVID-19 [3, 20]. In addition to reduced T cell counts, the surviving T cells appear dysfunctional [21]. In the more severe cases of COVID-19, this dysregulated immune response can lead to a cytokine storm, causing increased pulmonary pathology and respiratory distress and, a higher risk of poor clinical outcomes (e.g. death). Therefore, treatment with antiviral agents alone may not be sufficient to stop the devastating cytokine storm and pulmonary destruction in these patients. Thus, further studies to develop a better understanding of how the virus is recognized by the host and which viral factors drive immune dysregulation in COVID-19 will provide essential insights to help shape vaccine responses towards protective immunity.

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