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Monocyte-crosstalk drives interferon-mediated signaling following SARS-CoV-2 exposure

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Cells of the innate immune system represent the first line of defense against SARS-CoV-2 and play an essential role in activating adaptive immunity, which mediates long-term protection. In addition, the same cells are key drivers of tissue damage by causing the hyperinflammatory state and cytokine storm that makes COVID-19 a deadly disease. Thus, careful dissection of the host–pathogen interaction on a cellular level is essential to understanding SARS-CoV-2 pathogenesis and developing new treatment modalities against COVID-19. In their recent work, Goffinet and colleagues (Kazmierski *et al*, 2022) investigate the cell-intrinsic responses of human primary peripheral blood mononuclear cells (PBMCs) exposed to SARS coronaviruses.

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See also: **J Kazmierski *et al***

The authors first use a single-cell RNA-sequencing approach on all mononuclear cells and then focus on monocytes, which represent classical cells of the innate immune system. They show that SARS-CoV-2-exposed cells mount a JAK/STAT-dependent innate immune response, which seems to be mediated primarily by interferons (IFN). In SARS-CoV-2-infected patients, type I IFNs and interferon-stimulated genes (ISG) are known to orchestrate an efficient adaptive immune response against the virus. In light of the importance of IFN signaling, the here described *ex vivo* approach exploiting human PBMCs exposed to SARS-CoV-2 particles represents a highly valuable model to study SARS-CoV-2 host–pathogen interactions and to decipher cell-specific production of cytokines (Fig 1).

SARS-CoV-2-specific T- and B-cell responses have been broadly studied over the course of the pandemic. However, considerably less attention has been paid to innate immune triggers and signaling. Nevertheless, almost 3 years after the start of the pandemic, some features of innate immune signaling induced by SARS coronaviruses have been elucidated. SARS-CoV-2 can trigger several different innate immune pathways (Diamond & Kanneganti, 2022; Paludan & Mogensen, 2022). For instance, recent studies show that innate immune recognition of viral RNA via RIG-1/MDA5 and TLR7/8 activates interferon-signaling cascades leading to the secretion of type I and III IFNs (Schultze & Aschenbrenner, 2021; Thorne *et al*, 2021; Diamond & Kanneganti, 2022) (Fig 1). This discovery correlates well with findings made in the systemic evaluation of SARS-CoV-2-exposed immune cells discussed here.

A key question is whether these events require infection and active production of SARS-CoV-2 particles in cells of the innate immune system. Goffinet and colleagues address this topic carefully by showing that, in the cell culture of SARS-CoV-2-exposed PBMCs, viral RNA remains associated with cells for up to several days; however, several lines of evidence indicate that human blood-derived immune cells fail to support productive viral infection. This finding has also been confirmed by other studies independently (Yang *et al*, 2020). Furthermore, virus–receptor interaction required for the activation of innate immune cell signaling does not require the common SARS-CoV-2 receptor, the angiotensin-converting enzyme 2 (ACE2). While receptor requirements have not been addressed in this work, there is evidence that the major antigen of SARS coronaviruses, the spike protein, functions as a pathogen-associate molecular pattern on innate immune cells and triggers C-type lectin and TLR-2-dependent signaling cascades, which in turn leads to the activation of inflammasomes and the secretion of proinflammatory cytokines, such as IL-1, IL-6, and TNF-α (Theobald *et al*, 2021; Sefik *et al*, 2022). However, at least for activation of the NLRP3 inflammasome and IL-1 secretion, peripheral blood monocytes require a certain degree of prestimulation (e.g., via active infection or vaccination of the human host) (Rodrigues *et al*, 2021; Theobald *et al*, 2022). This may explain the lack of expression of proinflammatory cytokines, including IL-6, TNF-α, and IL-1, observed in the study of Goffinet and colleagues, which uses PBMCs of healthy individuals for the *ex vivo* SARS-CoV-2 exposure experiments. Therefore, it seems like the described model rather mimics a situation in which protective IFN-driven immunity is induced as we would expect in mild forms of the disease. Surprisingly though, single-cell RNA-seq experiments reveal that the SARS-CoV-2

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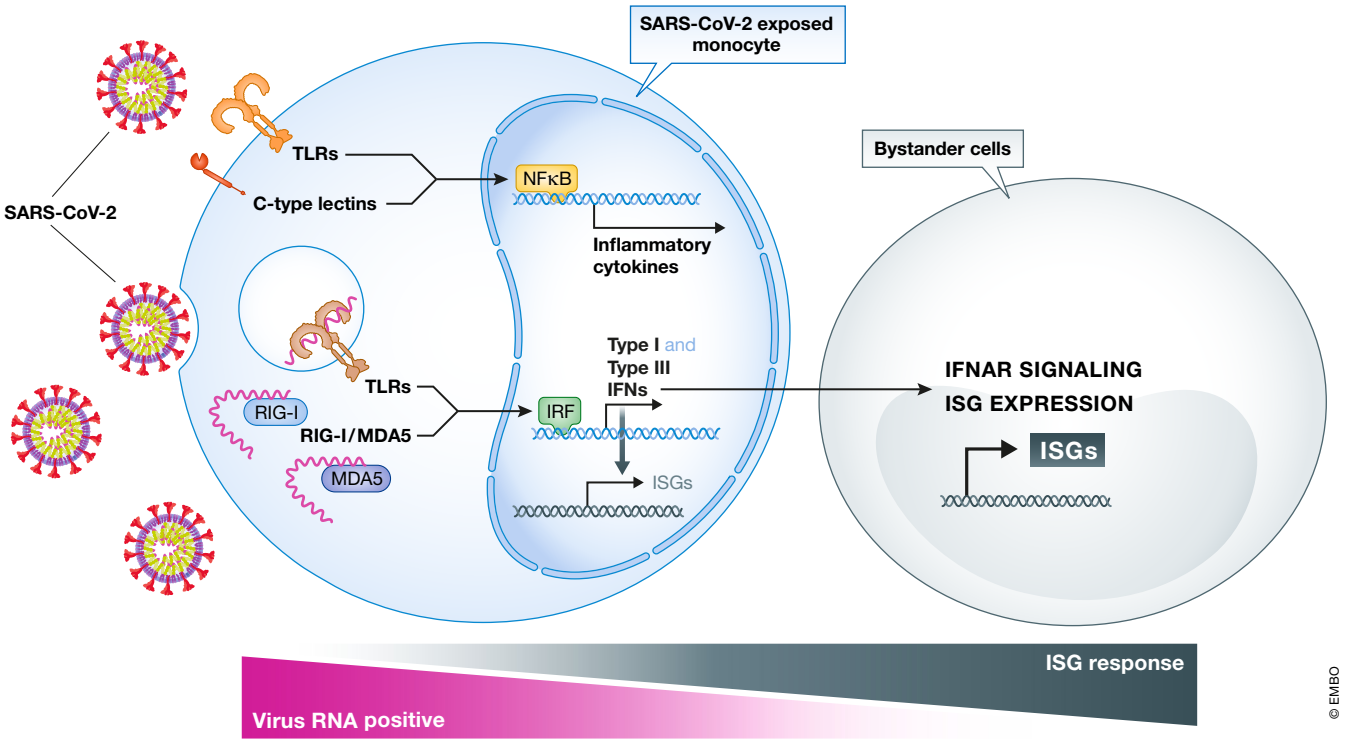

Figure 1. Molecular pathways and crosstalk in SARS-CoV-2-infected PBMCs.

Monocytes react via different molecular pathways towards a SARS-CoV-2 infection. Surface molecules, such as C-type lectins and Toll-like receptors, are able to detect molecular patterns on SARS-CoV-2, which as a consequence leads to NfκB activation and production of proinflammatory cytokines. On the contrary, SARS-CoV-2 single-stranded RNA triggers intracellular signaling cascades, such as Toll-like receptors or RIG-I/MDA5. Recognition of SARS-CoV-2 by monocytes leads to the activation of interferon-response genes and consequently to the section of type I and III interferons. Bystander monocytes, which are virus RNA-negative, are sensitized and therefore activate interferon-stimulated gene (ISG) signatures to higher levels than RNA-positive cells.

RNA-negative bystander monocytes induce the JAK/STAT-dependent ISG expression signature to a greater extent than viral RNA-positive cells (Fig 1). Goffinet and colleagues speculate that SARS coronavirus-encoded IFN antagonists dampen the innate immune response in SARS-CoV-2 RNA-positive cells, whereas RNA-negative bystander monocytes seem to receive signals that activate the protective IFN-dependent signature required to mount a robust antiviral immune response. Understanding the exact mechanism behind this virus-induced dampening effect represents a formidable task with great translational value. Goffinet and colleagues now have provided the cornerstone for these important investigations.

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