The type I interferon response in COVID-19: implications for treatment

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Despite early reports to the contrary, there is increasing evidence that patients with severe COVID-19 have a robust type I interferon response, which contrasts with the delayed, possibly suppressed, interferon response seen early in infection. A robust type I interferon response could exacerbate hyperinflammation in the progression to severe COVID-19 through diverse mechanisms. Further understanding of the roles of type I interferon at different stages of infection and in patients with mild versus severe COVID-19 will provide insights for the therapeutic use of interferon administration or JAK inhibitors in patients with COVID-19.

Type I interferon (IFN-I; IFNα and IFNβ) functions in both autocrine and paracrine manners to induce the expression of various interferon-stimulated genes (ISGs) that confer antiviral activities to host cells. Many species of viruses, including SARS-CoV-2, have evolved mechanisms to evade the antiviral function of IFN-I. In keeping with this, an early study of SARS-CoV-2 infection showed that IFN-I responses were limited, whereas the expression of various chemokines and IL-6 was increased, when analysing the transcriptomes of SARS-CoV-2-infected bronchial epithelial cells, infected ferrets and post-mortem lung tissues from patients with COVID-19 (REF.[1]). A more recent study that examined peripheral blood from patients with COVID-19 of varying severity also reported that IFN-I responses are highly impaired in patients with severe or critical COVID-19, as indicated by low levels of IFN-I and ISGs, despite increased production of tumour necrosis factor (TNF) and IL-6 and increased NF-κB-driven inflammatory responses[2]. As a result of these and other studies, recombinant IFN-I is being actively trialled as a treatment for COVID-19.

However, robust IFN-I responses have also been reported in patients with severe COVID-19. A transcriptome study of bronchoalveolar lavage fluid from patients with COVID-19 reported increased expression of numerous ISGs, in addition to markedly increased expression of pro-inflammatory genes and chemokine genes[3]. In a single-cell RNA sequencing study of peripheral blood mononuclear cells (PBMCs) from hospitalized patients with COVID-19, various ISGs were upregulated in classical monocytes, although the ISG signature was heterogeneous among cell types and patients[4]. Contradictory results regarding IFN-I responses in patients with COVID-19 might be explained by differences in definitions of disease severity, sampling time points and/or type of readout (for example, IFN-I itself or cellular responses to IFN-I) between studies.

Recently, our immune landscape study highlighted the role of IFN-I responses in the development of severe COVID-19 (REF.[5]). Single-cell RNA sequencing analysis was carried out using PBMCs not only from patients with mild or severe COVID-19 but also from patients with severe influenza. The patients with COVID-19 had unique hyperinflammatory signatures across all types of immune cell, particularly the upregulation of TNF- and IL-1-driven inflammatory responses, whereas IFN-I and IFN-II (IFNγ) responses were predominant in patients with severe influenza. IFN-I responses co-occurred with TNF- and IL-1-driven inflammatory responses in classical monocytes from patients with severe COVID-19, but not with mild COVID-19, which suggests that IFN-I might have an important role in exacerbating TNF- and IL-1-driven inflammation in the progression to severe COVID-19. Interestingly, severe COVID-19-specific gene signatures, including various ISGs identified in this study, were significantly enriched in the transcriptome of post-mortem lung tissue from patients with COVID-19 published in the earlier study by Blanco-Melo et al.[1], which supports the idea that IFN-I responses are upregulated in severe COVID-19. Furthermore, a recent longitudinal analysis of patients with moderate or severe COVID-19 corroborated these results by showing that IFNα in peripheral blood was sustained at high levels in patients with severe COVID-19 (REF.[6]).

The pro-inflammatory roles of IFN-I are well described in a mouse model of SARS[7]. In SARS-CoV-infected BALB/c mice, a delayed but considerable IFN-I response induces the accumulation of monocytes and macrophages and the production of pro-inflammatory cytokines, resulting in lethal pneumonia, vascular leakage and insufficient T cell responses. Pro-inflammatory roles of IFN-I were also shown recently in SARS-CoV-2-infected mice expressing the human ACE2 entry receptor[8]. Using mice deficient for an IFN-I response,

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such as *Ifnar*$^{-/-}$ mice or *Irf3*$^{-/-}$*Irf7*$^{-/-}$ mice, this study showed that IFN-I responses are required for the recruitment of pro-inflammatory monocytes and macrophages to the infected lungs.

In addition, IFN-I can aggravate inflammatory responses through epigenetic mechanisms. TNF is a classical pro-inflammatory cytokine but it also has a tolerizing function on monocytes and macrophages, causing hyporesponsiveness to additional Toll-like receptor (TLR) signals[9]. Intriguingly, IFN-I abolishes the tolerizing effects of TNF and renders monocytes and macrophages responsive to additional TLR signals[9]. Park et al.[9] defined a gene module that is unresponsive to TLR signals owing to TNF-induced tolerance but becomes responsive to TLR signals with IFN-I pretreatment. This gene module was significantly enriched in the transcriptome of classical monocytes from patients with severe COVID-19 (REF.[5]). This result indicates that IFN-I might break TNF-induced tolerance to TLR signals in patients with severe COVID-19, resulting in IFN-I-induced hyperinflammation through a feedforward mechanism.

Given the conflicting results that have been reported for the strength of IFN-I responses in patients with severe COVID-19, more precise information is required for the appropriate therapeutic use of IFN-I. Because of the broad antiviral activities of IFN-I, recombinant IFN-I proteins, including both IFNα and IFNβ, are being clinically investigated for the treatment of patients with COVID-19 either as a single agent or in combination with other antiviral agents. As of 6 August 2020, four studies have been completed and report a favourable response to early IFNβ use (for example, NCT04276688), and 18 studies are underway testing the clinical efficacies of IFNα or IFNβ. However, as IFN-I seems to exacerbate inflammation in the progression to severe COVID-19, the timing of administration and targeted subgroups for IFN-I treatment need to be considered with caution. A recent retrospective study of 446 patients with COVID-19 reported that early use of IFNα decreased mortality, whereas late use of IFNα increased mortality and delayed recovery[10]. Intriguingly, a home-based clinical trial using inhaled IFNβ to reduce the systemic side effects of IFN-I is currently under way (NCT04385095). Notably, IFN-III (IFNλ) is an alternative to IFN-I because IFN-III can exert antiviral activities without inflammatory effects. Currently, four studies are testing the clinical efficacies of recombinant IFNλ (NCT04343976, NCT04354259, NCT04388709 and NCT04344600).

For the treatment of patients with severe COVID-19, the use of JAK inhibitors, which can inhibit the IFN-I signalling pathway, should be considered in the context of the pro-inflammatory roles of IFN-I. A pilot study using baricitinib, a reversible JAK1 inhibitor, showed promising results in limiting the pro-inflammatory cytokine release that is associated with COVID-19 (NCT04358614). As of 6 August 2020, 40 clinical studies are underway testing various JAK inhibitors in patients with COVID-19. A major target of JAK inhibitors is IL-6, which is a key pro-inflammatory cytokine in severe COVID-19. However, each JAK inhibitor suppresses the activity of multiple cytokines because each JAK subtype is involved in the signalling of multiple cytokines and because many JAK inhibitors suppress multiple JAK subtypes owing to a lack of selectivity. Given that IFN-I and IL-6 share JAK1 and TYK2 as signalling molecules, the effect of JAK inhibitors, including TYK2 inhibitors, on IFN-I signalling and the clinical relevance of this effect, particularly in early infection when IFN-I responses are beneficial, need to be examined carefully.

Therefore, further study of the strength of IFN-I responses in mild versus severe COVID-19 and early versus late disease will be important for designing clinical studies for the treatment of patients with severe COVID-19 (including rational selection of therapeutic agents, timing of the treatment and target subgroups of patients with COVID-19). In addition, IFN-I-associated biomarkers that predict the progression to severe COVID-19 may help to improve the clinical management of patients with severe COVID-19 based on a precision strategy.

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Competing interests
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