# LETTER

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# The double edged interferon riddle in COVID-19 pathogenesis

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Dear Editor,

In their recent article [1], Jalkanen et al. discuss about the prospective usage of interferon beta 1 in managing COVID-19 and substantiating usage of intravenous route of administration over subcutaneous route. I would like to humbly add some views to it: there has been two varying reported type I interferon responses in COVID-19 pathogenesis [2]: one stating the suppression of host antiviral type I interferons (IFNs) and interferon stimulated genes (ISGs) and other stating increased expression of different ISGs, with further inductions of chemokines and cytokines [2].

The viral Nsps (particularly Nsp1) and the ORFs (particularly ORF 6) are known to antagonise the host antiviral IFNs initially by suppressing/delaying their expressions, leading to viral persistence and propagating inflammations. Hence, neither type I IFN nor type III IFN, which are known hard-wired for providing antiviral immunity, was activated in early stages of COVID-19. However, SARS-CoV-2 at 2 days post-infection (dpi), induced ISGs having antiviral action (Rsad2, Ifit, Mx2, Oas3, etc.) and at 7dpi, ISGs having potentiating IFN mediated inflammatory signalling (Ifihi,Irf7,Stat1,Ifnar1/ 2,Tyk2,etc.) [3]. As the disease progresses towards severity, the IFNs exacerbate the pathophysiology with specific inflammatory signatures [2]. Hence, cellular response to type 1 IFN (thru ISGs) towards later stages of infection is immunopathogenic.

Neutrophils provide the first line of innate immune defence. Neutrophil attracting chemokines (CXCL1,

\*Correspondence: rbiochem@gmail.com Kolkata, India CXCL2, CXCL8, S100A9) and cognate receptor (CXCR2) were found to be activated in early stages (1-3 dpi) [3]. COVID-19 is manifested with necrophilia having high neutrophil-to-lymphocyte ratio. Type 1 IFNs are known to inhibit neutrophil migration by downregulating neutrophil chemoattractants production (CXCL1/2) [4]. Other than phagocytosis, neutrophils have another capacity to contain pathogens, by forming neutrophil extracellular traps (NETs). NETs are mesh-like structures of DNA and proteins from degrading neutrophils (by neutrophil elastase) which entrap pathogens. Interestingly against leishmania, IFNAR-1- mice showed enhanced neutrophil elastase activity, with better infiltrations. Aberrant production of NETs have been known to cause severe COVID-like pathophysiologies-thrombosis, lung damage, ARDS, multiorgan damage, etc. [5]. Indeed, severe COVID-19 patients reported of higher amount of NETosis remnants like cell-free DNA, myeloperoxidase-DNA and citrullinated histone H3 [5]. These molecules further propagate inflammation by inducing IL-1 $\beta$  production thru inflammasome activation.

The initial type 1IFN suppression could lead to enhanced infiltration of neutrophils, NET formation and ensuing pathophysiologies. Early administration of IFN $\beta$  has proved beneficial [1, 2]; hence, the "double edged sword" be tried prudently with respect to time and dosage.

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## Authors' contributions

Rahul did the literature survey and wrote the manuscript.

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## Availability of data and materials

Literature survey.

Ethical approval and consent to participate Not applicable.

# Consent for publication

Yes.

## **Competing interests**

I do not have any competing interests.

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#### References

 Jalkanen J, Hollmen M, Jalkanen S. Interferon beta-1a for COVID-19: critical importance of the administration route. Crit Care. 2020. https://doi. org/10.1186/s13054-020-03048-5.

- Lee JS, Shin EC. The type I interferon response in COVID-19: implications for treatment. Nat Rev Immunol. 2020. https://doi.org/10.1038/s4157 7-020-00429-3.
- Zhou Z, Ren L, Zhang L, Zhong Z, Xiao Y, Jia Z, et al. Heightened innate immune responses in the respiratory tract of COVID-19 patients. Cell Host Microbe. 2020;27:883–90.
- Shahnangian A, Chow EK, Tian X, Kang JR, Gaffari A, Liu SY, et al. Type I IFNs mediate development of postinfluenza bacterial pneumonia in mice. J Clin Invest. 2009;119:1910–20.
- Zuo Y, Yalavarthi S, Shi H, Gockman K, Zuo M, Madison JA, et al. Neutrophil extracellular traps in COVID-19. JCI Insight. 2020;5:e138999.

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