Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Neutrophils as a pallbearer for SARS-CoV-2 disease burden

Authors' reply

We thank David Twa and colleagues for their interest in our findings and agree that it is intriguing that, despite the apparent systemic responses, some organs from patients who died of COVID-19 are more affected than others by neutrophilic extracellular traps (NETs). Although to the best of our knowledge, NETs have never been studied in much detail for other respiratory viral infections, there is strong evidence from respiratory viral infections that are virulent (influenza),[1,2] and also those that are less virulent (rhinovirus),[3] that NETs are formed locally and even that markers of NETs can be detected systemically.[1] In fact, Zeng and colleagues[1] found that markers of systemic NETs correlate with the outcome of influenza infections, which might also be relevant markers in COVID-19-related outcomes, as was proposed.[4] The differences in NETs between organs indicate organ-specific modulation. On the basis of their analysis, Twa and colleagues suggested that *ACE2* expression might underlie the differential presence of NETs. Notably, we found that *ACE2* expression in the lungs from patients with COVID-19 was higher than in the control tissue (appendix). Also, we found significantly increased *ACE2* expression in the sequential transcriptomes of nasal epithelial cells from patients with asthma[5] at days 3 and 6 after exposure to the common cold virus, rhinovirus 16, compared with one week before the viral challenge (p=0·007 [ANOVA], data not shown). ACE2 degrades proinflammatory peptides such as angiotensin 2 and des-Arg^9 bradykinine, and this activity, together with the generation of anti-inflammatory angiotensin (1-7), might attenuate inflammatory and also neutrophilic responses. We therefore suggest that the increase in *ACE2* expression is a common response to infection with a respiratory virus and might be a response restoring homoeostasis. A possible explanation for the apparent contradictory association between *ACE2* expression and neutrophil activation is that NETs are not being cleared, whereas *ACE2* expression is related to the events that triggered NET formation. The differences in NETs between organs might therefore also relate to differences in resolving NETs, which should be considered when the presence of NETs is used as a prognostic factor. Finally, it is important to realise that in the organs of most patients, we found little to no severe acute respiratory syndrome coronavirus 2 particles by both immunohistochemistry and quantitative PCR, indicating that despite the presence of ACE2, the porte d'entrée for severe acute respiratory syndrome coronavirus 2, there is no viral infection and replication and thus the pathology might be related to an autonomous, systemic process. Whether this process depends on the extent of NETs that are present requires further study.

We declare no competing interests.

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1 Zhu L, Liu L, Zhang Y, et al. High level of neutrophil extracellular traps correlates with poor prognosis of severe influenza A infection. *J Infect Dis* 2018; **217:** 428–37.

2 Ravanetti L, Dijkhuis A, Dekker T, et al. IL-33 drives influenza-induced asthma exacerbations by halting innate and adaptive antiviral immunity. *J Allergy Clin Immunol* 2019; **143:** 1355–70.e16.

3 Toussaint M, Jackson DJ, Swieboda D, et al. Host DNA released by NETosis promotes rhinovirus-induced type-2 allergic asthma exacerbation. *Nat Med* 2017; **23:** 681–91.

4 Ng H, Havervall S, Rosell A, et al. Circulating markers of neutrophil extracellular traps are of prognostic value in patients with COVID-19. *Arterioscler Thromb Vasc Biol* 2020; published online Dec 3. https://doi.org/10.1161/ATVBAHA.120.315267.

5 Ravi A, Chang M, van de Pol M, et al. Rhinovirus-16 induced temporal interferon responses in nasal epithelium links with viral clearance and symptoms. *Clin Exp Allergy* 2019; **49:** 1587–97.

See **Online** for appendix