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.

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Reply to "Protective effects of eosinophils against COVID-19: More than an ACE(2) in the hole?"

To the Editor:

We would like to thank Drake et al[1] for their valuable comment regarding the antiviral effect of eosinophils, which may explain why patients with type 2 high asthma were protected against severe disease (COVID-19) in our study.[2] An important aspect that warrants further investigation is to find a mechanistic explanation for high rates of eosinopenia in hospitalized patients with COVID-19[2-4] and more importantly, how to speed the recovery of eosinophil counts to properly exhibit their antiviral effects.

Previous data show that bacterial, viral, and parasitic acute inflammation is associated with the decrease in circulating eosinophils due to egress inhibition from the bone marrow.[5] Eosinopenia in acute inflammation may also result from distribution of eosinophils in the inflamed tissues[5]; however, pulmonary samples from individuals with COVID-19 show a predominant mononuclear inflammatory infiltrate (mostly lymphocytic), without the presence of eosinophils.[6] Although eosinopenia is not unique to severe acute respiratory syndrome coronavirus (SARS-CoV-2), it was shown to be more prevalent in COVID-19 than it is in acute influenza infection.[7] Therefore, other mechanisms, perhaps specific to SARS-CoV-2 infection, may explain these findings. It is possible that differences in the cytokine profile of patients with COVID-19 might influence their circulating eosinophils. For example, among the proinflammatory cytokines that are elevated in patients with severe COVID-19,[8] IFN-γ/TNF-α have been associated with FasL-induced apoptosis of eosinophils.[9] However, it is not understood which patients are prone to severe disease, eosinopenia, or who are those individuals recovering their eosinophils faster and why. It also remains to be determined if this is an asthma-specific protective effect or a more generalizable finding extending to other conditions.

We show in our study that patients with asthma with prior eosinophilia are more likely to recover their circulating eosinophils during COVID-19 hospitalization, and these patients had subsequently less risk of dying from SARS-CoV-2 infection.[2] Therefore, individuals with type 2 high asthma appear to have the advantage of pre–COVID-19 eosinophilia. However, it is unclear if this is their main tool in fighting against severe COVID-19 disease, or if other characteristics of these patients (eg, prior Th2 cytokine predominance that might influence the cytokine milieu released during COVID-19, gender differences, certain medications used for asthma control) are also of importance.

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Patient variability in severity of COVID-19 disease. Main suspect: vascular endothelium

To the Editor:

We read with care and interest the original article from Ballow and Haga[1] about the possible explanation for why some

individuals have life-threatening COVID-19 disease whereas others have no or mild symptoms.

Because this is not the conclusive report and we appreciate the attempt to explain the peculiar reactions of some patients with COVID-19, we would like to suggest some specific ideas with a view to more targeted therapeutic interventions.

First, it is not easy to determine the relation between risk factors predisposing people to a more severe reaction to COVID-19 infection with regard to vitamin D deficiency and genetic risk factors. On the other hand, genetic alterations suggest interesting ideas with regard to multigene expression, especially on large specific chromosomes for epithelial membrane proteins in the lungs, according to recent papers on this topic.[2]

Second, apparent contradictions in COVID-19 mortality and morbidity in patients with common variable immune deficiency allow the authors to produce a scholarly examination of the immune imbalance and dysregulation of innate and adaptive immune responses in patients with severe COVID-19. The factors analyzed, sometimes in a correlated manner, are (1) the importance of the type I interferon pathway; (2) immune-senescence; (3) age-independent comorbidities such as hypertension, diabetes, and obesity; (4) the uncontrollable proinflammatory response in the lungs driven by macrophage-activation syndrome; (5) the T cell and subtype response; and (6) the antibody response against the viral envelope S (spike) and N (nucleocapsid) proteins.

However, before concluding that "a combination of multiple genetic and non-genetic factors contribute to an individual's unique immune response and susceptibility to SARS-CoV-2 infection," in our opinion, it is of paramount importance to introduce the vascular endothelium into the discussion.[3] Endothelial damage to various organs was also highlighted by autopsy outcomes.[4]

With regard to the subject of the vascular endothelium, information reported on the AB0 blood group loci that were associated with severe SARS-CoV-2 infection may find a more complete and significant interpretation in this direction, as also may be the case regarding the integrity of endothelial glycoproteins.[5,6]

Thus, we encourage an examination of these points, not to negate any of the points made but to augment and improve this thought-provoking original article, which sheds further light on why some people develop serious COVID-19 disease after infection whereas others exhibit only mild symptoms.

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Reply to "Patient variability in severity of COVID-19 disease. Main suspect: vascular endothelium"

To the Editor:

We thank Drs Tricarico and Travagli[1] for their comments on our recent Rostrum publication.[2] Over the past year, we have learned much about the pathobiology and immunology of the disease caused by the SARS-CoV-2 virus. Vascular dysfunction, serum cytokines, and chemokines have important roles in the pathophysiology of COVID-19 disease, especially in severe cases. They raise an interesting comment regarding how severe COVID-19 can result from damage to the vascular endothelium and how this damage may induce thrombotic events that may correlate with ABO blood groups.

Although there is little question as to whether damage to the vascular endothelium has a role in COVID-19 progression and severity, there are questions regarding how this damage arises in SARS-CoV-2 infection. Certainly, studies have shown that patients with the non-O blood type have an elevated risk for thrombocytopathy and endotheliopathy. Cardiovascular risk factors such as diabetes,[3] hypertensive disorders,[4] and obesity[5] have also been shown to increase susceptibility to endotheliopathy and thrombosis; they correlate with increased morbidity and mortality in COVID-19 patients presenting with these comorbidities. Aging also decreases endothelial cell function through increased oxidative and nitrative stress responses.[6]

However, thrombosis and endothelial dysfunction may result from the response to the virus itself, outside preexisting genetic and health factors. For instance, Wu et al[7] recently showed that the receptor binding domain of the SARS-CoV-2 spike protein preferentially binds to cells expressing blood type A, potentially boosting the viral load. Thrombotic and endothelial dysfunction may result from an increased viral burden, because endothelial cells have also been shown to express the angiotensin-converting enzyme 2 receptor.[8] As we discussed in our article,[2] hyperinflammatory responses precipitated by inflammatory cytokines to SARS-CoV-2 infection may themselves elicit endothelial cell damage. In addition, thrombocytopathy and endotheliopathy may result from an errant humoral response that leads to the development of antiphospholipid antibodies. The production of these autoantibodies may cause symptoms of antiphospholipid syndrome,[9] of which vascular endothelial cell dysfunction is a key pathological hallmark.[10]

Nitric oxide (NO) has recently been addressed as an important component of vascular dysfunction in patients with COVID-19