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.

Board; has received honorarium for lectures from Thermo Fisher, Aimmune, DBV, Before Brands, multiple state allergy societies, the American College of Allergy, Asthma, and Immunology, and the Eurpoean Academy of Allergy and Clinical Immunology; is an associate editor for the *Annals of Allergy, Asthma, and Immunology*; and is a member of the Joint Taskforce on Allergy Practice Parameters. The rest of the authors declare that they have no relevant conflicts of interest.

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

To the Editor:

We read with great interest the recent publication by Ferastraoaru et al[1] in the January 2021 issue of *JACI: In Practice* that reported type 2 high asthma with eosinophilia is protective against severe coronavirus disease (COVID-19). As the authors note, this protective effect may be due to reduced viral binding and propagation in type 2 high asthmatic airways as the result of downregulated expression of the severe acute respiratory syndrome coronavirus (SARS-CoV-2) receptor, angiotensin-converting enzyme 2 or ACE(2), on airway epithelium. It is notable, however, that many prior studies have reported antiviral and immunomodulatory functions of eosinophils in humans and in animal models, which in light of the present findings, are potentially complementary or alternative mechanisms that explain this effect. Eosinophils express a variety of pattern recognition receptors capable of detecting viral RNA genomes, including Toll-like receptors 3 and 7, RIG-like receptors, and NOD-like receptors.[2] Once activated, eosinophils release mediators with direct antiviral activity such as eosinophil cationic protein and eosinophil-derived neurotoxin, whose ribonuclease activity degrades viral RNA genomes, and nitric oxide, which has been shown to reduce infectivity of 2 other RNA respiratory viruses, parainfluenza virus and respiratory syncytial virus.[2] Eosinophils also produce T_H1-related cytokines involved in antiviral defense, including IFNγ and IL-12, and they express major histocompatibility complex class 1 and 2 molecules that enable antigen presentation and recruitment of viral-specific CD8 T cells to the lung.[2]

Although much of our mechanistic understanding of eosinophil's antiviral effects is derived from *in vitro* studies of human and mouse eosinophils, several experimental observations support the concept that eosinophils are antiviral *in vivo* as well. For example, mice and guinea pigs with allergen-induced airway eosinophilia have lower titers of parainfluenza virus in the lung 4 days after infection,[3,4] and transgenic mice with eosinophilia due to IL-5 overexpression also exhibit accelerated viral clearance.[4] In influenza-infected mice, adoptive transfer of eosinophils into airways reduces viral titers,[5] whereas double transgenic eosinophil-deficient mice that overexpress IL-5 lack this antiviral response, indicating that eosinophils specifically, not IL-5, mediate the antiviral effect.[4] Similarly, in a study of experimental rhinovirus infection in humans, mild asthmatics treated with the anti-IL5 antibody mepolizumab had higher nasal viral titers than placebo-treated individuals, suggesting that eosinophil's antiviral functions are conserved between animals and humans.[6]

As both eosinophils and viral infections are important causes of asthma attacks, eosinophil activation in virus-infected airways is likely a double-edged sword capable of causing both harm during asthma exacerbations triggered by seasonal respiratory viruses and protection against serious and fatal infections from pandemic SARS-CoV-2. Indeed, despite a common evolutionary lineage with seasonal coronavirus variants, SARS-CoV-2 and prior pandemic coronaviruses, Middle East respiratory syndrome and SARS, share unique genomic features that account for their immunogenicity. Given that higher SARS-CoV-2 titers are associated with increased mortality,[7] eosinophil's ability to directly and indirectly attenuate viral replication may protect against development of a runaway inflammatory response that underlies the onset of severe COVID-19 disease.

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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