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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Editorial

Eosinophils in antiviral immunity and (perhaps) a benefit of having asthma during the SARS-CoV2 pandemic

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Eosinophils are potent proinflammatory leukocytes defined by their expression of preformed cationic granules. Eosinophils have historically primarily been understood to have evolved to mediate toxic immune responses to parasites, while, more problematically, being toxic to airway epithelial cells and other healthy tissues.[1] Recently, however, a role of eosinophils in eliminating viral pathogens has emerged, including studies reporting the contribution of eosinophils in the elimination of respiratory syncytial virus (RSV), influenza, parainfluenza and, rhinovirus. In this issue of the *Annals*, Ho et al[2] suggests that they may also provide protection against coronavirus disease 2019 (COVID-19).

Eosinophils are equipped with an assortment of molecular tools that enable them to recognize, respond and coordinate an antiviral response to viruses, and, in particular, to RNA viruses. Viruses may gain entry into eosinophils either by means of binding to surface viral receptors or endocytic pathways. In the case of any virus gaining entry, eosinophils express pattern recognition receptors including toll-like receptors (TLRs) that recognize viral genomes (TLR3, TLR7, and TLR9).[3] Stimulation of these receptors triggers eosinophils to degranulate, release proinflammatory cytokines, and generate superoxide and nitric oxide free radicals—all of which are capable of combating viral pathogens. For example, the release of eosinophil-derived superoxide and nitric oxide free radicals have direct antiviral effects on RSV and parainfluenza.[4] Among the cytokines produced by eosinophils are the type I interferons, interleukin 12, and others—cytokines that contribute to the emergence of an antiviral state. Furthermore, similar to polymorphonuclear cells, eosinophils release DNA traps in response to viruses. Such eosinophil-derived traps emerge, as an example, in response to RSV and, although contributing to viral elimination, simultaneously the DNA-associated "glue" contributes to the severity of bronchiolitis.

In terms of a particularly robust antiviral armamentarium that specifically targets RNA viruses, eosinophils produce potent ribonucleases. Indeed, as noted, eosinophils were originally defined by their expression of the cationic proteins, including the 2 proteins historically termed eosinophil-derived neurotoxin and eosinophil cationic protein. However, currently, reflecting their more recognized roles as potent ribonucleases (RNases), these 2 proteins have been replaced with the more appropriate designations: RNase 2 for eosinophil-derived neurotoxin and RNase 3 for eosinophil cationic protein. These RNases can directly access the viral nucleus and, as a result, are particularly effective at destroying respiratory RNA viruses.

In addition to acting as innate effector cells, eosinophils can also contribute to the emergence of an antiviral adaptive immune response. In a murine model, on exposure to RSV, eosinophils upregulate the expression of major histocompatibility complex class I and CD86, allowing them to act as antigen-presenting cells that can directly activate virus-specific CD8-positive cytotoxic T cells. Furthermore, both human and murine eosinophils express major histocompatibility complex class II and costimulatory molecules, allowing them to present viral antigens to CD4-positive T-helper cells.[5]

Although these data illustrate the antiviral potential of eosinophils, the clinical significance of eosinophils in human antiviral response remains somewhat controversial. Some of this controversy is derived from the observation that patients with eosinophilic asthma are at increased risk of viral-induced exacerbations of their asthma. One explanation for this phenomenon is that eosinophils in the respiratory tract are a double-edged sword. Although eosinophils may be effective against respiratory viruses, this antiviral potency occurs at the expense of enhanced eosinophilic inflammation, and this overactivation of eosinophils contributes to tissue damage, airflow obstruction, bronchospasm, and all the features associated with asthma exacerbation.[6] This dichotomous relationship of eosinophils to viral restriction occurring concomitantly with an asthma exacerbation is perhaps best exemplified by studies performed with mepolizumab. Although mepolizumab dramatically reduces the frequency of asthma exacerbations, including, presumably, rhinovirus-associated asthma exacerbations, pretreatment with mepolizumab in a rhinovirus challenge model was associated with an approximately 10-fold increase in the number of virions present in the airway![7]

This leads us to the current severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic. Since the emergence of SARS-CoV-2 in Wuhan, People's Republic of China, comorbidities have been associated with the severity of COVID-19. Although hypertension, diabetes mellitus, chronic obstructive pulmonary disease, and tobacco use have been associated with the severity of COVID-19, early data from the People's Republic of China described a low prevalence of asthma in hospitalized patients, suggesting that underlying asthma was perhaps not a risk factor for poor outcomes.[8] Since this early report, recent studies have echoed these findings, suggesting that asthma might even be protective against severe COVID-19.

Several explanations have been proposed for this paradox. The cell entry of SARS-CoV-2 initially involves binding to the angiotensin 2 receptor, after which, transmembrane protease serine 2 cleaves the

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viral spike protein, allowing SARS-CoV-2 to bind more effectively. This angiotensin 2 receptor expression is reduced on the airway epithelial cells of people with asthma, perhaps reflecting the biological activity of interleukin 13.[9] An additional explanation involves the use of systemic and topical corticosteroids in asthma, with these steroids potentially attenuating the severity of the COVID-19–associated "cytokine storm".

In the current issue of the *Annals of Allergy, Asthma & Immunology*, Ho et al[2] review 10,523 patients diagnosed with COVID-19 and report that patients with asthma had a lower mortality rate, lower hospitalization rate, and a lower intensive care unit admission rate compared with those without asthma, even after adjusting for concurrent therapies and comorbidities. Intriguingly, protection was strongly associated with the presence of higher blood eosinophils (≥200 cells/μL), and this mortality benefit of eosinophilia was recognized in those with and without asthma. This result is similar to what has been observed in another large population study that reported an increased risk of severe COVID-19 in nonallergic compared with eosinophilic patients with asthma.[2] Both these studies support the premise that the beneficial effect of asthma may be more associated with the presence of an eosinophilic process than either the presence of asthma itself or asthma-associated therapies. Indeed, this concept is further supported by studies that have associated eosinopenia with severe COVID-19 and even death.[10]

In summary, this study by Ho et al[2] provides further support for the argument that eosinophils may play an important role in antiviral immunity and that this may extend to infections caused by SARS-CoV-2. At present, this is purely circumstantial and investigations are warranted to confirm the ability of eosinophil-derived products (especially their RNases) to destroy SARS-CoV-2. Regardless of the mechanism, clinicians should be aware of the positive prognostic implication eosinophilic inflammatory disease has on COVID-19. Furthermore, clinicians need to be cognizant of the 50% of asthmatics without eosinophilia, as COVID-19 may pose a greater threat to this subset of patients. This developing relationship between eosinophilia, asthma, and COVID-19 highlights the importance of viewing asthma as a heterogeneous disease and emphasizes the need for accurate biomarkers of asthma endotypes.

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References

1. Lindsley AW, Schwartz JT, Rothenberg ME. Eosinophil responses during COVID-19 infections and coronavirus vaccination. *J Allergy Clin Immunol*. 2020;146(1):1–7.
2. Ho KS, Howell D, Rogers L, Narasimhan B, Verma H, Steiger D. The relationship between asthma, eosinophilia, and outcomes in COVID-19 infection. *Ann Allergy Asthma Immunol*. 2021;127(1):42–48.
3. Wong CK, Zhang J, Ip WK, Lam CWK. Intracellular signal transduction in eosinophils and its clinical significance. *Immunopharmacol Immunotoxicol*. 2002;24 (2):165–186.
4. Mikhail I, Grayson MH. Asthma and viral infections: an intricate relationship. *Ann Allergy Asthma Immunol*. 2019;123(4):352–358.
5. Samarasinghe AE, Melo RCN, Duan S, et al. Eosinophils promote antiviral immunity in mice infected with influenza A virus. *J Immunol*. 2017;198(8):3214–3226.
6. Rosenberg HF, Domachowske JB. Eosinophils, eosinophil ribonucleases, and their role in host defense against respiratory virus pathogens. *J Leukoc Biol*. 2001;70 (5):691–698.
7. Sabogal Piñeros YS, Bal SM, van de Pol MA, et al. Anti-IL-5 in mild asthma alters rhinovirus-induced macrophage, B-cell, and neutrophil responses (MATERIAL). A placebo-controlled, double-blind study. *Am J Respir Crit Care Med*. 2019;199 (4):508–517.
8. Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med*. 2020;180(7):934–943.
9. Kimura H, Francisco D, Conway M, et al. Type 2 inflammation modulates ACE2 and TMPRSS2 in airway epithelial cells. *J Allergy Clin Immunol*. 2020;146(1):80–88. e8.
10. Abidi K, Belayachi J, Derras Y, et al. Eosinopenia, an early marker of increased mortality in critically ill medical patients. *Intensive Care Med*. 2011;37(7):1136–1142.