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Eosinophils are potent proinflammatory cells, primarily due to their preformed granules, which are packed with cytotoxic proteins, including major basic protein (one of the most basically charged molecules in the body), eosinophil peroxidase, and 2 RNases (eosinophil cationic protein and eosinophil neurotoxin). In addition to their proinflammatory effects, evidence is emerging, albeit primarily in mice, that eosinophils have pleotropic roles as regulatory cells involved in protective immunity, including antiviral responses and shaping diverse physiological responses, such as organ development and metabolism. Although eosinophils are normally considered blood cells, they reside in various tissues. Most notably, eosinophils reside in the gastrointestinal tract, which is their primary residence, and the lung, where a population of regulatory eosinophils, which have unique features compared with inflammatory eosinophils, has been identified. 4

There are a number of diseases associated with eosinophil expansion in which eosinophils are causally related to the disease pathology, such as subsets of moderate and severe asthma. Accordingly, a number of clinically approved biological antibody-based precision therapies are now available that directly target eosinophils, resulting in eosinophil depletion. 5 These drugs include those that neutralize the eosinophil growth and activating factor IL-5 (eg, mepolizumab and reslizumab) and drugs that directly induce eosinophil depletion by antibody-dependent cellular cytotoxicity (eg, the anti–IL-5 receptor drug benralizumab). 6 These drugs have remarkable beneficial effects in a growing number of diseases, including asthma, hypereosinophilic syndrome, and eosinophil granulomatous polyangiitis (formerly known as Churg Strauss syndrome), and additional clinical indications are actively being pursued. As a result, there is now an increasing number of patients with biological drug–induced eosinopenia. 7 Although patients with abnormally low eosinophil levels (referred to as eosinopenia) might be considered at risk for diseases normally controlled by eosinophils, there have been no major side effects associated with these therapies to date. In addition to biological drug–induced eosinopenia, eosinophil depletion occurs in response to multiple triggers of acute inflammation, 8 including during sepsis, and multiple studies have consistently shown that low eosinophil levels correlate with poor outcome in critically ill patients. 9
There are now key coronavirus disease 2019 (COVID-19)-related questions concerning eosinophils whose answers affect recommended prevention and care. First, do patients with eosinophilia-associated diseases have an altered course of COVID-19? Second, do patients with eosinopenia have unique COVID-19 disease features? This is a particularly relevant question because eosinopenia has already been reported in patients with acute respiratory deterioration during infection with severe acute respiratory syndrome (SARS) coronavirus (CoV) 2 (SARS-CoV-2), the causative agent of COVID-19.10 Third, do eosinophils contribute to the lung pathology induced during COVID-19 and will they contribute to adverse events associated with emerging COVID-19 vaccines? Indeed, eosinophil-associated lung pathology is known to occur following certain viral infections (eg, respiratory syncytial virus [RSV]) and importantly is a known complication in previous severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1) vaccination studies (see Table I).11-17 On the basis of previous experience with SARS-CoV vaccines, it is expected that COVID-19 vaccines will need careful safety evaluations for immunopotentiation that might increase infectivity and/or eosinophilic infiltration.18

EOSINOPHIL RESPONSES DURING RESPIRATORY VIRUS INFECTIONS

The role of eosinophils in mucosal immune responses in the respiratory tract has largely focused on the detrimental impact that these cells can have in inflammatory responses due to their potent proinflammatory function. However, preclinical studies (mainly in mice) have shown that eosinophils are equipped with an assortment of molecular tools that enable them to recognize, respond, and orchestrate antiviral responses to respiratory viruses.19 Human eosinophils express several endosomal Toll-like receptors (TLRs), including TLR3, TLR7, and TLR9, that detect viral microbe–associated molecular patterns.20,22 TLR7 enables eosinophils to recognize single-stranded RNA viruses such as coronavirus, and stimulating this receptor in human eosinophils triggers eosinophil cytokine production, degranulation, superoxide and nitric oxide (NO) generation, and prolonged cellular survival.21-23 Eosinophil-derived neurotoxin (EDN/RNase2) and eosinophil cationic protein (ECP/RNase3) from human eosinophils reduce infectivity of RSV by a ribonuclease-dependent mechanism.24,25 Both human and murine eosinophils produce NO via inducible NO synthase, which can have direct antiviral effects on paramyxovirus and RSV.26 Eosinophils are able to produce extracellular traps composed of eosinophilic granule proteins bound to genomic and mitochondrial DNA, and murine eosinophils can release these DNA traps in response to RSV infection in vitro, especially in oxidative lung tissue environments.27 Eosinophils are also capable of quickly mobilizing preformed granule pools of TH1 cytokines, including IL-12 and IFN-γ, which are important for mounting effective antiviral immune responses.30 In a murine model of allergic asthma, pulmonary eosinophils upregulate MHC-I and CD86 in response to influenza virus infection, where they can directly interact with CD8+ T cells and promote the recruitment of virus-specific CD8+ T cells into the lungs to enhance antiviral immunity.31 Activated murine and human eosinophils also express MHC-II molecules and costimulatory molecules and can function as antigen-presenting cells for viral antigens, leading to T-cell activation and cytokine secretion.32,33 IL-5 transgenic mice, which constitutively overproduce IL-5 and have systemic eosinophilia, have accelerated viral clearance during infection with RSV.26 Conversely, mice genetically engineered to be eosinophil-deficient have lower viral clearance of RSV than do wild-type controls.26 Adoptive transfer of eosinophils from Aspergillus fumigatus antigen–sensitized mice into the airways of influenza virus–infected mice decreases viral titers and increases virus-specific CD8+ T cells in comparison to that of animals who did not receive eosinophils.31 Interestingly, human subjects with asthma were treated with the anteosinophil drug mepolizumab (an anti–IL-5 humanized mAb) or placebo and subsequently challenged with rhinovirus; mepolizumab-treated patients demonstrated significant increases in their rhinovirus viral titers in the upper airway, supporting an antiviral role for eosinophils.34 Although these data substantiate the antiviral potential of eosinophils, the clinical significance of eosinophils in antiviral responses in human disease continues to remain debatable. Patients with eosinophilic asthma have an increased risk for viral-induced asthma exacerbations, and there is mounting evidence that patients with eosinophilic asthma may actually have reduced innate responses against respiratory viruses.35-37 Importantly, biologic agents that decrease pulmonary eosinophil levels reduce asthma exacerbations, and patients with asthma treated with these agents have not been reported to have increased viral infections.36,38-43 Rosenberg et al44 suggested that eosinophils in the respiratory tract might represent a “double-edged sword,” promoting antiviral responses against some respiratory viruses that could become dysregulated during allergic disease given their increased numbers and/or activation status, ultimately resulting in an exaggerated host response that can lead to host tissue damage. The growing number of biologic agents that target eosinophils may be useful tools to help clarify the role eosinophils have in different antiviral responses. Taken together, although preclinical studies have demonstrated antiviral activity for eosinophils, their clinical relevance in immune responses to different respiratory viruses remains unclear and needs further investigation.

EOSINOPHIL RESPONSE IN COVID-19

Rhinovirus, RSV, and influenza virus are common triggers of viral-induced asthma exacerbations, whereas coronaviruses are far less common triggers for acute asthma exacerbations.34,6,45-48 Asthma has not yet been identified as a major risk factor for severity of SARS-CoV-1 infections.49 With regard to SARS-CoV-2, Zhang et al10 recently reported that none of the 140 hospitalized patients with confirmed COVID-19 in a hospital in Wuhan, China, reported asthma or comorbid atopic disease. Another recent review of 548 patients admitted with COVID-19 to another hospital in Wuhan reported only 5 cases of asthma (prevalence of 0.9%), markedly lower than the prevalence of asthma within the adult population in Wuhan (6.4%).40 Leukocytosis, with increased absolute neutrophil counts, has been associated with more severe presentations of COVID-19,50-53 Interestingly, Zhang et al reported that more than half the patients admitted with COVID-19 (53%) had eosinopenia (defined as absolute eosinophil counts <0.02 × 10^9 cells/L) on the day of hospital admission.50 Similarly, Du et al54 reviewed the medical records of 85 fatal cases of COVID-19 and noted that 81% of the patients had absolute eosinophil counts below the normal range (absolute eosinophil counts <0.02 × 10^9 cells/L)
| Study            | Vaccine type                  | SARS-CoV-1 antigen | Adjuvant | Booster rounds | Neutralizing antibodies | Vaccine-induced pathology |
|------------------|-------------------------------|--------------------|----------|----------------|--------------------------|---------------------------|
| Deming et al, 2006 | Recombinant viral particle   | S protein (VRP-S)  | None     | 1× (3-7 wk after first) | Yes                      | No                        |
| Du et al, 2007    | Subunit vaccine: S protein RBD| RBD318-510-hFc*    | Initial: Freund’s complete adjuvant Boosters: Freund’s incomplete adjuvant | 3× (every 3 wk ×2, final at 12 mo) | Yes                      | No                        |
| Yasui et al, 2008 | Recombinant viral particle   | Spike (S)          | None     | None            | Yes (9 d after infection) | Yes, mild (neu)           |
| Yasui et al, 2008 | Nucleocapsid (nuc)            | None               | None     | No (9 d after infection) | Yes, severe (eos + neu)  | No                        |
| Yasui et al, 2008 | Membrane (M)                  | None               | None     | No (9 d after infection) | No                       | No                        |
| Yasui et al, 2008 | Envelope (E)                  | None               | None     | No (9 d after infection) | No                       | No                        |
| Bolles et al, 2011 | DIV (formalin/UV)             | Whole virus        | ± Alum   | 1× (2-3 wk after first) | Yes (DIV + alum) (4 d, after infection) | Yes; eos (4 d, after infection) |
| Bolles et al, 2011 | Whole virus                   | ± Alum             | 1× (2-3 wk after first) | ND | Yes; eos + neu + mac (4 d after infection) | No                        |
| Bolles et al, 2011 | Whole virus                   | ± Alum             | 1× (2-3 wk after first) | ND | Yes; eos + neu + mac (4 d after infection) | No                        |
| Tseng et al, 2012 | DIV (formalin/UV)             | Whole virus        | ± Alum   | 1× (4 wk after first) | Yes (2 mo after booster) | Yes; eos (2 d after infection) (reduced + alum) |
| Tseng et al, 2012 | Beta propiolactone— inactivated virus (BPV) | Whole virus | ± Alum | 1× (4 wk after first) | Yes (2 mo after booster) | Yes; eos (2 d after infection) (no difference + alum) |
| Tseng et al, 2012 | Subunit vaccine: Full-length S protein | Spike (S) | ± Alum | 1× (4 wk after first) | Yes (2 mo after booster) | Yes; eos (2 d after infection) (reduced + alum) |
| Tseng et al, 2012 | Chimeric virus-like particle (VLP) | Spike (S) | ± Alum | 1× (4 wk after first) | Yes (2 mo after booster) | Yes; eos (2 d after infection) (no difference + alum) |
| Iwata-Yoshikawa et al, 2014 | UV-inactivated whole virus (UV-V) | Whole virus | ± Alum | 1× (6-7 wk after first) | Yes (before infection and 3 d and 10 d after infection) | Yes; eos, lymph |
| Honda-Okubo et al, 2015 | Subunit vaccine: Partially truncated S protein | Spike (S) | ± TLR agonists | 1× (6-7 wk after first) | Yes (before infection and 3 d and 10 d after infection) | No |
| Honda-Okubo et al, 2015 | Subunit vaccine: Partially truncated S protein | Spike (S) | ± Advax1 | 1× (3 wk after first) | Yes (3 d after infection) | Yes, severe eos (6 d after infection) |
| Honda-Okubo et al, 2015 | Subunit vaccine: Partially truncated S protein | Spike (S) | ± Advax2 | 1× (3 wk after first) | Yes (3 d after infection) | Yes, mild eos (6 d after infection) |

DIV: Double-inactivated whole virus; eos, eosinophil; lymph, lymphocyte; mac, alveolar macrophage; ND, not done; neu, neutrophil; RBD, receptor-binding domain; S<sup>ΔTM</sup>, Spike protein-transmembrane domain deleted; UV, ultraviolet light; VRP, virus replicon particle; VV, vaccinia; V, virus. Alum, Aluminum salts; TLR agonist [LPS, poly(I:C), poly(U)]; Advax1, delta inulin microparticles; Advax2, delta inulin microparticles and CpG.

<sup>*</sup>Fusion protein of SARS-CoV-1 RBD (193 amino acids long) and Fc domain of human IgG1.
at the time of admission. Lymphopenia has also been a common finding in patients with COVID-19, and blood eosinophil counts correlated positively with lymphocyte counts in both severe and nonsevere cases. Liu et al. noted eosinopenia at the time of initial presentation in a small cohort of patients who were treated with lopinavir. Notably, eosinophil levels improved in all patients before discharge, suggesting that resolution of eosinopenia may be an indicator of improving clinical status. The pathophysiology for eosinopenia in COVID-19 remains unclear but is likely multifactorial, involving inhibition of eosinophil egress from the bone marrow, blockade of eosinophilopoiesis, reduced expression of chemokine receptors/adhesion factors, and/or direct eosinophil apoptosis induced by type 1 IFNs released during the acute infection. Importantly, no eosinophil enrichment into the pulmonary tissue has been observed in samples from patients with COVID-19 at early stages of disease or in postmortem analyses. Moreover, postmortem analysis of lung tissue from a patient who died from COVID-19 demonstrated signs of acute respiratory distress syndrome that was dominated by mononuclear inflammatory infiltrates, mostly lymphocytes. Consequently, consistent with SARS-CoV-1, asthma or other allergic comorbidities do not seem to increase the risk for poor outcomes with SARS-CoV-2 infections given the current evidence available. Conversely, multiple studies have identified older age, male sex, hypertension, coronary heart disease, and diabetes as being consistent risk factors for severe COVID-19.

The mechanisms for the male predominance of COVID-19 severity are not known, but it is notable that allergic lung responses to RSV have increased severity in male mice by a thymic stromal lymphopoietin (TSLP)-dependent mechanism, and eosinophil-associated diseases such as eosinophilic esophagitis and hypereosinophilic diseases have a predilection for males. Taken together, although the current data are limited, there is little indication that eosinophils have a protective or exacerbating role during SARS-CoV-2 infection. Eosinopenia, however, may serve as a prognostic indicator for more severe COVID.

VACCINE-INDUCED IMMUNOPATHOLOGY LINKED TO CORONAVIRUSES

Following the outbreak of the SARS epidemic in late 2002, investigators raced to develop candidate SARS-CoV-1 vaccines. Diverse strategies were tested, including the use of attenuated or inactivated whole CoV particles, DNA-based vaccines, recombinant viral particles, and recombinant subunit vaccines. Sera from patients convalescing from SARS revealed robust antibody titers against the spike protein (S protein) and the nucleocapsid protein. Vaccine candidates that induced neutralizing antibodies targeting the S protein demonstrated efficacy in blocking viral replication, a concept later confirmed by passive antibody transfer studies. Unfortunately, anti–SARS vaccine–associated pathology emerged in early ferret (hepatitis and pulmonary eosinophilia), cynomolgus monkey (Th2-type immunopathology with eosinophilia), and mouse (pulmonary eosinophilia) studies. SARS-CoV-1–driven, eosinophil-associated Th2 immunopathogenesis also occurred with refection (green monkey model), suggesting that immune enhancement of CoV-associated disease may be relevant in future outbreaks of heterologous CoVs. Eosinophil-associated disease enhancement following exposure after vaccination is unfortunately not a new phenomenon. Historical reports from the 1960s link administration of a candidate formalin-inactivated RSV vaccine to severe, eosinophil-associated pulmonary disease following natural infection. This severe eosinophilic pulmonary disease hospitalized most study participants and led to at least 2 deaths. Memories of such disease enhancement postvaccination strongly influenced subsequent RSV F protein subunit vaccine development and trial design. The development of a safe and efficacious SARS-CoV-2 vaccine will require the development of vaccine candidates that take into account the risk of similar vaccine-associated immunopathology.

In the decade following these early observations, a series of mouse studies (see Table I) evaluated the factors driving the observed Th2-skewed vaccine immunopathology. Two independent studies using recombinant viral particles (Venezuelan equine encephalitis virus or vaccinia) used isolated SARS structural proteins to investigate the source of immunopathology. Nucleocapsid protein vaccination was implicated as a major driver of vaccine-associated pulmonary eosinophilia, although passive transfer of anti–nucleocapsid protein antibody was not sufficient to drive enhanced Th2 disease, suggesting a possible role for anti–nucleocapsid protein–specific T cells. Th2-mediated disease enhancement was also linked to age, as vaccination of aged mice (>12 months old) with double-inactivated SARS-CoV-1 led to increased morbidity/mortality and accentuated eosinophilic pulmonary disease. Follow-up studies comparing vaccination strategies, vaccine preparations (whole virus/virus-like particles vs subunits vs subunit fragments), boosting strategies and timing, and the inclusion of alum versus other adjuvants (TLR agonists) have yielded variable results. In early studies, chimeric recombinant virus–like particle vaccines displaying only the SARS S protein did not induce eosinophilia. In contrast, isolated S protein subunit vaccines (Spike[S]) appeared capable of Th2 immunopotentiation. S protein–derived fragments containing just the receptor-binding domain have also been proposed as vaccine antigens, but these vaccine formulations have required more aggressive use of adjuvants and more boosters (3–4 times more) than other approaches. Investigations into the Th2 immunopotentiation capacity of these compounds have been limited but reassuring, with 1 study showing no evidence of pulmonary eosinophilia in postchallenge animals and a follow-up study showing balanced Th1/Th2 cytokine induction following vaccination. Some investigators have implicated the inclusion of the Th2-skewing adjuvant alum in causing the immunopotentiation, and subsequent studies have shown that the inclusion of Th1-skewing adjuvants with both whole virus and subunit vaccine candidates has attenuated or blocked the development of pulmonary eosinophilia with SARS-CoV-1 challenge. Alternatively, contaminating exogenous proteins from serum-containing media (ie, BSA) in vaccine preparation or viral stocks may explain the observed Th2 skewing in certain experiments; however, the absence of eosinophilic infiltrates in mock-vaccinated control animals makes this possibility less likely. Overall, the SARS-CoV-1 vaccination literature documents recurrent, postvaccination disease enhancement in diverse vaccine preparations and across multiple animal models; however, this side effect declines with the use of more tightly defined antigens (S protein receptor-binding domain peptide) and the use of Th1-skewing adjuvants.
Conclusions

There are emerging eosinophil-related considerations concerning COVID-19 (Table II). Although current data are limited, there is little supportive evidence that patients with eosinophil-associated diseases will have an altered course of COVID-19, provided that they are not immunosuppressed from concurrent medications or by their primary disease process. Likewise, though preclinical studies have provided compelling experimental evidence that eosinophils have potential antiviral activity, there is no evidence that patients with eosinopenia induced by the recently approved antieosinophil therapeutics have increased susceptibility to viruses. Whether the acquired eosinopenia associated with COVID-19 is directly contributing to the disease course has not yet been determined, but it is notable that pulmonary eosinophilia is not part of the lung pathology so far attributed to SARS-CoV-2. It will be important however to assess the presence of eosinophils and the deposition of their granule products in the lung of a large cohort of patients with COVID-19, to control for exposure to glucocorticoids, and to determine the role of eosinophils in the COVID-19 lung

Table II. Eosinophil responses related to COVID-19

| Issue                                                                 | Likely significance                                                                                                                                                                                                 |
|----------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Atopy-related eosinophilia                                          | Atopy does not appear to have an exacerbating role in COVID-19                                                                                                                                                         |
| Eosinophil antiviral activity                                       | The antiviral activity of eosinophils is unlikely involved in COVID-19 because the antiviral activity of eosinophils has not yet been observed in humans                                                              |
| Biological drug–induced eosinopenia                                 | There are no data to date substantiating any risk for infections following depletion of eosinophils                                                                                                                    |
| COVID-19–associated eosinopenia                                      | The eosinopenia associated with COVID-19 is likely a secondary phenomenon and not directly contributing to the disease course                                                                                           |
| Lung eosinophilia associated with immunopotentiation by SARS vaccines| Vaccine candidates must demonstrate the absence of eosinophil-associated disease enhancement before widespread deployment                                                                                              |

FIG 1. SARS-CoV immunity. The structural proteins of the SARS-CoV viral particle are shown and putative T\textsubscript{H}1- vs T\textsubscript{H}2-mediated immune responses detailed. The Spike (S) glycoprotein mediates binding of the virus to the angiotensin-converting enzyme-2 protein and subsequent fusion/entry into host cells. Sera from convalescing patients have revealed that anti–nucleocapsid protein and anti–S protein antibodies predominate the humoral immune response to SARS-CoV-1 but that only anti–S protein antibodies (especially those targeting the receptor-binding domain region) are neutralizing and protective. Beneficial antiviral responses appear to be linked to T\textsubscript{H}1-skewed immunity, whereas T\textsubscript{H}2 immunopotentiation in multiple animal model systems is associated with vaccination-enhanced disease, leading to pulmonary eosinophilia. To date, these potentially adverse consequences have been observed only in animal model systems following virus challenge with certain vaccine formulations (see Table I). Various SARS-CoV-2 vaccine candidates are currently under development (see box), which should be scrutinized for safety before widespread deployment. CTL, Cytotoxic T lymphocyte; ssRNA, single-stranded RNA.
pathology. Finally, and likely most importantly, there is considerable concern about whether SARS-CoV-2 exposure postvaccination would cause eosinophil-associated lung pathology through immunopotentiation (see Fig 1). Although these concerns mainly have been derived from murine studies using vaccine candidates from the original SARS-CoV-1 virus, similar responses have also been seen in other species (eg, ferrets and monkey studies); it is also notable that SARS-CoV-1 and SARS-CoV-2 share more than 80% identity. Although the ongoing COVID-19 outbreak places new emphasis on the critical need for an effective SARS-CoV-2 vaccine, safety must be a central focus for any vaccine designed for general use. Current clinical reports show that most (up to 81%) patients with COVID-19 have mild disease, and therefore, trials of vaccine candidates must rigorously demonstrate the absence of eosinophil-associated disease enhancement before widespread deployment.

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