

Lung eosinophils—A novel “virus sink” that is defective in asthma?

Eosinophils represent one of the most studied cells in the development and pathophysiology of various immune-mediated disorders and conditions. Moreover, they serve as important biomarkers (diagnostic, therapy-driving, prognostic) in daily allergy praxis and can be affected by several therapeutic interventions.¹ Eosinophils differentiate from a pluripotent progenitor under the influence of several cytokines and growth factors. Amongst these, interleukin-5 (IL-5) seems to be critical for eosinophil differentiation and maturation in the bone marrow. After reaching maturity, eosinophils enter the circulation, and in response to stimuli such as eotaxins, they migrate into the tissues.

While eosinophils are central to the development of various pathologies, they also have many physiological and immunoregulatory functions, which are sometimes overlooked.^{2,3} Several such physiological functions have been described recently. These include roles of eosinophils in adipose tissue homeostasis and glucose metabolism control (through eosinophil-derived IL-4, macrophage polarization and generation of insulin sensitizing mediators) and in the regulation of intestinal mucosal immunity (production of IgA, mucus production, modulation of mucosal microbiome).^{4,5} A particularly interesting and surprising finding is the presence of homeostatic tissue-resident eosinophils (rEos) in the lung parenchyma.⁶ rEos constitute a unique and distinct population, which, in contrast to classical inflammatory eosinophils (iEos), have key regulatory and immunosuppressive functions. Lung rEos, which differ from iEos in number, localization and morphological, phenotypic and transcriptomic properties, remain unchanged during allergen challenge and airway inflammation.⁴ This suggests that bronchial asthma and other eosinophil-mediated disorders could be the consequence of an imbalance between iEos and rEos rather than the simple expansion of iEos. Furthermore, rEos which express the IL-5 receptor and can respond to IL-5 in vitro are not dependent on IL-5 for their presence in the lungs or blood and do not seem to be altered by anti-IL-5-targeted biological therapy, a property that would seem important for the safety profile of current and future eosinophil-based therapies.^{5,6}

Despite the fact that eosinophils contribute to the asthma pathology and airway remodelling through several mechanisms (eg, by production of specific granular substances or reactive oxygen species), several studies suggested their potentially protective roles in asthma, especially during virus infections and exacerbations. Some eosinophil granular proteins (eg, eosinophil-derived neurotoxin, eosinophil cationic protein) have antiviral activities against single-stranded RNA viruses such as respiratory syncytial virus.⁷ Another

potential antiviral mechanism is the production of nitric oxide by eosinophils in response to activation of Toll-like receptor 7, the expression of which is increased by IFN γ .⁸ Furthermore, virus- or viral peptide-exposed eosinophils can induce CD8⁺ T cell proliferation and activation, thus promoting cellular immunity against viruses.⁹ Several animal models demonstrate that eosinophils can support virus clearance, even in lethal virus infection, and limit the virus-induced lung injury.^{10,11} However, the antiviral capacity of eosinophils differs between different sensitization models; sensitization with ovalbumin does not elicit antiviral responses to pneumonia virus of mice (PVM) in eosinophils, whereas sensitization with *Aspergillus fumigatus* does and fully protects mice from lethal PVM infection.¹² Given that antiviral eosinophil responses are not observed in all circumstances, it needs to be considered whether their antiviral capacity may depend more on the quality and strength of activation than on the numbers of activated eosinophils.

In this issue of Allergy journal, Sabogal et al (2019) report another novel and important property of eosinophils, highlighting their likely role in the antiviral defence of the lung. During virus-induced exacerbations of asthma, eosinophils accumulate in the airways. Whether this is a direct result of the antiviral response or a compensatory mechanism for defective protective properties of eosinophils still remains unclear. Several mediators from eosinophils (eg, eosinophil-derived neurotoxin) display antiviral effects.¹³ The previous studies by the same group of authors showed that anti-IL-5-mediated depletion of eosinophils led to enhanced influenza virus A (IVA) load in house dust mite-sensitized mice¹⁴ or rhinovirus-16 (RV-16) load¹⁵ in patients with asthma.

In the present study, eosinophilia in IL-5 transgenic mice was associated with faster recovery after infection with a nonlethal dose of IVA. The majority of airway eosinophils took up labelled IVA and became activated. Similarly, eosinophils from healthy donors were able to effectively bind and inactivate respiratory syncytial virus and IVA particles, becoming activated in the process. These observations suggest that eosinophils can act as a “virus sink.” In contrast, eosinophils from patients with severe asthma displayed a reduced virus-binding capacity. This was also the case in mild to moderate asthma without inhaled corticosteroid (ICS) treatment, but not in ICS-treated patients, whose eosinophils had a virus-binding capacity comparable to healthy donors. These findings raise the question whether preactivated eosinophils have a diminished antiviral capacity. Interestingly, pretreatment with the anti-IL-5 antibody mepolizumab inhibited eosinophil activation (CD69 expression) following RV-16 challenge. In

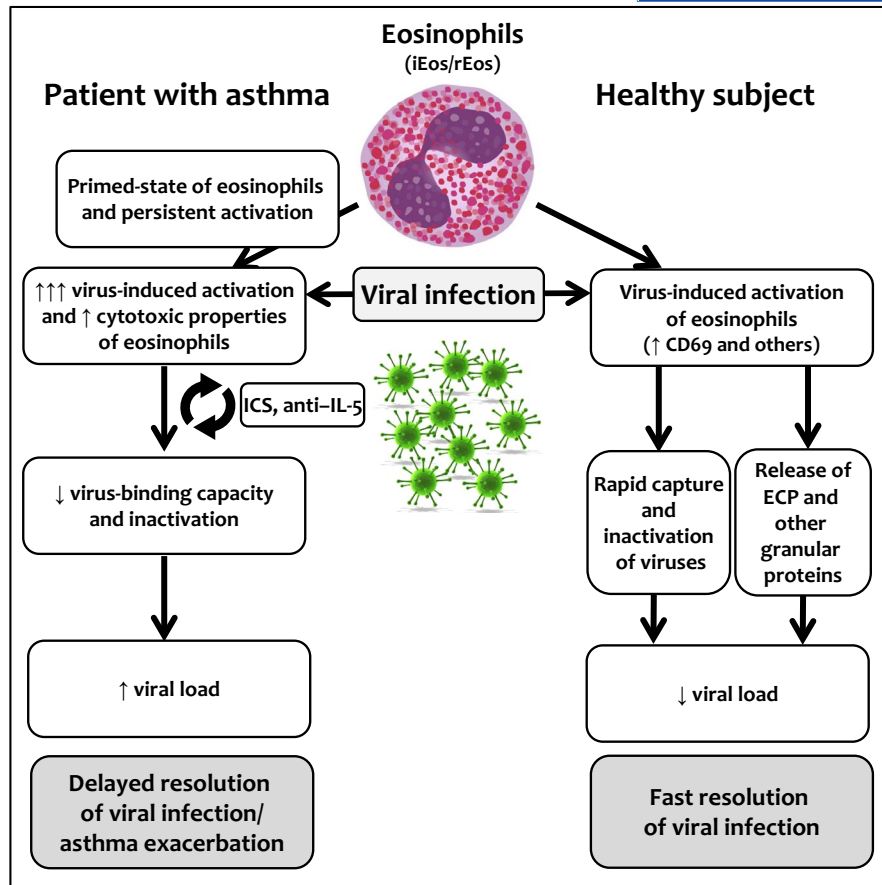


FIGURE 1 Antiviral activity of eosinophils in asthma and health. In healthy subjects, viral infection activates eosinophils resulting in increases of various surface activation markers (eg, CD69) and the release of eosinophil cationic protein and other granular proteins. Furthermore, activated eosinophils rapidly capture and inactivate virus particles, thus contributing to the control of viral load and swift resolution of infection. This property of eosinophils probably represents an important antiviral immune defence mechanism. In asthmatics, eosinophils are in primed state and continuously activated. Upon viral infections, they display increased cytotoxic properties. Due to pre-existing activation, eosinophils in asthma have a reduced capacity to bind and inactivate virus. This probably allows a higher viral load to develop and contributes to virus-induced asthma exacerbations. This antiviral insufficiency of eosinophils in asthma can potentially be reversed by inhaled corticosteroids and anti-IL-5 pathway-targeted treatments. The relative contribution of iEos and/or rEos to the antiviral response is not known and has to be established. Abbreviations: anti-IL-5, anti-interleukin-5 pathway-targeted treatments; ECP, eosinophil cationic protein; ICS, inhaled corticosteroids; iEos, inflammatory eosinophils; rEos, regulatory (homeostatic) eosinophils

conclusion, the authors provide compelling evidence that eosinophils can activate beneficial intracellular antiviral mechanisms, limiting viral load and contributing to disease control, which may be diminished in asthma (Figure 1). The exact nature of such antiviral mechanisms in eosinophils remains to be elucidated. A potential deficiency in antiviral capacity in preactivated eosinophils raises the possibility that future asthma treatments aimed at reducing eosinophil activation rather than eosinophil elimination may be beneficial.

In conclusion, in the next few years significant advances in our understanding of physiological and pathophysiological roles of eosinophils are to be expected. These are likely to change our current views of eosinophil-associated disorders. The newly described paradigm of an imbalance between homeostatic and inflammatory eosinophils already provides new perspectives on the pathogenesis of bronchial asthma, and the role of homeostatic rEos in viral infections and their clearance needs to be clarified. Moreover, protective functions of eosinophils (eg, antiviral effects) may be harnessed by future

asthma therapies, potentially providing effective interventions to prevent and treat asthma exacerbations.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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