

A survivor: The eosinophil as a regulator in asthma

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Ah, the eosinophil! Since its description by Ehrlich in 1879, it has remained an enigmatic cell blamed for all kinds of havoc.¹ Because these cells have the ability to release potent granular proteins, cytokines, enzymes, and growth factors, they are often considered proinflammatory. Indeed, when it comes to parasitic infections, eosinophils or their products are needed to effectively clear helminth infections.¹ Eosinophils have also been implicated in antibacterial and antiviral immunity.^{2,3} However, the role we most often ascribe to these cells is in chronic inflammatory diseases, such as asthma, eosinophilic gastrointestinal disease, and idiopathic hypereosinophilic syndrome. The large numbers of eosinophils found in local tissues in these disease states has led to the eosinophil being linked to tissue damage and remodeling.¹ Indeed, mouse strains that are deficient in eosinophils (Δ dblGATA and PHIL mice) do not adequately develop airway remodeling in asthma models.⁴ However, in human asthma therapeutic trials, the reduction in eosinophil numbers has not had the overwhelming success many had predicted.⁵ As a result, there remains significant debate over whether eosinophils actually cause disease or are simply markers of other inflammatory stimuli.

The hypothesis that eosinophils are inflammatory generally rests on the idea of these cells working on their own. Obviously, this is not what really happens in the inflammatory milieu. In fact, it has been shown that eosinophils actually interact with both innate and adaptive immune cells and can influence subsequent immune responses.⁴ These studies have confirmed the effector functions of eosinophils but have also ascribed new abilities, such as immunomodulation, to these cells. An example of this is the ability of eosinophils to actually aid the longevity of *Trichinella spiralis* larvae, despite the long-held view of eosinophils being potent antiparasitic cells.⁶ Clearly, there is more to the eosinophil than its role as a simple proinflammatory cell type.

In this issue of the *Journal*, Takeda et al⁷ challenge the traditional view of the “bad” eosinophil in airway remodeling.

These investigators observed that mice sensitized to ovalbumin have airway inflammation after 7 ovalbumin challenges. However, if the mice receive an additional 4 ovalbumin challenges, the inflammation resolves. This suggests that some component of the earlier immune response was important in driving the subsequent regulatory/resolution phase of the model. Somewhat surprisingly, these investigators found that mice deficient in eosinophils did not show resolution of airway inflammation with additional ovalbumin challenges.

In fact, using bone marrow transfers, the authors were able to demonstrate that the resolution seen with the extra allergen challenges required IL-10–producing hematopoietic cells. Bringing this back to the eosinophil, they found that airway eosinophils produced IL-10 with extra allergen challenges. Together, these results suggest that the eosinophil might be the IL-10–producing cell needed for resolution of airway inflammation in this model.

Although this study demonstrated that eosinophils can produce IL-10 (something that has been known since the 1990s⁸), it is important to note that no evidence was found that eosinophils were the only IL-10–producing cell or that the eosinophil-produced IL-10 was necessary for resolution of the inflammatory response. One alternative explanation would be that the eosinophil is upstream of regulatory T cells, whose IL-10 is needed to resolve the inflammation. Whether the eosinophil needs to produce IL-10 to initiate such a response was also not examined. It is important to note that determining the location/role of eosinophil-produced IL-10 in this resolution phase would require quite complex studies using mice in which the various IL-10–producing hematopoietic cells could be depleted, and these were beyond the scope of the current investigation.

This ever-morphing role of the eosinophil suggests that there might be significant functional heterogeneity in these cells. Because Takeda et al⁷ transferred bone marrow cells into PHIL mice before any ovalbumin sensitization or challenge, it remains unknown whether the IL-10–producing eosinophils represent a functional change in eosinophils originally recruited to the local tissue. Alternatively, the repeated ovalbumin exposure might have led to development in the marrow and subsequent airway recruitment of a new regulatory subset of eosinophils. This alternative explanation would be similar to another granulocyte, the neutrophil, for which functionally diverse subsets have been reported in both mice and human subjects.^{9,10} It remains to be seen whether the eosinophil also exists in multiple subsets (as well as how plastic these subsets are), and the current study⁷ provides food for thought in this respect.

Although the study by Takeda et al⁷ adds to the complexity of the eosinophil lineage, it also raises some additional questions. Chief among these is whether a similar regulatory role exists for human eosinophils. If this were the case, it could suggest that therapies targeted against all eosinophils might lead to dysregulated immune responses. Thus far, human anti-IL-5 studies have consistently shown profound suppression of

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FIG 1. The eosinophil grave. The death of the eosinophil (“Sir Eos”) has been oft proclaimed, but once again this cell type demonstrates that it is more than just a bag of cytokines and enzymes. Picture taken by M. Grayson at LEGOLAND, Carlsbad, California.

eosinophil hematopoiesis and blood eosinophilia, without any evidence of uncontrolled inflammation.¹ The success of anti-IL-5 treatment for asthmatic patients with persistent airways eosinophilia⁵ also argues against a singular critical regulatory role for the eosinophil. Another issue with the current report is the role of repeat allergen challenges. It is unclear why 7 challenges would be insufficient to drive the regulatory functions of eosinophils but the additional 4 would do so. Furthermore, what happens with additional allergen exposures?

Is the regulatory eosinophil really just a limited phenomenon because of the timing of allergen exposure? These questions await further explorations, as do studies documenting the presence or absence of these IL-10-producing regulatory eosinophils in asthmatic patients.

Like the phoenix, the eosinophil keeps surprising us with its new incarnations in the immune response (Fig 1). Clearly, we are still learning new and important information about this colorful cell. The study by Takeda et al⁷ falls into this category, providing a novel perspective on eosinophil functions and suggesting that there might be multiple facets (and perhaps subtypes) to this otherwise inflammatory granulocyte. We look forward to future studies further outlining the multiple potential roles of these cells in human disease.

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