

The origins of basophils and eosinophils in allergic inflammation

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The bone marrow actively participates in the production of IgE-positive inflammatory cells (eosinophils, basophils, and mast cells), which are typically recruited to tissues in atopic individuals. Understanding the signaling between the tissue and the bone marrow at the molecular level may well open up new avenues of therapy for allergic inflammation. (J Allergy Clin Immunol 1998;102:S74-6.)

"Moses received the Law from Sinai, and passed it on to Joshua, who passed it on to the Elders, who then passed it on to the members of the Great Assembly." —

Tractate Avot, from the Mishna

This article has to do with origins and passages: the origins of allergic inflammation and Dr Dolovich's role in the chain of continuity and teachings that have contributed to the passage of the "laws" of allergy. Just as it could not have been anticipated that a young, first-generation Canadian from northern Manitoba, Dr Jerry Dolovich, would become a distinguished clinician and scientist, delving into allergic mechanisms, so too has the nonintuitive notion only recently become apparent that basophil and eosinophil progenitors in the bone marrow have an impact on the development of the allergic tissue inflammation.

BASOPHIL/EOSINOPHIL PROGENITORS IN RHINITIS AND ASTHMA

A common precursor for eosinophils and basophils in the presence of permissive growth factors (eg, IL-3, IL-5, and GM-CSF) can be shown to give rise in vitro to colonies of cells in methylcellulose assay systems.¹⁻⁵ Enumeration of such basophil/eosinophil progenitors in various allergic reactions, principally allergic rhinitis, formed the subject of one of the earliest collaborations between myself and Dr Dolovich. With the help of Drs Hirokuni Otsuka and Dean Befus, we showed that there was an increase in these progenitors in the blood of patients with allergic rhinitis, and that these fluctuated in accordance with the symptoms and signs of this condition (Fig 1).⁵⁻⁸ A concept that arose from the inverse relationship shown between the numbers of progenitors in the blood and mature cells in the tissue was that there existed

a dynamic process of progenitor release into circulation and traffic into tissues with differentiation in situ in a wide variety of eosinophil- and basophil-rich allergic reactions.⁹ Similar findings have been shown for mast cells in various mast cell-rich tissue reactions to nematodes. Progenitors can be isolated from the mesenteric lymph node adjacent to the gastrointestinal mucosa where mast cell hyperplasia is about to take place,^{5,10,11} and factors such as IL-3 are present within that microenvironment to aid the differentiation of mast cells.^{2,5,12} More recently, the blood levels of these progenitors have been shown to decrease as they increase in the intestine.¹³

On the basis of this concept, a number of studies in human allergic asthmatic subjects have been undertaken, together with Dr Dolovich and a number of colleagues at McMaster University in the Asthma Research Group. Peter Gibson, one of the other contributors to this Festschrift and a former postdoctoral fellow working with Drs Dolovich and Hargreave and myself, showed that one of the earliest changes in the blood of asthmatic subjects about to have a mild exacerbation resulting from controlled withdrawal of inhaled corticosteroids¹⁴ was a rise in peripheral blood basophil/eosinophil progenitors. When the steroid treatment was increased in this study and another in which the asthma was uncontrolled, the progenitors fell.^{15,16} This implied that the steroids had a suppressive effect on, presumably, a tissue-derived mechanism that could elicit progenitors into the blood, possibly from the bone marrow initially. Indeed, in allergic asthmatic subjects challenged with allergen (in studies done in collaboration also with Dr Paul O'Byrne), a specific increase in eosinophil/basophil, but not neutrophil/macrophage, progenitors would be elicited within 24 hours in the blood after allergen challenge¹⁷; this rise was seen in relation to the development of a late-phase response to a given allergen and not in individuals in whom only an early response to that same allergen develops (Fig 2).

More recent studies in a canine model of *Ascaris suum*-induced bronchial hyperresponsiveness, which is predominantly neutrophilic, have revealed that myeloid progenitors are elicitable from the bone marrow after allergen challenge to the airway.^{18,19} This allergen-induced increase in bone marrow progenitors destined to mature into the cells characterizing the inflammatory reaction in the lung could be abrogated by pretreatment with inhaled corticosteroids.^{19,20} Furthermore, a serum hemopoietic factor could be shown to be released into circulation after allergen challenge, within minutes to hours,¹⁹ and this too was suppressed by inhaled corticosteroids.^{19,20} Thus the concept that the bone marrow was

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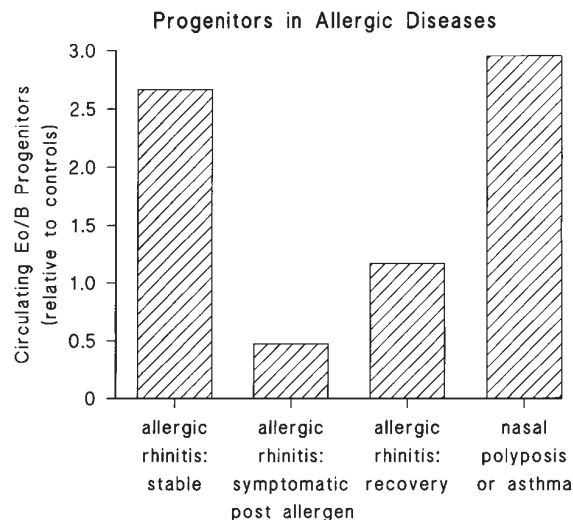


FIG 1. There are varying levels of circulating eosinophil/basophil (Eo/B) progenitors in allergic disorders. In stable atopic disease a large number of circulating progenitors is evident; levels fall during seasonal allergen exposure and recover afterwards. Nasal polyposis and asthma are characterized by chronic elevations of progenitors. (Adapted from Denburg JA. In: Holgate ST, Church MK, editors. *Allergy*. Copyright 1993, Gower Medical Publishing. Reprinted 1995 by Mosby.)

the origin and site of the development of progenitors feeding the accumulation of cells in the inflamed allergic airways was partially substantiated.

Recent studies have also focused on several new assay systems for identifying progenitors in the marrow and blood, as well as on direct studies of human bone marrow in allergic asthmatic subjects. The hemopoietic progenitor antigen, CD34, has been used to quantify and follow the fate of progenitors in the blood and marrow of patients with allergic disorders of the airways. A high ambient level of progenitors bearing CD34/CD45 could be shown in the blood and marrow of patients with atopy, relating well to levels of serum IgE.^{21,22} An IL-5-responsive colony-forming cell, giving rise to eosinophils and basophils, specifically increased in the marrow of atopic subjects.^{21,22} More interestingly, in recent studies in which allergen challenge was used to provoke airways inflammation and airway hyperresponsiveness, we have demonstrated a specific increase in CD34-positive cells bearing receptors for IL-3 and IL-5 in the bone marrow of asthmatic subjects, with a higher number and greater sensitivity of these cells to in vitro stimulation with IL-5 in the marrow of individuals who have late responses, but not isolated early responders.^{22,23} The nature of the signaling to the bone marrow after allergen challenge to the airways in human allergic asthmatic subjects that induces the expression of IL-5 receptors (ie, the earliest phenotype switch toward eosinophilic lineage) is still unknown.

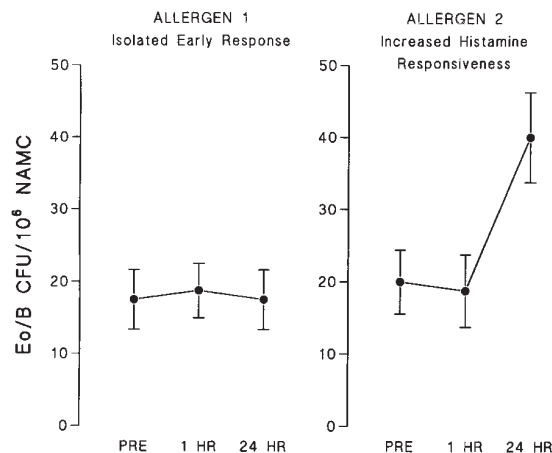


FIG 2. Eosinophil/basophil (Eo/B) progenitor levels (CFU) after allergen challenge: Specific rise associated with development of a late-phase response.

CONCLUSION

Thus, the origins of inflammatory cell progenitors in the bone marrow, which eventuate in mechanisms contributing to the ongoing inflammatory response in the airways, can be pinpointed and elaborated. The uncovering of this mechanism and its further study and understanding could not have been possible without the open-mindedness of Dr Jerry Dolovich, who continued to seek new ways of understanding allergic inflammation and incorporating new concepts into his world view until the day of his passing. The Asthma Research Group in Hamilton was brought together in large part by the cohesive force of Dr Dolovich and his ideas, and it will remain a prominent and rich environment in which to study allergic inflammation, in the footsteps of Dr Dolovich, for decades to come.

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