

# Bone Marrow Contribution to Eosinophilic Inflammation

Judah A Denburg<sup>+</sup>, Lorna Wood, Gail Gauvreau, Roma Sehmi,  
Mark D Inman, Paul M O'Byrne

Department of Medicine, McMaster University, 1200 Main Street West, Hamilton, Ontario, Canada L8N 3Z5

*Allergen-induced bone marrow responses are observable in human allergic asthmatics, involving specific increases in eosinophil-basophil progenitors (Eo/B-CFU), measured either by hemopoietic assays or by flow cytometric analyses of CD34-positive, IL-3R $\alpha$ -positive, and/or IL-5-responsive cell populations. The results are consistent with the upregulation of an IL-5-sensitive population of progenitors in allergen-induced late phase asthmatic responses. Studies in vitro on the phenotype of developing eosinophils and basophils suggest that the early acquisition of IL-5R $\alpha$ , as well as the capacity to produce cytokines such as GM-CSF and IL-5, are features of the differentiation process. These observations are consistent with findings in animal models, indicating that allergen-induced increases in bone marrow progenitor formation depend on hemopoietic factor(s) released post-allergen. The possibility that there is constitutive marrow upregulation of eosinophilopoiesis in allergic airways disease is also an area for future investigation.*

Key words: hemopoiesis - asthma - inflammation - IL-5 - eosinophils - basophils

The development of airway inflammation occurs in association with the upregulation of cytokines by several cell populations within airways tissues. This leads to recruitment of inflammatory cells via several complex and interacting mechanisms. Since some cytokines produced by the airways following allergen possess hemopoietic activity, we hypothesized that after release by the airway they may act on the bone marrow to increase inflammatory cell production.

## PERIPHERAL BLOOD EOSINOPHIL-BASOPHIL PROGENITORS

Atopy is associated with higher numbers of eosinophil-basophil progenitors, as measured by colony assays of human blood: in atopics there are greater numbers of eosinophil-basophil colony-forming units (Eo/B-CFU) (Denburg et al. 1985, Otsuka et al. 1986) and CD34<sup>+</sup> cells (Sehmi et al. 1996) than in non-atopic controls. Likewise, during an acute exacerbation of asthma, there is a significant rise in blood Eo/B-CFU, which falls upon clinical resolution of the exacerbation induced by inhaled corticosteroids (Gibson et al. 1990). Patients with allergic rhinitis show seasonal fluctuations in blood Eo/B-CFU (Otsuka et al. 1986, Linden et al. 1994), and subjects with late asthmatic responses following allergen inhalation demon-

strate significant increases in circulating Eo/B-CFU and CD34<sup>+</sup> cells at 24 hr (Gibson et al. 1991, Sehmi et al. 1997).

## BONE MARROW EOSINOPHIL-BASOPHIL PROGENITORS

Canine bone marrow myeloid progenitor cells (GM-CFU) increase 24 hr after inhalation of *Ascaris suum* antigen (Woolley et al. 1994), especially when it is associated with the development of hyperresponsiveness or airways inflammation (Inman et al. 1996). With regard to human bone marrow progenitors, the phenotype of marrow CD34<sup>+</sup> progenitor cells found in atopics (Sehmi et al. 1996) was further explored using allergen inhalation in subjects with late asthmatic responses, airway hyperresponsiveness and airway eosinophilia. This challenge provokes significant increases in marrow Eo/B-CFU (Wood et al. 1996), and, in particular, an increase in IL-3R $\alpha$ (+) or IL-5R $\alpha$ (+) CD34<sup>+</sup> cells. These observations are in agreement with our observations of the upregulation of an IL-5-sensitive population of progenitors in allergen-induced late phase responses (Sehmi et al. 1996).

## PHENOTYPE OF EOSINOPHIL-BASOPHIL PROGENITORS

Studies on the phenotype of eosinophil-basophil progenitors indicate an orderly sequence of acquisition of markers. Pluripotent progenitors, bearing CD34 alone, are found in bone marrow and cord blood followed by Fc $\epsilon$ RI acquisition (Rottem et al. 1992, 1994), as well as both high- and low-affinity Fc $\epsilon$ Rs on HL-60 cells which can

<sup>+</sup>Corresponding author. Fax: +905-521.4971. E-mail: denburg@fhs.mcmaster.ca  
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be induced to differentiate to basophils-eosinophils (Hutt-Taylor et al. 1988). Surface phenotype changes include the upregulation of CD23 and CD35, concomitant with downregulation of CD15 (Wong et al. 1996). Hybrid basophil-eosinophils found in cord blood cultures (Tanno et al. 1987) or *in vitro* by density gradient separation (Boyce et al. 1995, 1996) may represent transitional forms of Fc<sub>ε</sub>RI- and Fc<sub>ε</sub>RII-bearing granulocytes, explaining possible discrepancies among several studies regarding Fc<sub>ε</sub>R expression by eosinophils (Capron et al. 1995). Recently we have found that maturing eosinophils-basophils taken from atopic asthmatic subjects produce more GM-CSF and possibly IL-5 after allergen inhalation challenge *in vivo*. These observations support the concept of upregulation of an activated and differentiating eosinophil phenotype in allergic inflammation (Gauvreau et al. 1997).

#### BONE MARROW CONTRIBUTION TO ALLERGY AND ASTHMA

We have proposed the hypothesis that the origin of atopic disease may not be only in the airway but also reside in lineage skewing in the bone marrow (Denburg et al. 1996). Evidence obtained from patients undergoing bone marrow transplant suggests that an important determinant of atopic and asthmatic disease may be transferrable (Agosti et al. 1988), raising the possibility that part of the predisposition toward allergic inflammation may be due to a propensity of progenitors in atopic bone marrow to differentiate preferentially as eosinophils/basophils. Indeed, in mice with a genetic predisposition to airway hyperresponsiveness, a significant component of airway hyperresponsiveness is transferrable by bone marrow transplantation (De Sanctis et al. 1996).

#### HEMOPOIETIC CYTOKINES AS THERAPEUTIC TARGETS IN ASTHMA/ALLERGY

Since inhaled corticosteroids can reduce circulating eosinophils, basophils and Eo/B-CFU both *in vitro* (Denburg et al. 1994) and *in vivo* (Gibson et al. 1990), as well as prevent increases in canine bone marrow GM-CFU following allergen challenge (Woolley et al. 1994), there may be a systemic effect of inhaled steroids on the marrow that is important in reducing airway inflammation. This would imply that hemopoietic mechanisms are involved in the pathogenesis of chronic airways inflammation, and that blocking certain eosinophilopoietic signals such as IL-3 or IL-5 might be therapeutically useful in asthma or other eosinophilic airways inflammatory reactions. Treatment with an antibody to IL-5 can indeed block allergen-induced eosinophilia and airway

hyperresponsiveness for prolonged periods (Kung et al. 1995, Mauser et al. 1995) depending on the dose of antibody given. A more complete understanding of the role of the bone marrow may provide the basis for the development of novel therapeutic interventions in allergy and asthma.

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