From bone marrow to airways in allergen-induced airway inflammation

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Allergen-induced traffic of bone marrow eosinophils, neutrophils and lymphocytes to airways.
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Regulation of bone marrow and airway CD34+ eosinophils by IL-5
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Allergen stimulates bone marrow CD34+ cells to release IL-5 in vitro; a mechanism involved in eosinophilic inflammation?
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Human blood and bone marrow CD34+ cells produce IL-5; autocrine regulation of eosinophilopoiesis?
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From bone marrow to airways in allergen-induced airway inflammation
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The airway (AW) inflammation in asthma includes eosinophils, neutrophils and T-lymphocytes. The accumulation of inflammatory cells within the AW is considered to be a result of increased production of inflammatory cells within the bone marrow (BM), a release into the circulation and subsequent migration into the AW but so far there is limited evidence that BM cells have the capacity to migrate into the AW in allergen-induced AW inflammation. Eosinophils develop from CD34⁺ progenitor cells under the influence of IL-5, IL-3 and GM-CSF. Recent studies have shown increased numbers of these CD34⁺ progenitor cells in BM and AW of allergic subjects.

The aims of this thesis were to; A) evaluate whether BM-derived inflammatory cells have capacity to traffic into the AW in response to allergen exposure, B) determine the effects of allergen exposure and IL-5 in the AW and BM inflammatory response, including CD34⁺ cells and C) evaluate mechanisms involved in the regulation of BM eosinophilopoiesis. To assess this, we used mouse models of allergen-induced AW inflammation. Cells produced during the allergen exposure period were identified using a thymidine analogue, bromodeoxyuridine (BrdU). BM or peripheral blood (PB) derived-CD34⁺ cells from either mouse or human were stimulated in vitro to determine whether these cells can release eosinophilopoietic cytokines.

Adoptive transfer of BM inflammatory cells (BrdU⁺ cells) showed traffic of not only eosinophils but also of neutrophils and lymphocytes into the AW in response to an AW allergen exposure. Allergen exposure of sensitized wild type (C57BL/6) and mice overexpressing IL-5 specifically in their CD3 cells (NJ.1638) increased the number of BrdU⁺ eosinophils, neutrophils, lymphocytes and CD34⁺ cells in AW. Furthermore, it increased the relative number of eosinophils in BM. Overexpression of IL-5 further enhanced the AW and BM eosinophilic response.

Systemic treatment with an anti-IL-5 antibody (TRFK-5) in allergen-exposed mice reduced the relative number of BrdU⁺ and CD34⁺ eosinophils in the BM three days after the administration. In broncho-alveolar lavage fluid (BALf) the reduction was most clear five days after the administration.

Adoptive transfer of IL-5 overproducing CD3⁺ splenocytes to sensitized wild type mice caused enhanced relative number of BM eosinophils. Further investigations by transferring CD4⁺ and CD8⁺ T-lymphocyte subsets from either wild type or mice overexpressing IL-5 to immunodeficient mice (SCID-bg) suggested that the BM eosinophilia at least partly is regulated by CD8⁺ lymphocytes, although IL-5 enhances the response.

Allergen stimulation of mouse BM CD34⁺ cells caused release of IL-5, but not IL-3 and GM-CSF in vitro. However, un-specific stimulation induced release of all three cytokines. An IL-5Ra-antagonist (E12K) reduced the maturation of PB CD34⁺ cells to eosinophils in vitro.

In conclusion, this study argues that inflammatory cells that have been produced in the BM, and are released into the blood, traffic to the AW following airway allergen exposure. IL-5 plays a central role in allergen-induced AW inflammation and substantially contributes to the enhanced BM eosinophilopoiesis. The BM eosinophilopoiesis is at least partly regulated by CD8⁺lymphocytes although additional mechanisms may occur. One such possible mechanism could be that the CD34⁺ cells themselves respond to allergen exposure and thereby may act in an autocrine way, enhancing the eosinophilic response.

Keywords: bone marrow, allergic airway inflammation, CD34⁺cell, CD8⁺T-lymphocytes, eosinophils, eosinophilipoiesis, neutrophils, lymphocytes, IL-5, IL-3, GM-CSF, TRFK-5, IL-5Ra