Letter to Editor

How are Eosinophils Supplied from Bone Marrow to Eosinophil-Infiltrated Tissues, When Blood Eosinophilia is Not Observed? The Case of Acute Eosinophilic Pneumonia

Dear Editor,

Patients suffering from a variety of disorders with increased numbers of eosinophils in tissues may not exhibit a higher count of eosinophils in peripheral blood (PB).[1,2] This unexpected occurrence is always reported without presenting any explanation.[3,4] However, a growing body of scientific evidence provides us with information helpful to put forward a tentative proposal for interpreting this apparent paradox.

Acute eosinophilic pneumonia (AEP), a rare febrile illness leading to progressive respiratory failure, constitutes a typical illustration of such a clinical feature. It is usually characterized by a normal eosinophil count in PB while some of the highest infiltrations of the lung tissue by eosinophils and some of the largest increases in eosinophil percentages in the bronchoalveolar lavage fluid (from the normal <2% to >25% of the total cell count) are observed.[3,4] The specific recruitment of eosinophils into the damaged pulmonary tissue is dependent on a highly regulated process that can roughly be divided into two steps: (i) activation of bone marrow (BM) resulting in both the increased production of new eosinophils and their release into the circulation; (ii) accumulation of eosinophils within the respiratory tract, caused by a combination of their recruitment to the damaged sites in the lung and intratissual delay of apoptotic death: all processes are controlled by cytokines acting as modulators. These are small glycoproteins produced by cells of the immune system, which regulate immunity, inflammation, and hematopoiesis.[5] (cytokines such as interleukins, IL and chemokines; see below). All relevant eosinophilic modulators involved in these two molecular machineries and egressing from BM and recruited into the lungs, can be categorized with the denomination of only three cytokines that exhibit the most specific control of eosinophilic activities, both at baseline and during inflammatory responses: IL-5, eotaxin subfamily of chemokines (eotaxins), and granulocyte-colony-stimulating factor (G-CSF). In particular, IL-5 promotes the differentiation of immature eosinophils into mature eosinophils, assists their release from BM into PB, and delays their apoptotic death. Eotaxins recruit eosinophils and/or eosinophil progenitors (EPs; see below) into sites of inflammation. G-CSF plays a critical role in the proliferation and mobilization of progenitor cells from BM into PB. These observations show that the driving force of eosinophil accumulation in the alveolar space is mainly governed by: (i) the high concentration of IL-5 in the inflamed pulmonary spaces, its propagation via the bloodstream to BM, and its release into circulation of mature eosinophils with consequent blood eosinophilia; and (ii) the highly increased level of eotaxins within inflamed pulmonary tissues associated with recruitment of eosinophils by chemotaxis (a positive gradient of the chemoattractant eotaxins) to the site of inflammation. This scheme correctly describes blood and tissural eosinophilia when lungs are infected with a helminth that locally induces a robust IL-5 production [Figure 1a]. On the contrary, very low serum IL-5 levels are usually found in AEP patients[6] (possibly due to predisposing genetic factors at the lung tissue level[4]) with consequent absence of an abundant flow of eosinophils from BM to the inflamed lungs. How can then airway eosinophilia of AEP patients be explained? In what follows, a model capable to overcome this apparent paradox has been proposed.

Eosinophils are produced in BM from EPs capable of giving rise to a lineage that leads to mature eosinophils. Even under steady state conditions, EPs circulate in the bloodstream in very small numbers. However, an enforced egress of these immature cells can be enacted by a variety of systemic inciting factors such as G-CSF (generated in lungs in response to allergens)[7] — the most potent cytokine currently also available for the therapeutic mobilization of many progenitor lineages.

Recent studies have demonstrated[8-10] that inflammatory mediators, generated locally and translocated systemically during airways inflammation in AEP, promote the recruitment of EPs to the sites of pulmonary inflammation. Therefore, to rationalize the apparent lack of the mature eosinophil transfer from BM into the lungs of patients having AEP as trigger for the systemic inflammatory response, it is here proposed that a high number of EPs migrate from BM (stimulated by G-CSF) and enter

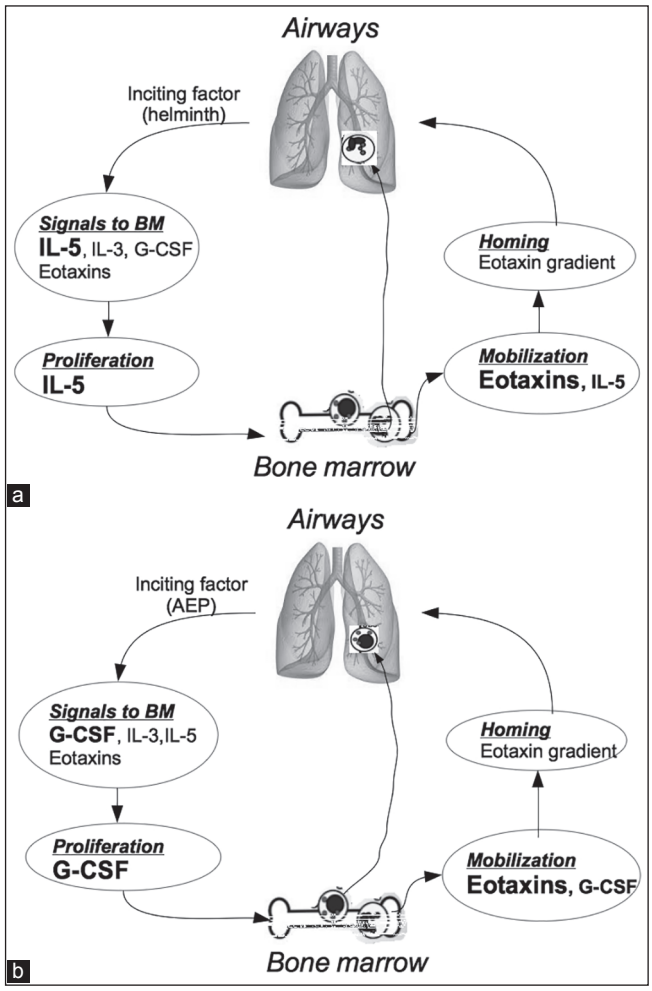

Figure 1: Communication between airways and bone marrow (BM) in response to lung inflammation (a) Parasitic stimuli in the airway induce mainly the release into the bloodstream of interleukin (IL)-5. (b) Tissue eosinophilia in patients with acute eosinophilic pneumonia (AEP) is chiefly governed by granulocyte colony-stimulated factor (G-CSF)

the lung tissues under the orchestrated control of eotaxins. Once within the tissue, the maturation of EPs is determined by locally produced cytokines.[8,9] Therefore, in this model based on the transfer of EPs (rather than mature eosinophils) from BM to the lungs, [Figure 1b] the transport of these granulocytes through PB occurs by a seemingly invisible modality because the immature progenitors may migrate undetected. In fact, for most patient samples, the available automated hematology analyzers display only a five-part differential leukocyte count (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), totally missing progenitor cells.

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