

Gastrointestinal eosinophils

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Eosinophils are widely accepted to be proinflammatory leukocytes that account for a small subset of circulating blood cells. While most eosinophils reside in the gastrointestinal tract under healthy states, we have recently started to elucidate the regulation and function of this population of eosinophils (Fig. 1). Under baseline (healthy) conditions, gastrointestinal eosinophils predominantly reside in the lamina propria in the stomach and intestine. Interestingly, eosinophils migrate to the gastrointestinal tract during embryonic development and their concentrations in perinatal mice are comparable to those in adults, indicating that eosinophil homing occurs independently of intestinal flora. The chemokine eotaxin, an eosinophil selective chemoattractant that is constitutively expressed throughout all segments of the gastrointestinal tract, is required for eosinophil homing to the lamina propria. During Th2 associated inflammatory conditions (e.g. interleukin (IL)-5 overexpression or oral allergen challenge), elevated levels of eosinophils occur in the lamina propria in an eotaxin-dependent manner. In addition, allergen challenge promotes eosinophil migration to the outer cortex and interfollicular

regions of Peyer's patches, and this process is critically regulated by IL-5 and less significantly by eotaxin, suggesting the involvement of other eosinophil chemokines in this lymphoid compartment. Furthermore, following mucosal allergen challenge, eosinophils under the regulation of IL-5 accumulate in the esophagus, an organ normally devoid of eosinophils at baseline. Preliminary investigations have shown that gastrointestinal eosinophils express the $\alpha 4 \beta 7$ integrin and that this molecule is responsible, in part, for eosinophil homing. Finally, recent analysis has shown that the gastrointestinal pathology induced during experimental gastrointestinal allergy models is largely dependent upon eosinophils. In summary, eosinophils are resident cells of the gastrointestinal immune system, their levels are increased by antigen exposure under Th2-associated conditions, and eotaxin and IL-5 differentially regulate their trafficking in a tissue specific manner. We propose that eosinophils are integral members of the gastrointestinal immune system and are likely to be important in innate, regulatory and inflammatory immune responses.

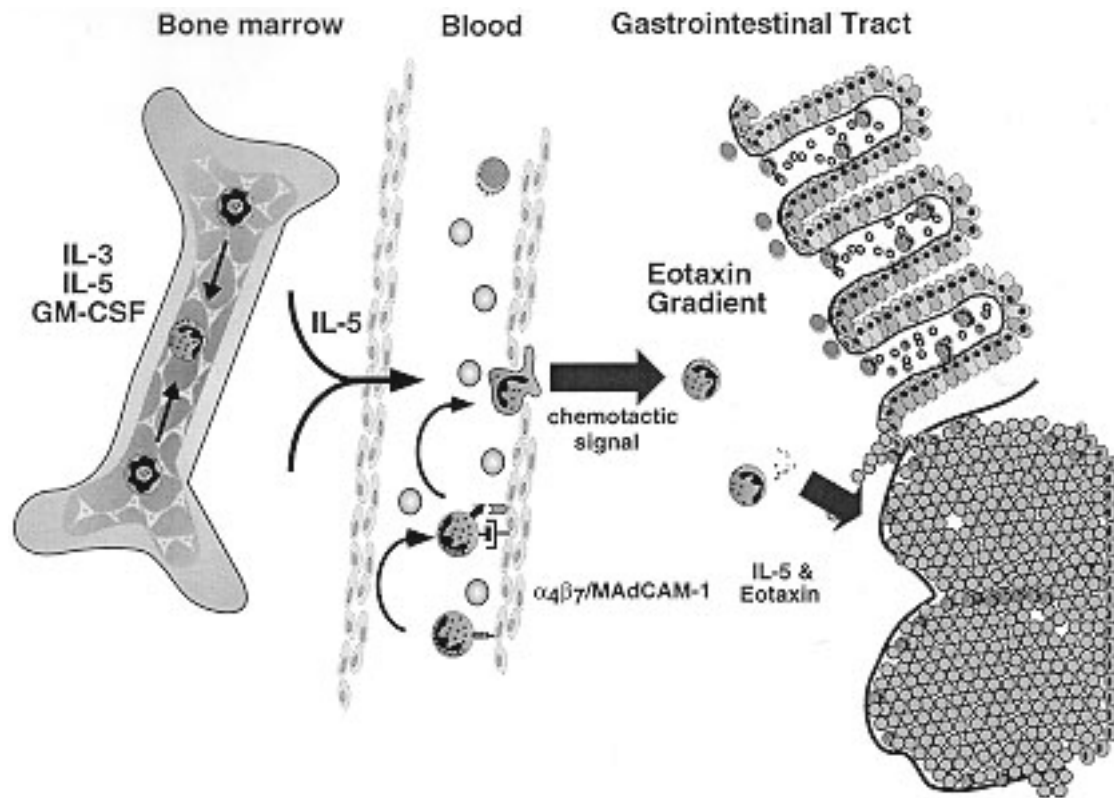


Figure 1. Schematic representation of eosinophil trafficking to the intestine. Eosinophils develop in the bone marrow where they differentiate from hematopoietic progenitor cells into mature eosinophils. Factors that control this process have not been fully defined; however, IL-3, IL-5, and GM-CSF are important in eosinophil expansion during conditions of hypereosinophilia. Eosinophil migration out of the bone marrow into the circulation is primarily regulated by IL-5. Circulating eosinophils subsequently interact with the endothelium by processes involving rolling, adhesion, and diapedesis. In the gastrointestinal tract, the adhesion $\alpha 4 \beta 7$ ligand on eosinophils interacts with the endothelial receptor mucosal vascular addressin MAdCAM-1. Eosinophils are mobilized into the lamina propria in response to a chemotactic gradient primarily established by the chemokine eotaxin liberated from mononuclear cells in the crypts. Additionally, eosinophils are mobilized into the interfollicular and paracortical regions of Peyer's patches. The chemotactic response is enhanced by IL-5, an important eosinophil cytokine for eosinophil priming and survival. Depending upon the chemokine concentration gradient, gastrointestinal eosinophils can also migrate into the villi, residing in proximity to lymphocytes and have the potential to degranulate, resulting in tissue damage.

References

1. ROTHENBERG ME. Eosinophilia. *N Engl J Med* 1998;**338**:1592–1600.
2. MATTHEWS AN, FRIEND DS, ZIMMERMANN N, et al. Eotaxin is required for the baseline level of tissue eosinophils. *Proc Natl Acad Sci USA* 1998;**95**:6273–6278 .
3. MISHRA A, HOGAN SP, LEE JJ, FOSTER PS, ROTHENBERG ME. Fundamental signals regulate eosinophil homing to the gastrointestinal tract. *J Clin Invest* 1999;**103**:1719–1727.
4. HOGAN SP, MISHRA A, BRANDT E, FOSTER PS, ROTHENBERG ME. A critical role for eotaxin in experimental oral antigen-induced eosinophilic gastroenteritis. *Proc Natl Acad Sci U S A* 2000;**97**:6681–6686.
5. MISHRA A, HOGAN SP, BRANDT EB, ROTHENBERG ME. Peyer's patch eosinophils: identification, characterization, and regulation by mucosal allergen exposure, interleukin-5, and eotaxin. *Blood* 2000;**96**:1538–1544.