

Pro-Con Symposium:
Are Basophils Important in Allergy?
Pros

Wednesday, 7 December 2011

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Outline

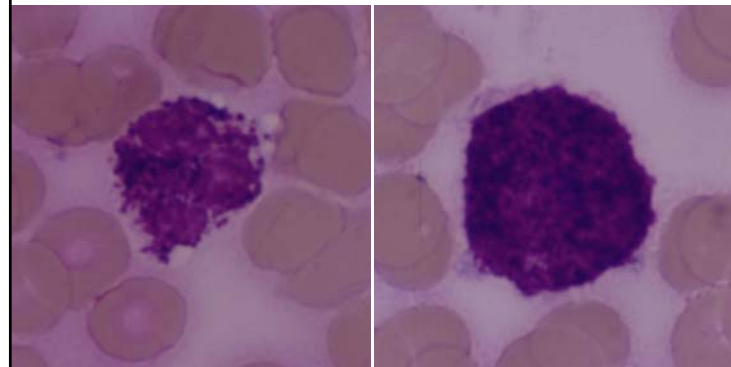
- Differences between human basophils and mast cells (they act complementary).
- Only basophils can produce IL-4, which induces Th2 cells from naïve T cells, in the primary immune response.
- Human basophils but not mast cells can release cysteinyl leukotrienes and histamine in the late phase asthmatic response.
- Murine basophils have a variety of unique roles in immunity and inflammation.

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Basophils and Mast Cells

They resemble each other in morphological and functional features.



Mast cells have euchromatin (=capable of proliferating), while **basophils** have heterochromatin (=end stage cells).

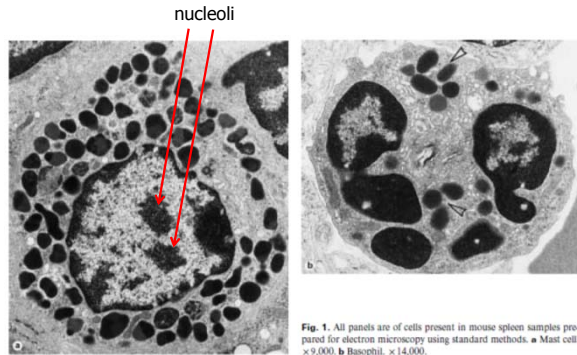
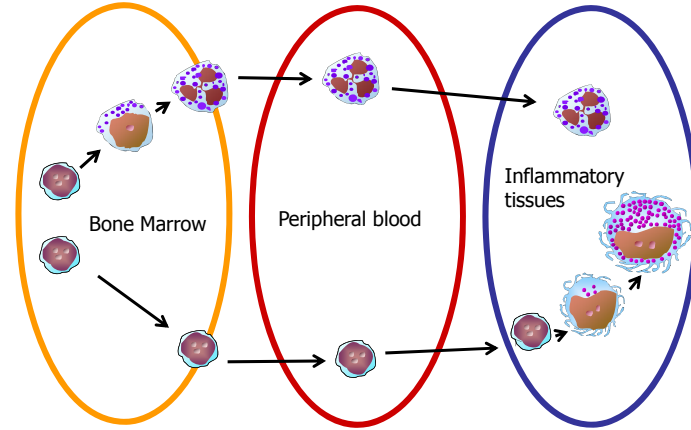


Fig. 1. All panels are of cells present in mouse spleen samples prepared for electron microscopy using standard methods. a Mast cell. $\times 9,000$. b Basophil. $\times 14,000$.
Dvorak AM, Sciuto TE. Int Arch Allergy Immunol. 2004

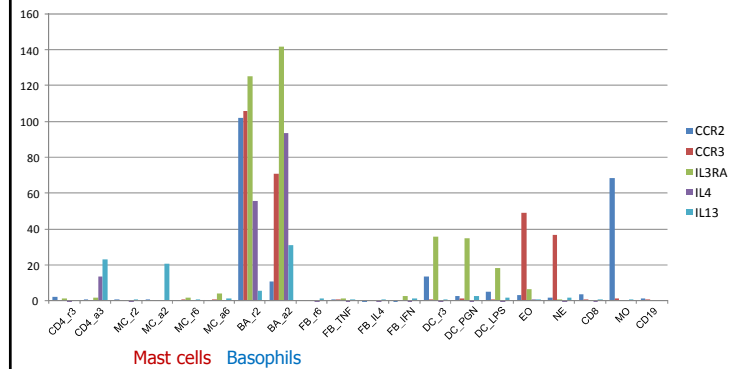
Mast cells complete maturation in gate-keeping tissues, while **basophils** do so in bone marrow



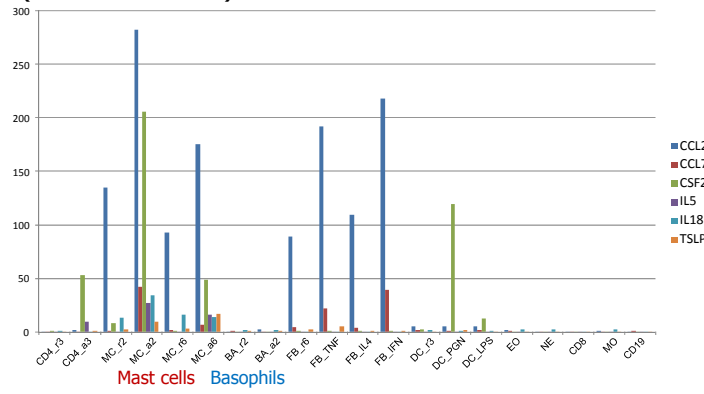
We have been investigating the gene expression profiles of various cell types related to allergic diseases.

<http://www.nch.go.jp/imal/GeneChip/public.htm>

Basophils dominantly express IL-4, IL-13, IL-3R, CCR2 and CCR3 among all cytokine-chemokines and their receptors compared to other cells.

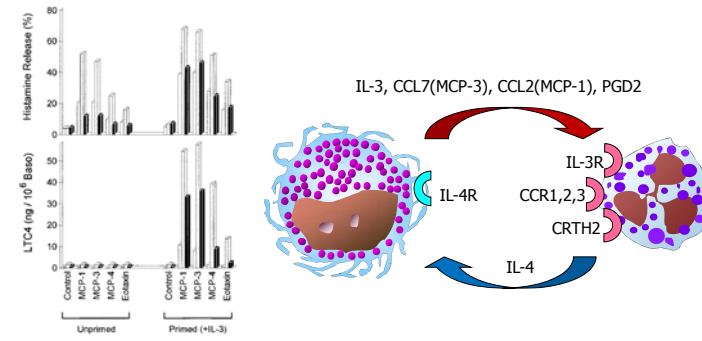


Mast cells dominantly express CCL2 and CCL7 among all chemokines compared to other cells. Also, they express IL-4R, IL-3 and PGD2 enzymes at high levels (data not shown).



Mast cells and basophils act complementary.

Activated mast cells tend to express cytokines and chemokines whose receptors basophils highly express. Basophils also tend to express cytokines whose mast cells express high levels of receptors.

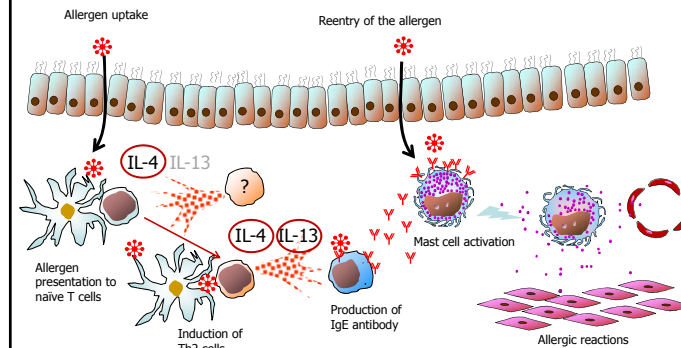


Uguccioni M, et al. *J Clin Invest* 1997; 100:1137. Saito H, et al. *Clin Exp Allergy Review* 2006;6:85

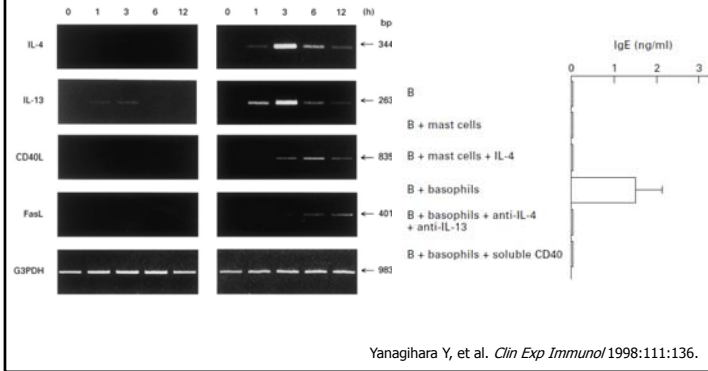
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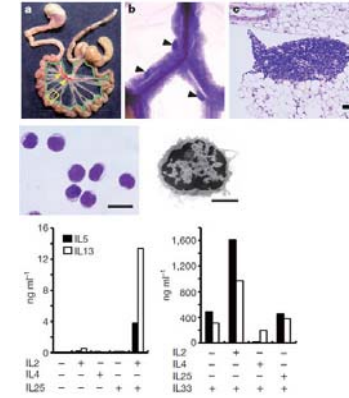
IL-4 but not IL-13 is indispensable to induce Th2 cells from naïve T cells, although IgE production by B cells can be supported by IL-4 or IL-13.



Basophils but not (human) **mast cells** produce IL-4 and thereby induce IgE production by B cells.



Even natural helper cells or innate lymphoid cells capable of producing IL-5 and IL-13 at high levels do not produce IL-4.



Basophils are capable of producing IL-4 even in the absence of IgE.

Secretion of IL-4 from Human Basophils

The Relationship between IL-4 mRNA and Protein in Resting and Stimulated Basophils¹

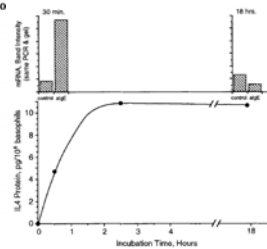
Donald MacGlashan, Jr.,² Jane M. White, Shau-Ku Huang, Santa J. Ono, John T. Schroeder, and Lawrence M. Lichtenstein

Table III. IL-4 release from FMLP- and C5a-stimulated basophils

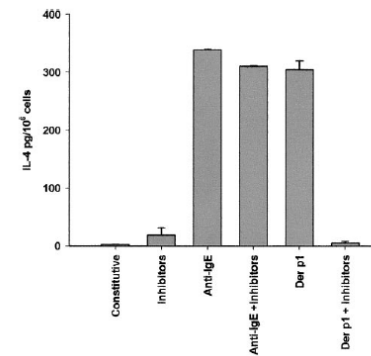
Stimulus	Expt.	Purity	%HR ^a	IL-4R ^b
FMLP (1 μM)	1	89	95	2.8
	2	88	100	10.9
	3	35	80	43.7
C5a (100 ng/ml)	1	88	37	7.8

^a % of histamine release.

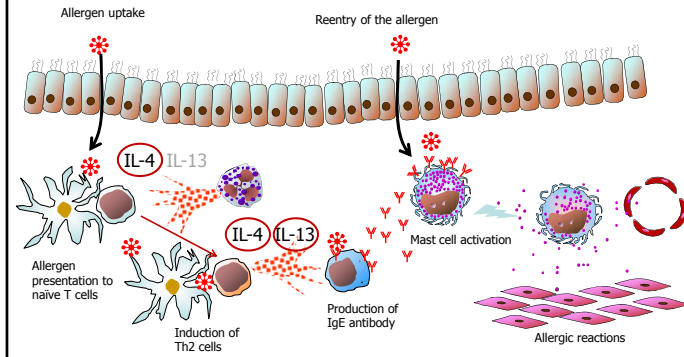
^b IL-4 release in pg/10⁶ basophils.



Allergen Der p1 can induce production of IL-4 by **basophils** without IgE.



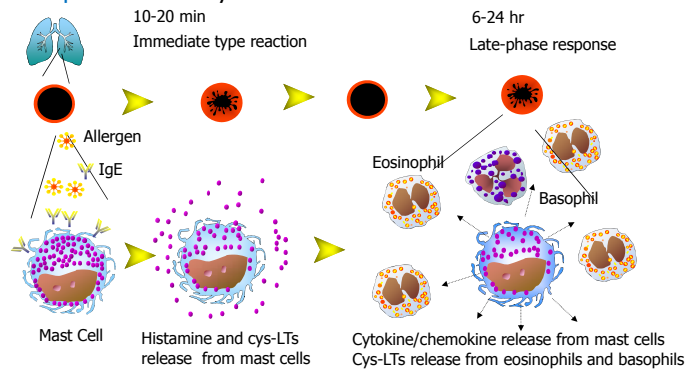
Basophil-derived IL-4 may be indispensable to induce Th2 cells from naïve T cells.



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Late phase asthmatic response is typically found in most of asthma attacks which we have to treat and is mainly caused by cysteinyl leukotrienes released by eosinophils and **basophils** but not by **mast cells**.



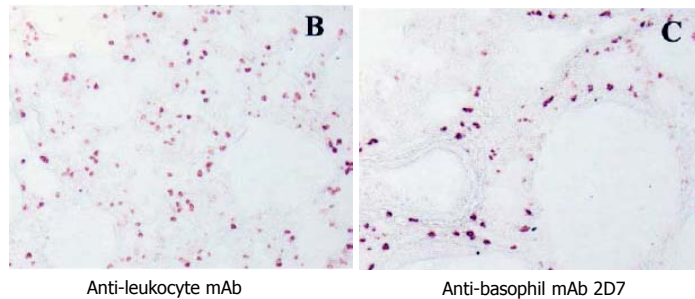
Lichtenstein LM, Bochner BS. *Ann N Y Acad Sci* 1991;629:48.

Basophils produce LTC₄ at 30-fold higher levels compared to eosinophils.

	Basophils	Eosinophils
Secretagogues:	C5a, C3a, fMLP PAF (weak) MBP, polyamines MCP-1, SDF-1 α , MIP-1 α antigen	C5a, C3a, PAF fMLP (weak) Chemokines
Mediators:	Histamine, 1 μ g/10 ⁶ LTC₄, 60 pmol/10⁶ IL-4, 1000 pg/10 ⁶ IL-13, 200 pg/10 ⁶ Tryptase (weak)	None LTC ₄ , 2 pmol/10 ⁶ IL-4, 20 pg/10 ⁶ (intracellular) None

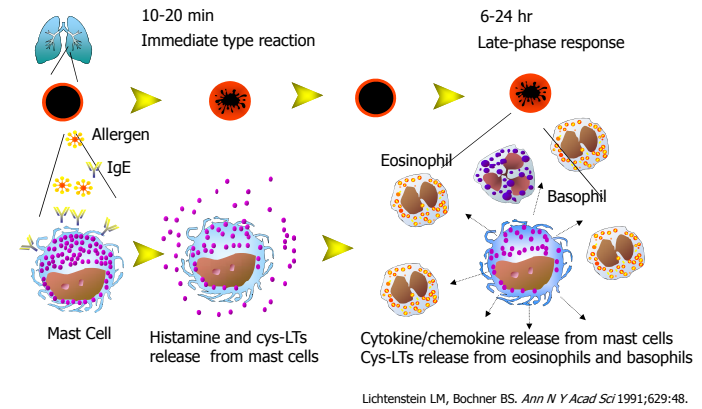
Hawrylowicz CM, MacGlashan DW, Saito H, Simon H-U, Wardlaw AJ. "Effector cells of allergy". p.351-373. In "Allergy, 3rd Edition"

Basophils are the majority among the leukocytes accumulated into the lungs of the fatal asthmatics.



Kepley CL, et al. *Am J Respir Crit Care Med* 2001;164:1053.

Basophils play an important role in late phase asthmatic response by leasing cysteinyl leukotrienes.



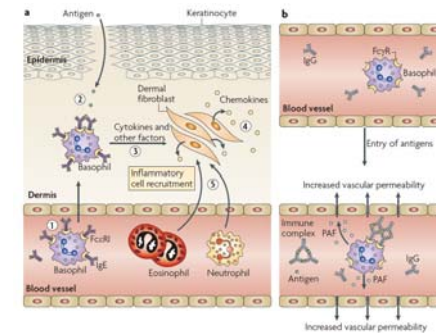
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a | Basophils initiate chronic allergic inflammation. IgE antibodies are captured by circulating basophils (step 1). When the same antigens enter the skin tissue, basophils are activated (step 2). Activated basophils secrete cytokines (step 3) that act on tissue-resident cells, such as fibroblasts, and induce them to produce more chemokines (step 4). Inflammatory cells, such as eosinophils and neutrophils, are then recruited to the skin lesion (step 5), resulting in chronic allergic inflammation.

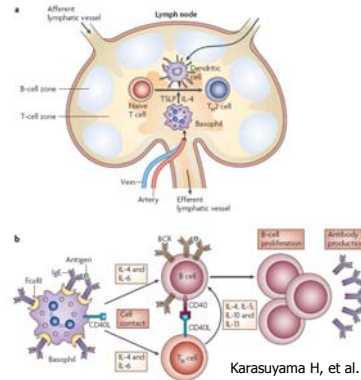
b | Basophils induce IgG-mediated systemic anaphylaxis. When IgG antibodies had been produced and the antigens enter the blood, antigen-IgG immune complexes are formed and captured by circulating basophils through FcγR. Basophils are activated and release PAF, which increases vascular permeability, thereby leading to systemic anaphylaxis.



Karasuyama H, et al. *Nat Rev Immunol* 2009;9:9.

a. Basophils drive Th2 cell differentiation during the primary immune response. In the draining lymph nodes, basophils secrete IL-4, which induce the differentiation of naive T cells into Th2 cells in cooperation with antigen-presenting dendritic cells.

b. Basophils enhance antibody production in the secondary immune response. In antigen-sensitized animals, following re-exposure to the same antigen, basophils efficiently bind free antigens through IgE–FcεRI complexes, become activated and secrete IL-4 and IL-6. These antigen-stimulated basophils interact with antigen-specific B cells and Th cells.



Basophils are important in allergy. Because;

- Basophils and mast cells act complementary, that is, basophils have unique roles in allergy.
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