

Biology of Eosinophils

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Disclosures

I have consulted for GSK and Ception/Cephalon
on anti-IL5 therapies

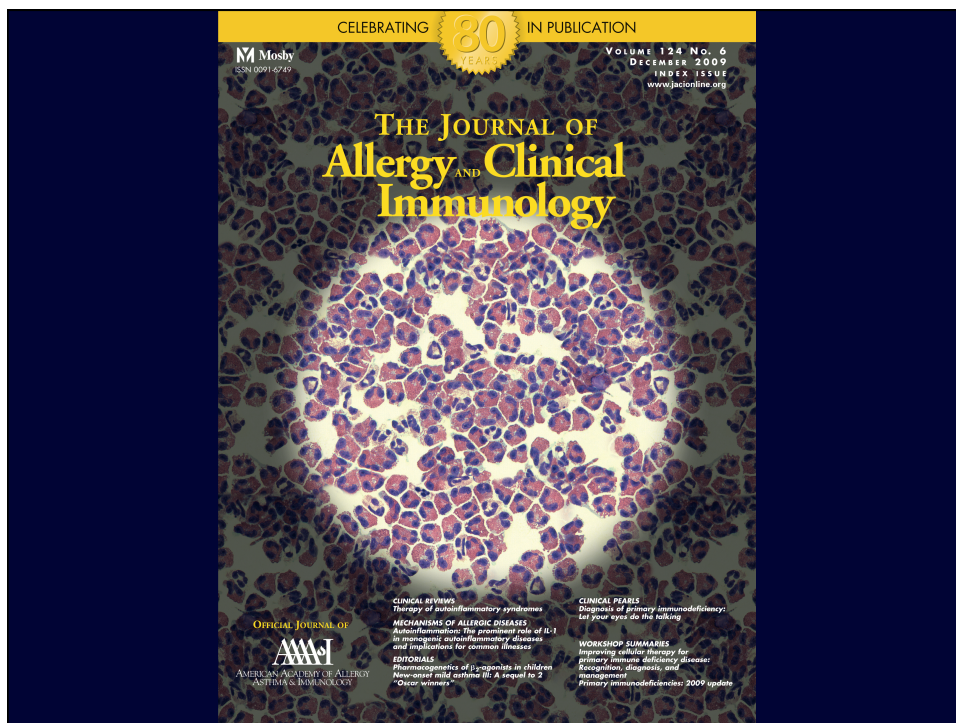
I currently consult for Sanofi-Aventis on various
therapies including anti-eosinophil therapies

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AI72265, Sanofi-Aventis, Dana Foundation

Other: Patents on Siglec-8 with my university

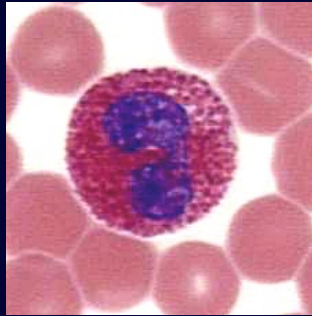
Learning Objectives

- 1) Basics of eosinophil biology, including hematopoiesis, phenotype and function
- 2) Overview of diseases associated with increased numbers of eosinophils
- 3) Features of hypereosinophilic syndromes



Eosinophils 101

- Identified by Paul Ehrlich in 1879 and named based on the staining: 'eosin (acid stain) loving'



Eosinophils 101

-Granules contain cationic proteins:

major basic protein (core)

eosinophil cationic protein

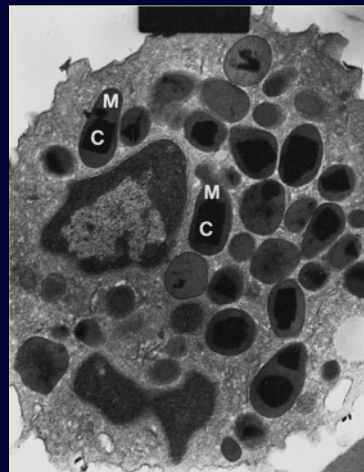
eosinophil-derived

neurotoxin

eosinophil peroxidase

- Contain and release cytokines (interleukins, growth factors) and lipid mediators (leukotrienes)

- Mediate parasite defense, allergic responses, tissue inflammation, immune modulation

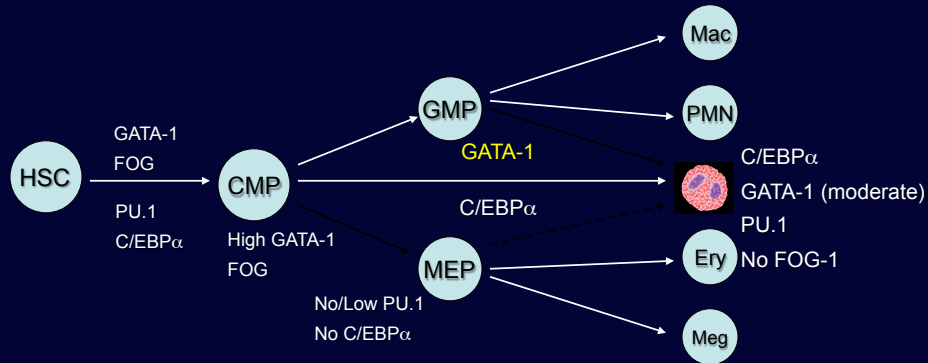


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Middleton's Allergy: Principles and Practice

Eosinophilopoiesis

There are combinatorial Transcription Factor codes that specify the eosinophil versus other myeloid lineages



Eosinophil surface phenotype

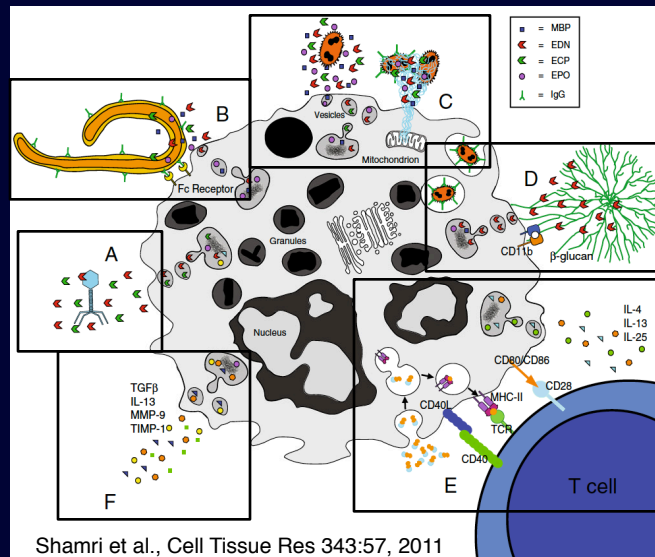
| Chemokine, complement and other chemotactic factor receptors | | Adhesion molecules | | Apoptosis, signaling and others | |
|--|-----------------------|---------------------|-------|---------------------------------|---------------|
| CD35 | CCR1 | CD11a | CD44 | CD9 | CD97 |
| CD88 | CCR3 | CD11b | CD49d | CD17 | CD98 |
| C3aR | CCR6 | CD11c | CD49f | CD24 | CD99 |
| PAFR | CXCR1 | CD15 | CD62L | CD28 | CD137 |
| LTD $_2$ R | CXCR3 | CD15s | CD162 | CD30 | CD139 |
| LTD $_2$ R | CXCR4 | CD18 | CD174 | CD37 | CD148 |
| fMLPR | GRTH2 | CD29 | | CD39 | CD149 |
| Histamine (H4 receptor) | | α d integrin | | CD43 | CD151 |
| | | β 7 integrin | | CD52 | CD161 |
| | | | | CD53 | CD165 |
| | | | | CD63 | Siglec-8 |
| | | | | CD65 | Siglec-10 |
| | | | | CD69 † | LIR1 |
| | | | | CD76 | LIR2 |
| | | | | CD81 | LIR3 |
| | | | | CD82 | LIR7 |
| | | | | CD86 † | |
| | | | | CD92 | |
| | | | | CD95 | |
| | | | | | |
| Immunoglobulin receptors and other members of the immunoglobulin superfamily | | Enzymes | | Cytokines | |
| CD4 | CD58 | CD13 | | CD25 | CD124 |
| CD16 † | CD66 | CD45 | | CD116 | CD125 |
| CD28 | CD89 | CD45RB | | CD117 | CD131 |
| CD31* | CD100 | CD45RO | | CD119 | IL-9R |
| CD32 | CD101 | CD46 | | CD120 | IL-13R |
| CD33 | HLA class I | CD55 | | CD123 | TGF β R |
| CD47 | HLA-DR † | CD59 | | | |
| CD48 | Fc $_{\epsilon}$ RI** | CD87 | | | |
| CD50* | | PAR-2 | | | |
| CD54 † | | | | | |

Bochner 2004
JACI 113:3

Why do we have eosinophils?

- Eosinophils go back to metazoan species
 - All five classes of vertebrates have a cell with the distinct physical and staining characteristics one associates with an eosinophil.
 - That makes eosinophils at least 350-400 million years old.
- Eosinophil granule protein genes and their cousins extend well beyond fish.
- They are best known for their role in host defense against parasitic infections, especially those cause by certain worms
- They therefore probably have a conserved role in innate immunity

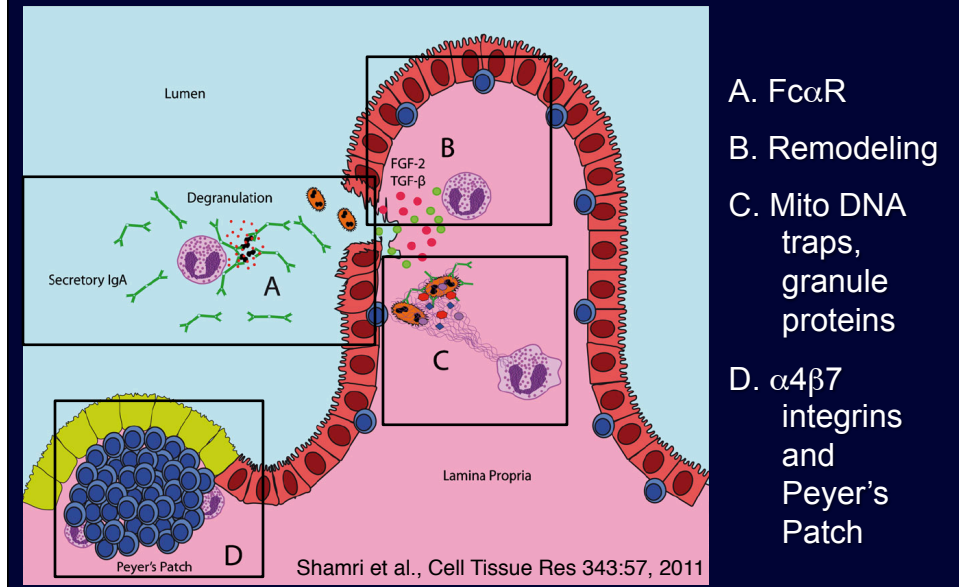
Proposed Contributions of Eosinophils to Innate Immune Host Defense and Repair



- A. RNases
- B. Fc γ RII
- C. Mito DNA traps
- D. Fungi
- E. T cell help
- F. Remodeling

Shamri et al., Cell Tissue Res 343:57, 2011

Proposed Contributions of Eosinophils to Innate Immune Host Defense in the Gut



Key Concepts on Eosinophilia

- Look at total eosinophil counts ONLY (% x WBC)
- Growth and survival factors include:
 - IL-3
 - IL-5
 - GM-CSF
- Selective accumulation facilitated by eotaxins (via CCR3), adhesion molecules (e.g., VLA-4, VCAM-1), and survival factors (especially IL-5 and GM-CSF)
- Tissue eosinophilia can occur without blood or bone marrow increases

Differential Diagnosis of Eosinophilia

"Allergic" Diseases

Atopic and related diseases
Medication-related eosinophilias

Infectious Diseases

Parasitic infections, (helminths)
Specific fungal infections

Hematologic/Neoplastic Disorders

Hypereosinophilic syndrome
Leukemia
Lymphomas
Tumor-associated
Mastocytosis

Immunologic Reactions

Specific immune deficiency diseases
Transplant rejection

Endocrine

Hypoadrenalism

Diseases with Specific Organ Involvement

- Skin (e.g., episodic angioedema with eosinophilia, eosinophilic cellulitis)
- Pulmonary (e.g., eosinophilic pneumonias)
- Gastrointestinal (e.g., eosinophilic gastroenteritis)
- Neurologic (e.g., eosinophilic meningitis)
- Rheumatologic (e.g., Churg-Strauss eosinophilia-myalgia syndrome)
- Cardiac (e.g., hypersensitivity myocarditis, Churg-Strauss syndrome, hypereosinophilic syndromes)
- Renal (e.g., drug-induced interstitial nephritis, cholesterol embolization, eosinophilic cystitis)

Middleton's Allergy: Principles and Practice

Eosinophilia: when the allergist worries

Normal blood levels: up to an absolute count of 500/mm³

500-1500/mm³

Allergic Rhinitis
Allergic Asthma
Food allergy
Urticaria
Eosinophilic esophagitis
(or normal)

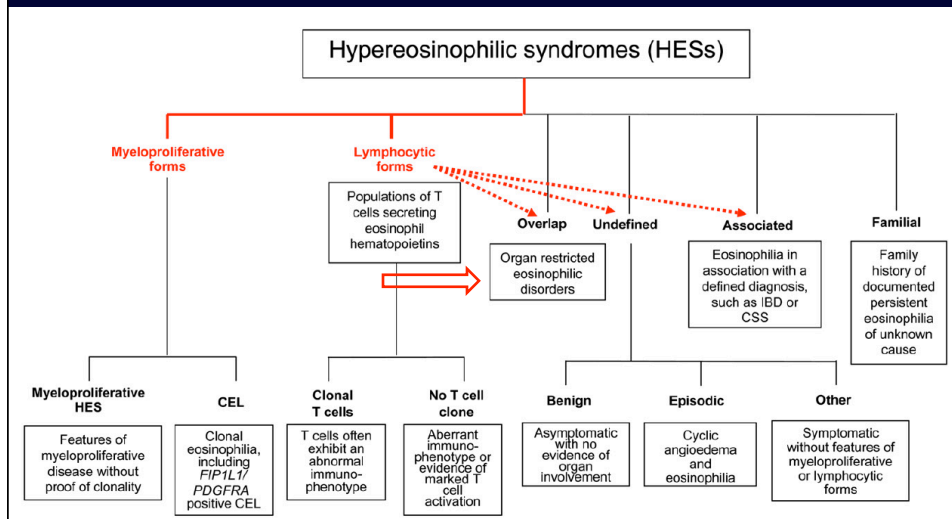
1500-5000/mm³

Non-allergic asthma
Nasal polyposis
ABPA
Helminth infection
Churg-Strauss Syndrome
Drug reactions

>5000/mm³

Leukemia
Episodic eosinophilia
Idiopathic HES

Classification of Eosinophilic Disorders

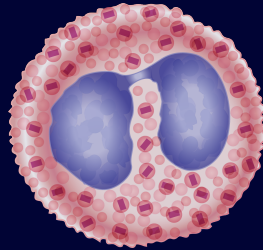


Simon et al., J Allergy Clin Immunol 126:45, 2010

When you want to get rid of eosinophils there are many ways to do this

- Inhibit hematopoiesis
- Inhibit adhesion
- Inhibit migration
- Inhibit survival signals
- Actively induce apoptosis

Examples of therapies selectively targeting eosinophils



Anti-IL-5 and IL-5R
(mepolizumab,
reslizumab, benralizumab);
CCR3 and its ligands;
Siglec-8

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THE JOURNAL OF

What targeting eosinophils has taught us about their role in diseases

Bruce S. Bochner, MD,^a and Gerald J. Gleich, MD^b *Baltimore, Md. and Salt Lake City, Utah*

Organ-specific eosinophilic disorders of the skin, lung, and gastrointestinal tract

Dagmar Simon, MD,^a Andrew Wardlaw, MD, PhD,^b and Marc E. Rothenberg, MD, PhD^c *Bern, Switzerland, Leicester, United Kingdom, and Cincinnati, Ohio*

Intact Activation)

Practical approach to the patient with hypereosinophilia

Florence Roufosse, MD,^a and Peter F. Weller, MD^b *Brussels and Gosselies, Belgium, and Boston, Mass*

Refining the definition of hypereosinophilic syndrome

Hans-Uwe Simon, MD, PhD,^a Marc E. Rothenberg, MD, PhD,^b Bruce S. Bochner, MD,^c Peter F. Weller, MD,^d Andrew J. Wardlaw, MD, PhD,^e Michael E. Wechsler, MD,^f Lanny J. Rosenwasser, MD,^g Florence Roufosse, MD, PhD,^h Gerald J. Gleich, MD,ⁱ and Amy D. Klion, MD^j *Bern, Switzerland, Cincinnati, Ohio, Baltimore and Bethesda, Md, Boston, Mass, Leicester, United Kingdom, Kansas City, Mo, Brussels and Gosselies, Belgium, and Salt Lake City, Utah*

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MECHANISMS OF ALLERGIC DISEASES
What targeting the eosinophil has taught us about their role in diseases

EDITORIALS
Intelligent granules: Are eosinophil crystalloid granules antimicrobial?
Parent oral immunotherapy is not ready for clinical use

ROSTRUM
Refining the definition of hypereosinophilic syndrome

CURRENT PERSPECTIVES
Practical approach to the patient with hypereosinophilia
Human IgE antibody serology: A primer for the practicing North American allergist/immunologist