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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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
Eosinophilopoiesis

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

![Eosinophil surface phenotype diagram](image)

- Adhesion molecules
  - Chemokine, complement and other chemotactic factor receptors
    - CD35, CCR1, CD88, CCR3, CD11a, CCR6, PAFR, CXCR1, LTB4R, CXCR3, LTD4R, CXCR4, ITIMPR, CRTH2, Histamine (H4 receptor)
  - Immunoglobulin receptors and other members of the immunoglobulin superfamily
    - CD4, CD16A, CD28, CD31, CD32, CD33, CD44, CD45, CD45RB, CD55, CD59, CD87, CD100, CD101, HLA class I, HLA-DR, FcγRII

- Apoptosis, signaling and others
  - CD9, CD97, CD14, CD17, CD19, CD24, CD25, CD30, CD33, CD43, CD52, CD65, CD87, CD92, CD95

- Enzymes
  - CD13, CD45, CD45RB, CD45RO, CD46, CD55, CD59, CD87, PAR-2

- Cytokines
  - CD25, CD124, CD116, CD125, CD117, CD131, CD119, IL-9, CD120, IL-13R, CD123, TGFβR

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 caused 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. FcγRII
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

A. FcαR
B. Remodeling
C. Mito DNA traps, granule proteins
D. α4β7 integrins and Peyer’s Patch

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)

Eosinophilia: when the allergist worries

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

<table>
<thead>
<tr>
<th>500-1500/mm³</th>
<th>1500-5000/mm³</th>
<th>&gt;5000/mm³</th>
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</thead>
<tbody>
<tr>
<td>Allergic Rhinitis</td>
<td>Non-allergic asthma</td>
<td>Leukemia</td>
</tr>
<tr>
<td>Allergic Asthma</td>
<td>Nasal polyposis</td>
<td>Episodic eosinophilia</td>
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<tr>
<td>Food allergy</td>
<td>ABPA</td>
<td>Idiopathic HES</td>
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<td>Urticaria</td>
<td>Helminth infection</td>
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<tr>
<td>Eosinophilic esophagitis (or normal)</td>
<td>Churg-Strauss Syndrome</td>
<td>Drug reactions</td>
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Classification of Eosinophilic Disorders

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