Biology of Eosinophils

Bruce S. Bochner, M.D.
Cosner Scholar in Translational Research
Professor of Medicine and Director
Division of Allergy and Clinical Immunology
Johns Hopkins Asthma and Allergy Center
Baltimore, Maryland

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

Grants and Research Support: NIAID R01 AI72265, Sanofi-Aventis, Dana Foundation

Other: Patents on Siglec-8 with my university

Learning Objectives

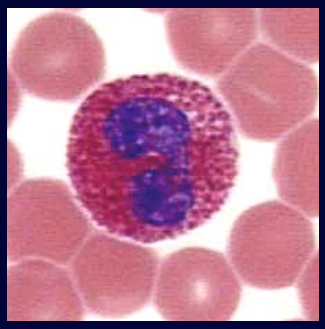
1) Basics of eosinophil biology, including hematopoiesis, phenotype and function

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'



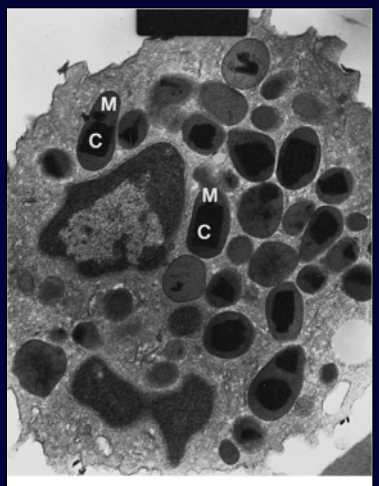
Eosinophils 101

-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)

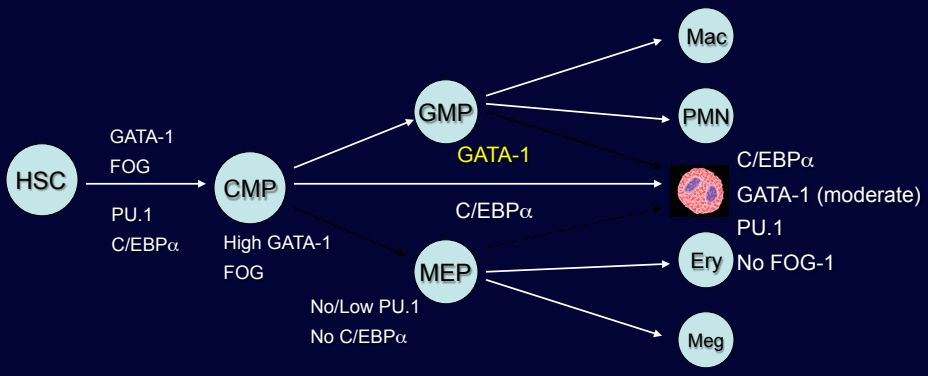
- Mediate parasite defense, allergic responses, tissue inflammation, immune modulation



Middleton's Allergy: Principles and Practice

Eosinophilopoiesis

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



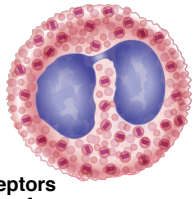
Eosinophil surface phenotype

Chemokine, complement and other chemotactic factor receptors

CD35	CCR1
CD88	CCR3
C3aR	CCR6
PAFR	CXCR1
LTB_4R	CXCR3
LTD_4R	CXCR4
fMLPR	CRTH2
Histamine (H4 receptor)	

Adhesion molecules

CD11a	CD44
CD11b	CD49d
CD11c	CD49f
CD15	CD62L
CD15s	CD162
CD18	CD174
CD29	
αd integrin	
β7 integrin	



Apoptosis, signaling and others

CD9	CD97
CD17	CD98
CD24	CD99
CD28	CD137
CD30	CD139
CD37	CD148
CD39	CD149
CD43	CD151
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

CD4	CD58
CD16†	CD66
CD28	CD89
CD31*	CD100
CD32	CD101
CD33	HLA class I
CD47	HLA-DR†
CD48	$Fc_εRI$**
CD50*	
CD54*†	

Enzymes

CD13
CD45
CD45RB
CD45RO
CD46
CD55
CD59
CD87
PAR-2

Cytokines

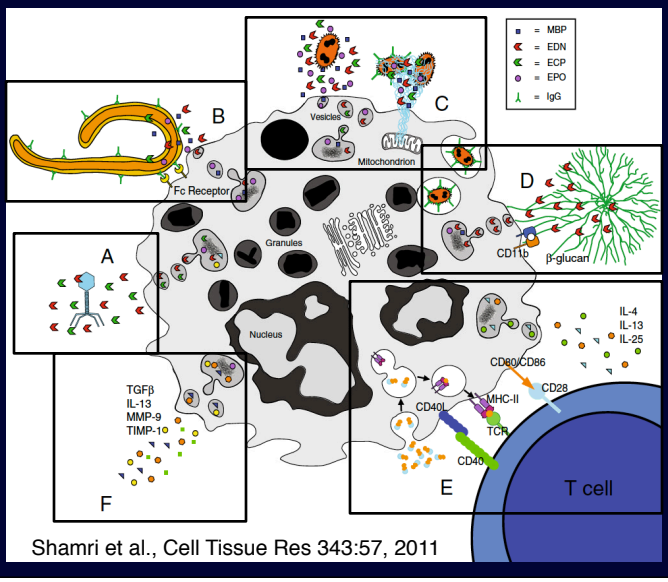
CD25	CD124
CD116	CD125
CD117	CD131
CD119	IL-9R
CD120	IL-13R
CD123	TGFβR

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 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



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

A. RNases

B. FcγRII

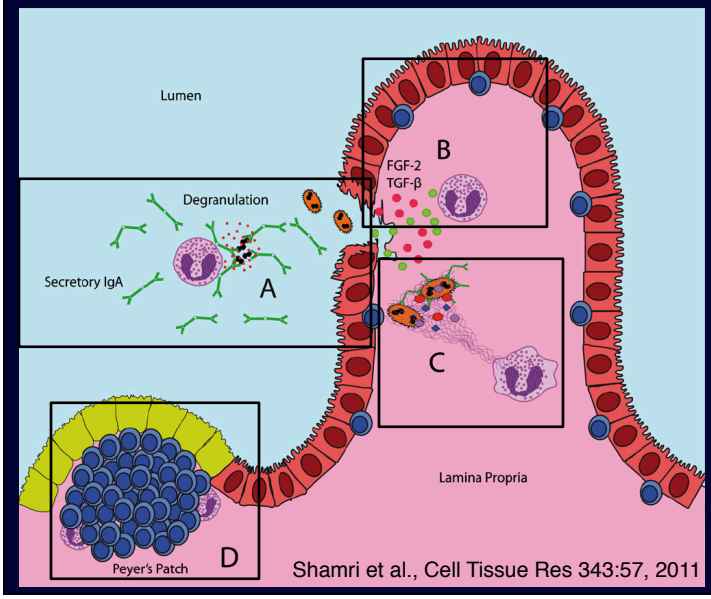
C. Mito DNA traps

D. Fungi

E. T cell help

F. Remodeling

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



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

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)

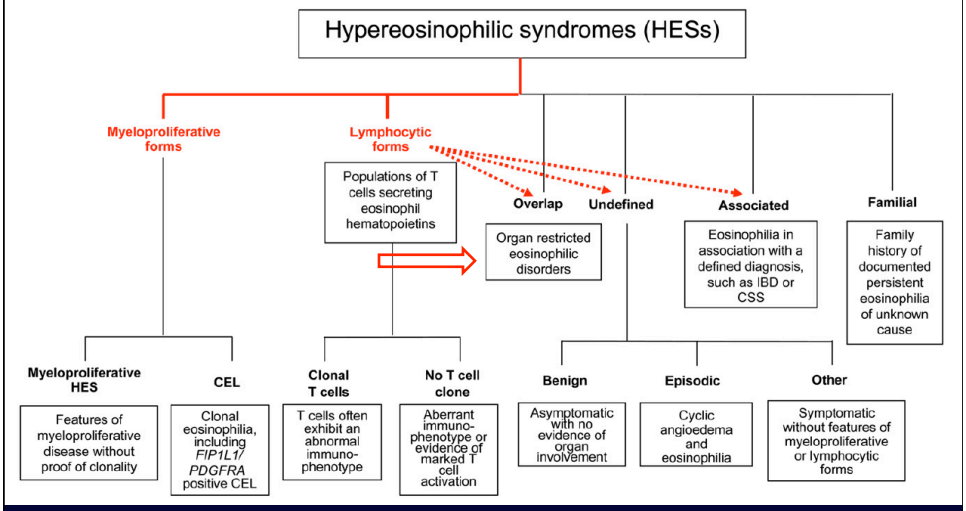
Middleton's Allergy: Principles and Practice

Eosinophilia: when the allergist worries

Normal blood levels: up to an absolute count of 500/mm^3

500-1500/mm^3	1500-5000/mm^3	>5000/mm^3
Allergic Rhinitis	Non-allergic asthma	Leukemia
Allergic Asthma	Nasal polyposis	Episodic eosinophilia
Food allergy	ABPA	Idiopathic HES
Urticaria	Helminth infection	
Eosinophilic esophagitis (or normal)	Churg-Strauss Syndrome	
	Drug reactions	

Classification of Eosinophilic Disorders

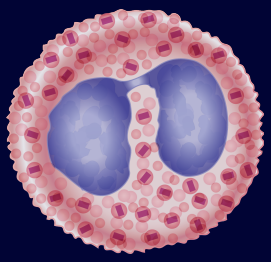


Simon et al., J Allergy Clin Immunol 126:45, 2010

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