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Human versus mouse eosinophils: "That which we call an eosinophil, by any other name would stain as red"

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Date of Original Release: September 2012. Credit may be obtained for these courses until August 31, 2014.

Overall Purpose/Goal: To provide excellent reviews on key aspects of allergic disease to those who research, treat, or manage allergic disease.

Target Audience: Physicians and researchers within the field of allergic disease.

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Activity Objectives

1. To define the cellular characteristics of human and mouse eosinophils.
2. To differentiate the mechanisms of degranulation of eosinophils in human subjects and mice in the setting of allergic disease.
3. To describe the ways that eosinophils act as a part of the innate immune system and as a regulator of the adaptive immune system.
4. To recognize the similarities between human and mouse eosinophils, which support the translational application of mice as a model for human disease.

Recognition of Commercial Support: This CME activity has not received external commercial support.

Disclosure of Significant Relationships with Relevant Commercial Companies/Organizations: J. J. Lee has received research support from the National Institutes of Health (NIH) and the American Heart Association; has received consultancy fees from Amgen; and receives royalties from the Mayo Foundation. E. A. Jacobsen, S. I. Ochkur, M. P. McGarry, R. M. Condjella, A. D. Doyle, H. Luo, K. R. Zellner, C. A. Protheroe, W. E. LeSuer, D. C. Colbert, R. A. Helmers, and N. A. Lee have received research support from the NIH and the American Heart Association; and receive royalties from the Mayo Foundation. L. Willetts has received research support from the NIH, American Heart Association, Lung Association of Alberta, and Canadian Institutes of Health Research. P. Lacy has received research support from the Canadian Institutes of Health Research, the Lung Association of Albert & NWT, Alberta Innovates-Health Solutions CRIO, National Sanitarium Association, and the Australian Research Council; and is employed by the University of Alberta. R. Moqbel has received research support from the Canadian Institutes of Health Research, the Lung Association of Alberta, and CIHR Canada MHRC, MICH; has received consultancy fees from GlaxoSmithKline Canada; is employed by the University of Manitoba; and has a patent in diagnosing respiratory diseases with urine metabolites identified by nuclear magnetic resonance.

The respective life histories of human subjects and mice are well defined and describe a unique story of evolutionary conservation extending from sequence identity within the genome to the underpinnings of biochemical, cellular, and physiologic pathways. As a consequence, the hematopoietic lineages of both species are invariantly maintained, each with identifiable eosinophils. This canonical presence nonetheless does not preclude disparities between human and mouse eosinophils, their effector functions, or both. Indeed, many books and reviews dogmatically highlight differences, providing

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Supported by the Mayo Foundation and grants from the United States National Institutes of Health (to N.A.L. [HL058723] and J.J.L. [HL065228 and RR0109709]), the American Heart Association (to N.A.L. [05556392], J.J.L. [0855703], and E.A.J. [11SDG7510043]), the Canadian Institutes of Health Research (to R.M. [MOP89748]), and the Lung Association of Alberta (to L.W.).

Received for publication June 22, 2012; revised July 25, 2012; accepted for publication July 25, 2012.

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0091-6749/$36.00

http://dx.doi.org/10.1016/j.jaci.2012.07.025

Terms in boldface and italics are defined in the glossary on page 573.

a rationale to discount the use of mouse models of human eosinophilic diseases. We suggest that this perspective is parochial and ignores the wealth of available studies and the consensus of the literature that overwhelming similarities (and not differences) exist between human and mouse eosinophils. The goal of this review is to summarize this literature and in some cases provide experimental details comparing and contrasting eosinophils and eosinophil effector functions in human subjects versus mice. In particular, our review will provide a summation and an easy-to-use reference guide to important studies demonstrating that although differences exist, more often than not, their consequences are unknown and do not necessarily reflect inherent disparities in eosinophil function but instead species-specific variations. The conclusion from this overview is that despite nominal differences, the vast similarities between human and mouse eosinophils provide important insights as to their roles in health and disease and, in turn, demonstrate the unique utility of mouse-based studies with an expectation of valid extrapolation to the understanding and treatment of patients. (J Allergy Clin Immunol 2012;130:572-84.)

Key words: *Eosinophils, mouse, human, rodent, primate, hematology*

Abbreviations used

CLC: Charcot-Leyden crystal
CMP: Common myeloid progenitor
EAR: Eosinophil-associated ribonuclease
ECP: Eosinophil cationic protein
EDN: Eosinophil-derived neurotoxin
EoP: Eosinophil lineage–committed progenitors
EPX: Eosinophil peroxidase
Gal-10: Galectin-10
GMP: Granulocyte macrophage progenitor
IL-5R: IL-5 receptor
MBP: Major basic protein
MIP: Macrophage inflammatory protein
PMD: Piecemeal degranulation

Preclinical rodent models, mouse models in particular, have been the most widely used in studies attempting to understand the mechanisms underlying human disease. The reasons for this prominence are numerous and varied, as reviewed by Rosenthal and Brown,[1] including the conservation of genome sequence complexity[2,3] and the commonality of biochemical,[4] cellular,[5] and physiologic[6] pathways. In light of these observations, it is surprising that the differences (and, more importantly, not the similarities) between human subjects and mice are often dogmatically highlighted.[7-9] Studies of eosinophils are also subject to this bias, with investigators questioning the value of research on mouse eosinophils and the validity of potential therapeutic options suggested for eosinophil-associated diseases.[10,11] As a consequence, observations suggesting differences in form and function between human and mouse eosinophils are often the focus of many studies and the explanation for the failure of mouse models of human eosinophilic diseases (eg, asthma).

The evolutionary conservation between human subjects (Primata) and mice (Rodentia) is well defined.[12] As a direct consequence, the hematopoietic lineages between these groups

GLOSSARY

5-LIPOXYGENASE: An enzyme that converts arachidonic acid into the first precursor of the cysteinyl leukotrienes.

A PROLIFERATION-INDUCING LIGAND (APRIL): A ligand involved in B-cell signaling and maturation.

ARACHIDONIC ACID: A polyunsaturated fatty acid derived from membrane phospholipids through the action of cytosolic phospholipase A_2.

CASPASES: Enzymes that are cysteinyl proteases that cleave after specific aspartyl residues. Caspases are involved in programmed cell death. A small number of autoimmune lymphoproliferative syndrome cases are caused by mutations in caspase 10.

CD11B: The α chain of complement receptor 3 (CR3), also known as CD11b/CD18 (an adhesion molecule).

CD45RA: A cell-surface marker that is an isoform of CD45. CD45RA is a cell-surface marker for naive T cells. CD45 is essential for T- and B-cell activation.

CHARCOT-LEYDEN CRYSTAL: Colorless crystals that can occur in the sputum after an asthmatic attack.

COSTIMULATORY MOLECULE: Costimulatory molecules are required for optimal cell activation. A commonly discussed costimulatory molecule on T cells is CD28. CD28 binds to 2 ligands expressed on antigen-presenting cells: B7.1 (CD80) and B7.2 (CD86). Ligation of CD28 augments T-cell receptor signals.

DOMINANT NEGATIVE MUTATION: A mutation with a gene product that adversely affects the normal wild-type gene product within the same cell.

FLOW CYTOMETRY: Cells are incubated with mAbs tagged with fluorescent dyes or fluorochromes that emit light when excited by a light source (eg, 488 nm, 633 nm). Cells pass one at a time through the light source, creating 2 types of light emission: scatter and fluorescence. Scatter is measured by using both forward and side detectors. Forward scatter relates to cell size, whereas side scatter is a measure of cell refractivity, which indirectly measures cell granularity.

HETEROCHROMATIC: Relating to heterochromatin, a densely staining chromatin that appears as nodules in or along chromosomes and contains relatively few genes.

MYELOPEROXIDASE: An enzyme that mediates the conversion of H_2O_2 to HOCl and the subsequent killing of phagocytosed bacteria, fungi, and viruses.

NEGATIVE T-CELL SELECTION: Elimination of T cells in the thymus that bind to the endogenous peptide presented by the MHC molecule. These cells are thought to have a high potential for being self-reactive.

NEW WORLD AND OLD WORLD PRIMATES: New World refers to the Americas, whereas Old World refers to Europe, Asia, and Africa. The distinction between these larger groups of primate species arises from their reproductive isolation occurring when South America split off from Africa (approximately 85 million years ago). The ensuing independent evolution of these 2 primate groups has resulted in biochemical, cellular, and morphologic distinctions. The rapid evolutionary events associated with immunologic responses have resulted in significant differences in immunity between New and Old World primates, which are highlighted by unique eosinophil-specific genes appearing in one or the other of these primate groups.

The Editors wish to acknowledge Daniel A. Searing, MD, for preparing this glossary.