Mechanisms of allergic diseases

(Supported by and educational grant from Merck & Co, Inc).

Series editors: Joshua A. Boyce, MD, Fred Finkelman, MD, William T. Shearer, MD, PhD, and Donata Vercelli, MD

Protective role of the lung collectins surfactant protein A and surfactant protein D in airway inflammation

Angela Haczku, MD, PhD *Philadelphia, Pa*

INFORMATION FOR CATEGORY 1 CME CREDIT

Credit can now be obtained, free for a limited time, by reading the review articles in this issue. Please note the following instructions.

Method of Physician Participation in Learning Process: The core material for these activities can be read in this issue of the Journal or online at the JACI Web site: www.jacionline.org. The accompanying tests may only be submitted online at www.jacionline.org. Fax or other copies will not be accepted.

Date of Original Release: November 2008. Credit may be obtained for these courses until October 31, 2010.

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.

Accreditation/Provider Statements and Credit Designation: The American Academy of Allergy, Asthma & Immunology (AAAAI) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. The AAAAI designates these educational activities for a maximum of 1 *AMA PRA Category 1 Credit*™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

List of Design Committee Members: *Author:* Angela Haczku, MD, PhD

Activity Objectives

1. To understand the unique structure of soluble pattern recognition receptors (collectins), their localization, and their functional versatility.

2. To understand the role of the lung collectins in pathogen recognition, airway defenses, and airway inflammation.

Recognition of Commercial Support: This CME activity is supported by an educational grant from Merck & Co., Inc.

Disclosure of Significant Relationships with Relevant Commercial Companies/Organizations: Angela Haczku has received grants from the National Institutes of Health, Sepracor, Centocor, and GlaxoSmithKline.

The acute inflammatory airway response is characterized by a time-dependent onset followed by active resolution. Emerging evidence suggests that epithelial cells of the proximal and distal air spaces release host defense mediators that can facilitate both the initiation and the resolution part of inflammatory airway changes. These molecules, also known as the hydrophilic surfactant proteins (surfactant protein [SP]–A and SP-D) belong to the class of collagenous lectins (collectins). The collectins are a small family of soluble pattern recognition receptors containing collagenous regions and C-type lectin domains. SP-A and SP-D are most abundant in the lung. Because of their structural uniqueness, specific localization, and functional versatility, lung collectins are important players of the pulmonary immune responses. Recent studies in our laboratory and others indicated significant associations of lung collectin levels with acute and chronic airway inflammation in both animal models and patients, suggesting the usefulness of these molecules as disease biomarkers. Research on wild-type and mutant recombinant molecules *in vivo* and *in vitro* showed that SP-A and SP-D bind carbohydrates, lipids, and nucleic acids with a broad-spectrum specificity and initiate phagocytosis of inhaled pathogens as well as apoptotic cells. Investigations on gene-deficient and conditional overexpresser mice indicated that lung collectins also directly modulate innate immune cell function and T-cell–dependent inflammatory events. Thus, these molecules have a unique, dual-function capacity to induce pathogen elimination and control proinflammatory mechanisms, suggesting a potential suitability for therapeutic prevention and treatment of chronic airway inflammation. This article reviews evidence supporting that the lung collectins play an immune-protective role and are essential for maintenance of the immunologic homeostasis in the lung. (J Allergy Clin Immunol 2008;122:861-79.)

Key words: *Macrophage, dendritic cell, surfactant, SP-D, SP-A, innate immune regulation*

The pulmonary immune system is faced with the dual task of elimination of inhaled pathogens and maintenance of an inflammation-free mucosal environment. Although physical barriers filter out most of the inhaled material, a large amount of small, potentially toxic, infectious or allergenic particles (<5 μm in diameter) still reaches the distal air spaces, where they encounter components of the innate immune system. Under normal, nondiseased conditions, these include the alveolar macrophages, dendritic cells, and lung collectins.

From the Department of Medicine, University of Pennsylvania.

Supported by an American Lung Association Career Investigator Award, R01AI055593, and R01HL076646.

Received for publication August 30, 2008; revised October 13, 2008; accepted for publication October 13, 2008.

Reprint requests: Angela Haczku, MD, PhD, Pulmonary, Allergy and Critical Care Division, Translational Research Laboratories, Room 1209, 125 S 31st Street, Philadelphia PA 19104. E-mail: haczku@mail.med.upenn.edu.

0091-6749/$34.00

doi:10.1016/j.jaci.2008.10.014

Terms in boldface and italics are defined in the glossary on page 862.

Abbreviations used

ABPA: Allergic bronchopulmonary aspergillosis
BAL: Bronchoalveolar lavage
C1: Complement component 1
C1qr: Complement 1q-receptor
C/EBP: CCAAT/enhancer-binding protein
CL: Collectin
CRD: Carbohydrate recognition domain
DPPC: Dipalmitoylphosphatidylcholine
ER: Endoplasmic reticulum
MBL: Mannose-binding lectin
NFAT: Nuclear factor of activated T cells
NF-κB: Nuclear factor-κB
NKT: Natural killer T
RSV: Respiratory syncytial virus
SIRP: Signal inhibitory regulatory protein
SP: Surfactant protein
SP-R210: Surfactant protein receptor 210
STAT: Signal transducers and activators of transcription
TARC: Thymus and activation-regulated chemokine
TLR: Toll-like receptor
TTF: Thyroid transcription factor

GLOSSARY

ADIPONECTIN: Adiponectin decreases T_H2 inflammation in mouse models of asthma and decreases insulin resistance in mouse models of diabetes. Treatment with adiponectin increases IL-10 production from macrophages. Pulmonary tissue expresses 3 adiponectin receptors (T-cadherin, AdipoR1, R2).

C1q: The first component of the classic complement cascade, C1 is composed of a trimeric complex of C1q, r, and s. C1q is the C1 subunit that binds aggregated immunoglobulin, resulting in the activation of C1r (a serine protease). Free C1q binds the C1q receptor, which increases phagocytic capacity of neutrophils and macrophages. C1q deficiency, inherited in an autosomal-recessive pattern, is associated with a lupus-like rash, fever, arthritis, and glomerulonephritis.

CD69, CD25: CD69 is a marker of activated T lymphocytes, B cells, eosinophils, neutrophils, and platelets. CD25 is the α-chain of the IL-2 receptor and is found on activated T cells as well as regulatory T cells, eosinophils, and B cells.

CODON USAGE BIAS, TRANSLATIONAL STABILITY, TRANSCRIPTIONAL CONTROL, SYNONYMOUS/NONSYNONYMOUS MUTATIONS: *Codon usage bias* refers to the differences in the frequency of usage for a certain base triplet for a given amino acid among organisms. This phenomenon can play a role in molecular evolution because codon usage bias will influence the available tRNA pool and thus the translational efficiency of any given nucleotide triplet for the same amino acid, theoretically making some proteins more efficiently translated than others. *Translational stability* refers to the stability of the mRNA before its translation into protein, whereas *transcriptional control* occurs via promoter and enhancer sequences to alter the rate of gene transcription. Codon usage bias, translational stability, and transcriptional control all serve as mechanisms for ultimately affecting protein levels. *Synonymous mutations* are base pair changes in an exon that do not change the amino acid code in the protein. *Nonsynonymous mutations* are base pair changes that alter an existing amino acid codon, resulting in a change in the protein sequence.

EXON DUPLICATION AND SHUFFLING: Mechanisms for genomic diversity and evolution include exon duplication and shuffling. The theory of exon shuffling explains the assembly/formation of new genes that can occur by the assembly of exon fragments, made possible because of the genomic organization of alternating exons and introns (coding and noncoding regions) and alternate splicing with recombination. Exon duplication can be considered one form of exon shuffling.

GALACTOSYLCERAMIDE: A glycolipid antigen that is presented by CD1d to invariant natural killer T (NKT) cells. NKT cells are detected using tetramers loaded with α-galactosylceramide. Presentation of α-galactosylceramide to NKT cells leads to the production of IL-12 by antigen-presenting cells and of IL-4, IL-13, IL-10, and TGF-β by NKT cells.

IL-10, IL-12, IFN-γ: IL-10, IL-12, and IFN-γ are all cytokines that dampen the T_H2 response. IL-12 is a dimer of p40/35 that induces IFN-γ production and a shift to T_H1 phenotype. IL-12p40 and IL-12 receptor deficiency leads to severe nontuberculous mycobacterial infections. IL-10 is produced by regulatory T cells and increases in therapies that reduce inflammation, such as specific immunotherapy. IL-10–deficient mice develop spontaneous colitis similar to human Crohn disease.

LPS: LPS is a component of the outer membrane of gram-negative bacteria. Smooth LPS has O-polysaccharides, whereas rough LPS lacks O-polysaccharides. Smooth strains of bacteria are more virulent, elicit an antibody response, and are more resistant to clearance.

MANNOSE-BINDING LECTIN (MBL): The lectin pathway for complement activation uses MBL binding to mannans on bacterial surface resulting in activation of the MBL associated serine proteases 1 and 2, analogous to activated C1. MBL binds a number of monosaccharides including mannose, N-acetylglucosamine, and L-fucose. MBL associated serine proteases cleave C4 and C2 with subsequent cleavage of C3 and activation of the terminal complement cascade. MBL deficiency may be related to increased infectious susceptibility, including in the respiratory tract.

NEGATIVE GLUCOCORTICOID RESPONSE ELEMENT: Glucocorticoid receptors are nuclear steroid receptors that dimerize and bind to the glucocorticoid response elements to activate or repress transcription. Decreased gene transcription can occur when glucocorticoid receptors bind to a negative glucocorticoid response element consensus sequence (ATYACnnTnTGATCn).

SIGNAL TRANSDUCERS AND ACTIVATORS OF TRANSCRIPTION (STAT), AP-1, NUCLEAR FACTOR OF ACTIVATED T CELLS (NFAT): *AP-1:* Heteromeric complexes of jun and fos that activate transcription of the IL-2, IL-4, IL-5, TNF, and GM-CSF promoters. *NFAT:* A Rel transcription family member. Calcineurin-induced dephosphorylation of NFAT is required for nuclear localization. NFAT is modulated by cyclosporine and tacrolimus, which both bind to immunophilins and block the phosphotase activity of calcineurin. *STAT:* STAT act as phosphorylated dimers that bind to palindromic DNA elements in response to Janus-activated kinase pathways. STAT1, STAT2, STAT3, STAT4, STAT5, and STAT6 are downstream of IFN, IL-2, IL-6, IL-10, IL-12, IL-2, and IL-4, IL-13 signaling.

THYMUS AND ACTIVATION-REGULATED CHEMOKINE (TARC): Also known as chemokine ligand 17 (CCL17), TARC binds to the chemokine receptor 4 (CCR4), which is increased on T_H2 cells and activated dendritic cells, promoting trafficking to sites of inflammation in asthma and atopic dermatitis.

TOLL-LIKE RECEPTOR (TLR)–4, CD14: TLRs are transmembrane receptors in the innate immune system that activate antigen-presenting cells. TLR ligands are microorganism/pathogen associated molecular patterns. TLR-2 binds to lipotechoic acid on gram-positive bacteria; TLR-4 binds lipotechoic acid as well as LPS on gram-negative bacteria. Endogenous ligands for TLR-4 include fibronectin and β-defensin-2. TLR-4 uses CD14 to activate the nuclear factor-κB (NF-κB) pathway and production of IL-6, IL-12, and TNF-α. Mutations of TLR-mediated immunity can result in primary immunodeficiency made up of recurrent pyogenic infections with poor polysaccharide antibody response (IL-1 receptor–associated kinase 4 [IRAK-4]) and herpes simplex virus encephalitis (TLR-3).

The Editors wish to acknowledge Seema Aceves, MD, PhD, for preparing this glossary.