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

T_H17 and T_H22 cells: A confusion of antimicrobial response with tissue inflammation versus protection

Mübeccel Akdis, MD, PhD,[a] Oscar Palomares, PhD,[b] Willem van de Veen, MSc,[a] Marloes van Splunter, Dipl Biol,[a] and Cezmi A. Akdis, MD[a] *Davos, Switzerland, and Madrid, Spain*

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: June 2012. Credit may be obtained for these courses until May 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.

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: Mübeccel Akdis, MD, PhD, Oscar Palomares, PhD, Willem van de Veen, MSc, Marloes van Splunter, Dipl Biol, and Cezmi A. Akdis, MD

Activity Objectives

1. To identify the various $CD4^+$ T_H cell subsets, including T_H1, T_H2, T_H9, T_H17, T_H22, and T follicular helper cells.
2. To review the differentiation and cytokine signatures of the T_H cell subsets.
3. To understand the role of the T_H cell subsets in disease.

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

Disclosure of Significant Relationships with Relevant Commercial Companies/Organizations: M. Akdis has received grants from the Swiss Nation Science Foundation and the European Union Commission. O. Palomares declares that he has no no relevant conflicts of interest.W. van de Veen has received grants from the Swiss National Science Foundation and the European Commission. M. van Splunter has received grants from CK-CARE. C. Akdis has received grants from Novartis, the European Union Commission, the Swiss National Science Foundation, the Global Allergy and Asthma European Network, and the Christine Kühne Center for Allergy Research and Education; has consulted for Actellion, Aventis, Stallergenes, and Allergopharma; is president of the European Academy of Allergy and Clinical Immunology; is a fellow and interest group member of the American Academy of Allergy, Asthma, & Immunology; is a former committee member of the Global Allergy and Asthma European Network; and is director of the Christine Kühne Center for Allergy Research and Education.

Substantial progress in understanding mechanisms of immune regulation in allergy, asthma, autoimmune diseases, tumors, organ transplantation, chronic infections, and pregnancy is in an exciting developmental phase that might lead to a variety of targeted therapeutic approaches. Recent progress in the interaction between immune/inflammatory cell subsets through cytokines, particularly the extension of the knowledge on reciprocal regulation and counterbalance between subsets of T_H1, T_H2, T_H9, T_H17, T_H22, T follicular helper cells and different subsets of regulatory T cells, as well as corresponding and co-orchestrating B-cell, natural killer cell, dendritic cell, and innate lymphoid cell subsets, offers new possibilities for immune intervention. Studies on new subsets confirm the important role of T cells in the instruction of tissue cells and also demonstrate the important role of feedback regulation for the polarization toward distinct T-cell subsets. T_H17 and T_H22 cells are 2 emerging T_H cell subsets that link the immune response to tissue inflammation; IL-17A and IL-17F and IL-22 are their respective prototype cytokines. Although both cytokines play roles in immune defense to extracellular bacteria, IL-17 augments inflammation, whereas IL-22 plays a tissue-protective role. This review focuses on current knowledge on T_H17 and T_H22 cells and their role in inflammation, with special focus on the mechanisms of their generation and driving and effector cytokines, as well as their role in host defense,

From [a]the Swiss Institute of Allergy and Asthma Research (SIAF), University of Zurich, Davos, and [b]the Department of Biochemistry and Molecular Biology, School of Chemistry, Complutense University of Madrid (UCM).

The authors' laboratories are supported by Swiss National Foundation grants 320030-132899 and 320030-140772/1; the Christine Kühne-Center for Allergy Research and Education (CK-CARE); European 7th Framework projects MeDALL (Mechanisms of the Development of Allergy; no. 261357) and PREDICTA (Post-Infectious Immune Reprogramming and Its Association with Persistence and Chronicity of Respiratory Allergic Diseases; no. 260895). O.P. is a Ramon y Cajal Scholar funded by MINECO and the European Social Fund.

Received for publication April 18, 2012; revised May 2, 2012; accepted for publication May 2, 2012.

Corresponding author: Cezmi A. Akdis, MD, Swiss Institute of Allergy and Asthma Research (SIAF), Obere Str. 22, CH-7270, Davos Platz, Switzerland. E-mail: akdisac@siaf.uzh.ch.

0091-6749/$36.00

doi:10.1016/j.jaci.2012.05.003

Terms in boldface and italics are defined in the glossary on page 1439.

autoimmunity, and allergic diseases. (J Allergy Clin Immunol 2012;129:1438-49.)

Key words: *T cells, inflammation, T_H17, T_H22, epithelial cells, asthma, allergy*

Abbreviations used
CMC: Chronic mucocutaneous candidiasis
DC: Dendritic cell
FOXP3: Forkhead box P3
γ_c: γ-chain
IL-22BP: IL-22 binding protein
NK: Natural killer
ROR: Retinoic acid receptor–related orphan receptor
RUNX: Runt-related transcription factor
T-bet: T-box transcription factor
Treg: Regulatory T

The immune response of ***memory T cells*** is essential in the inflammation and immune regulation seen in patients with many diseases related to tissue inflammation, such as allergic rhinitis, asthma, and atopic dermatitis, as well as organ transplantation, tumors, autoimmunity, and infections. $CD4^+$ ***naive T cells*** can differentiate into T_H1, T_H2, T_H9, T_H17, T_H22, and T follicular helper cells depending on the vitamins and other substances in the micromilieu, the adjuvanicity of the innate immune response stimulating substances coexposed with the antigen, the status that defines the responsiveness of T cells, the type and developmental stage of antigen-presenting cells, and the cytokines in the microenvironment. On the basis of their respective effector cytokine profiles and interactions with resident tissue cells, these T-cell subsets can promote different types of inflammatory responses (Fig 1). For the development of a certain type of immune response and to display their effector functions, these T cells, ***dendritic cells*** (DCs), innate lymphoid cells, and tissue cells in the environment develop a cytokine milieu that represents the type of immune response. During the development of allergic disease, effector T_H2 cells produce IL-4, IL-5, IL-9, and IL-13,[1,2] and probably other recently identified interleukins are released from tissue cells and DCs, such as IL-25, IL-31, IL-33, which altogether contribute to T_H2 response and inflammation.[3-5] These cytokines play roles in allergen-specific IgE production, eosinophilia, and mucus production. T_H1 cells, with their prototype cytokine ***IFN-γ***, play a role in defense against intracellular pathogens and activation-induced cell death of the skin and mucosal epithelium and T cells.[6,7]

Most of the functions attributed to T_H1 cells are now better understood after the discovery of T_H17 cells. T_H17 cells are characterized by IL-17A, IL-17F, and IL-22 expression as major cytokines.[8,9] IL-17A, initially called IL-17, is the founding member of a structurally distinct cytokine family. It binds as a homodimer or a heterodimer with IL-17F to its receptor, IL-17RA.[10] IL-17A is expressed by activated $CD4^+$ T_H17 cells,[9] but its expression has also been detected in $CD8^+$ T cells, ***γδ T cells***, natural killer (NK) cells, and neutrophils.[10] Consistent with the broad expression pattern of its receptor, IL-17A acts on a variety of cells, which respond by upregulating the expression of proinflammatory cytokines, chemokines, and metalloproteases.

GLOSSARY

AUTOSOMAL DOMINANT HYPER-IgE SYNDROME: A condition that results from mutations in the signal transducer and activator of transcription 3 *(STAT3)* gene. *STAT3* is a transcription factor.

ANTIMICROBIAL PEPTIDES (AMPs): Components of the innate immune system that are capable of inserting into bacterial phospholipids to slow microbial growth. AMP levels are decreased in the skin of patients with atopic dermatitis.

CHRONIC GRAFT-VERSUS-HOST DISEASE (GVHD): T cells from a hematopoietic stem cell transplant react against the recipient's antigens. Chronic GVHD is defined as the persistence or appearance of symptoms from 100 days after transplantation. Risk factors for chronic GVHD include a history of acute GVHD, older age of the recipient at the time of transplantation, transplantation from a multiparous female donor into a male recipient (with reactivity to Y chromosome–associated antigens), and incompatibility at minor histocompatibility loci.

DENDRITIC CELLS: Hematopoietic cells that function as antigen-presenting cells for naive lymphocytes. Their name is derived from their multiple, thin membranous projections.

DIGOXIN: A cardiac glycoside used for atrial fibrillation, heart failure, and supraventricular tachycardia. Digoxin inhibits the Na^+/K^+ ATPase pump in myocardial cells, causing increased intracellular Na^+, which in turns results in increased Ca^{++} influx through the Na^+/Ca^{++} exchange pump. The result is enhanced cardiac contractility. Digoxin also directly suppresses the atrioventricular node.

γδ T CELL: A subpopulation of T cells located at epithelial barriers and sites of inflammation. γδ T cells are capable of binding to antigens directly without MHC presentation. They can also react to MHC molecules without an associated peptide. In addition to playing a role in defense against multiple different types of bacteria, they can accumulate at inflammatory sites in patients with autoimmune disease.

IFN-γ: A cytokine with a multitude of effects in addition to promoting $CD4^+$ T-cell differentiation into T_H1 cells. Other actions of IFN-γ include activation of macrophages, upregulation of MHC class II expression, maturation of $CD8^+$ T cells into cytotoxic T cells, activation of endothelial cells and neutrophils, and promotion of antiviral defenses.

KERATINOCYTE: An epidermal cell that produces keratins, sulfur-containing fibrous proteins that form the basis of epidermal tissues, such as hair or nails.

MEMORY T CELL: A subset of $CD4^+$ and $CD8^+$ cells characterized by the cell-surface marker CD45RO. They are capable of surviving for long periods of time without antigenic stimulation. Memory B cells have been demonstrated to survive into the tenth decade of life.

NAIVE T CELL: CD4 and CD8 T cells emigrate from the thymus as naive T cells. Naive T cells produce IL-2 but only low levels of other cytokines. They are not strong helpers to B cells. They can survive without antigen but require the presence of MHC molecules. Naive T cells circulate from the blood to the spleen and lymph nodes.

PLASMACYTOID DENDRITIC CELLS: A type of dendritic cell with a distinct histologic morphology that can produce high levels of type I interferon and are thought to play special roles in antiviral host defense and autoimmunity.

POLYMORPHISM: The existence of a gene in several allelic forms.

TOLL-LIKE RECEPTOR 6: A Toll-like receptor that binds to lipoproteins and lipoteichoic acid found on pathogens, such as gram-positive bacteria and *Mycoplasma* species.

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